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Association Between Fish Consumption and Nephropathy in American Indians—The Strong Heart Study

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Abstract

Objective—The present study examined the association between fish consumption and nephropathy in American Indians.

Methods—In the family cohort of the Strong Heart Study, we investigated 2,261 participants with baseline examination between 2001 and 2003 and follow-up examination between 2006 and 2008. The average follow-up period was 5.4 years. We defined fish consumption as the sum of dietary intake of tuna, fried fish, and nonfried fish obtained from a validated food frequency questionnaire. Nephropathy was defined as microalbuminuria (urinary albumin–creatinine ratio [ACR]: 30 to 299 mg/g), macroalbuminuria (urinary ACR: ≥300 mg/g), or an estimated glomerular filtration rate of <60 mL/min/1.73 m^2. Using regression models, we examined the association between fish consumption measured at baseline and 2 outcomes in nephropathy present at follow-up, albuminuria, or renal impairment, and change in urinary ACR or estimated glomerular filtration rate between baseline and follow-up examinations.

Results—The prevalence of microalbuminuria, macroalbuminuria, and renal impairment was 13%, 3%, and 4%, respectively. The fish items consumed by the participants were predominantly deep-fried. We found no associations between fish consumption and any measure of nephropathy after adjusting for demographic, clinical, lifestyle, and dietary factors.

Conclusions—Dietary intake of predominantly fried fish was not associated with a lower risk of nephropathy in American Indians.

American Indians have a high prevalence of obesity, diabetes, and their associated complications, including nephropathy.[1–4] The US Renal Data System reports that diabetes accounts for 54% of the new cases of end-stage renal disease (ESRD). The risk of ESRD in American Indians, with or without diabetes, is nearly twice than that of whites, and the rates of ESRD continue to increase in young American Indians.[5] The current management of diabetic nephropathy focuses on controlling blood pressure and blood glucose optimally, and on blocking the renin–angiotensin–aldosterone system.[6] The high rates of diabetes and

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nephropathy in American Indians warrant exploring new strategies, such as diet, that may prevent or slow the progression of renal disease.

The n-3 long-chain polyunsaturated fatty acids (n-3 LC-PUFAs) found in fish may modify the risk of diabetic nephropathy by decreasing blood pressure,[7] improving serum triglycerides,[8] or reducing inflammation.[9] Observational studies show that dietary intake of fish or n-3 LC-PUFAs may reduce nephropathy in diabetes. In a cross-sectional analysis, weekly consumption of a minimum of 2 portions of fish, as compared with less than 1 portion, was associated with a lower risk of macroalbuminuria in a British population with primarily type 2 diabetes.[10] Dietary intake of n-3 LC-PUFAs (approximately 1 portion of oily fish per week) was inversely associated with urinary albumin excretion rate in North American population with type 1 diabetes.[11] Interventional studies collectively suggest that oral supplementation with fish oils can lower urinary protein excretion, but have no significant effect on glomerular filtration in individuals with chronic kidney disease of any origin.[12]

In this study, we examined the association between dietary intake of fish and urinary albumin excretion and glomerular filtration in American Indians, with or without diabetes, participating in the family cohort of the Strong Heart Study (SHS).

Methods

Study Populations

The study population consisted of participants in the family cohort of the SHS. The SHS is an epidemiologic study designed to measure preclinical and clinical cardiovascular diseases and their risk factors in American Indians. The original cohort recruited 4,549 participants aged 45 to 72 years from 13 American Indian tribes and communities from near Phoenix, Arizona, in south–western Oklahoma, and in western and central North and South Dakota, between 1989 and 1991. Between 2001 and 2003, investigators recruited a cohort of 94 families and 3,776 individuals aged ≥15 years, which included 825 participants from the original SHS cohort. The follow-up examination of the family cohort was conducted between 2006 and 2008. At baseline and follow-up examinations, participants completed a physical examination which included anthropometric measurements, a fasting blood draw, collection of urine specimens, and a clinical examination conducted by a physician. Trained interviewers conducted personal interviews to collect information on demographics, medical history, and lifestyle factors, including smoking, alcohol consumption, and physical activity, in standardized questionnaires modified for use in American Indians.[13]

In this study, we examined the association between dietary intake of fish at baseline, and each of albuminuria and renal impairment measured at follow-up. We also examined the association of dietary intake of fish on change in urinary albumin–creatinine ratio (ACR) and in estimated glomerular filtration rate (eGFR) between the 2 examinations. We excluded 221 participants with eGFR >130 mL/min/1.73 m^2 (glomerular hyperfiltration) in all analyses on renal function. This study was approved by the Indian Health Service, appropriate institutional review boards, and the participating tribes.[13]

Inclusion and Exclusion Criteria

Our analyses included 2,261 participants who attended both baseline and follow-up examinations. The participants with extreme values of energy intake, that is, <600 kcal/day (n = 70) or >8,000 kcal/day for men (n = 43) and >6,000 kcal/day for women (n = 80), those who left >10% of the items blank on the food frequency questionnaire (FFQ) (n = 47), those with missing dietary data (n =26), and those on dialysis (n = 23) or who had a renal transplant (n = 3) were excluded from the study.

Biochemical Analyses

Participants provided a random spot urine specimen at each examination. Urinary albumin (mg/L) was measured by nephelometric immunochemical assay and urinary creatinine (g/L) was measured using the alkaline picrate method for calculation of urinary ACR. Overnight fasting plasma creatinine and triglycerides were measured by enzymatic methods using reagent kits from Boehringer Mannheim Diagnostic (Indianapolis, IN) on a chemistry analyzer. HemoglobinA1c was measured using high-performance liquid chromatography.[14] All participants received a 75-g oral glucose tolerance test; however, the test was not given if they had diabetes treated with insulin or oral hypoglycemic agents, their medical records indicated 2 random blood glucose of >250 mg/dL, their fasting blood glucose was 225 mg/dL as determined by Accu-Chek II (Baxter Healthcare Corp. Grand Prairie, TX), or they declined to undergo the test.[15]

Definition of Exposures

At baseline, participants completed a Block FFQ, conducted by trained interviewers, designed to assess dietary intake for the previous year. It consisted of 119 items, including foods that represent the diet of American Indians. We defined fish consumption as the sum of the average daily intake of tuna, fried fish, and nonfried fish in g/day. Participants indicated how frequently they consumed any of these items in the past year. The fish consumption was divided into following 4 categories: 0 g/day, 0.1 to 3.7 g/day, >3.7 to 15.0 g/day, and >15.0 g/day (approximately 1 portion of fish/week). Median intake for participants who ate >0 g/day, but <15.0 g/day, was 3.7 g/day.

Definition of Outcomes

Nephropathy was defined as the presence of microalbuminuria (urinary ACR =30 to 299 mg/g), macroalbuminuria (urinary ACR, ≥300 mg/g),[16] or renal impairment (eGFR, <60 mL/min/1.73 m^2, based on the Modification of Diet in Renal Disease Study formula).[17]

Statistical Analyses

Characteristics of participants at baseline were stratified by dietary intake of fish, using means and standard deviations for normally distributed continuous variables, medians and interquartile ranges for non-normally distributed continuous variables, and percentages for categorical variables. We tested the differences across the categories of dietary intake of fish with χ^2 tests for categorical variables and analyses of variance or Kruskall–Wallis tests for normally or non-normally distributed continuous variables.

Because ordinal regression models violated the assumption of proportional odds, we used generalized ordinal regression models to explore the association between dietary intake of fish and albuminuria. Odds ratios (ORs), using the lowest category of intake as the reference, were used to estimate relative risk and were presented with their 95% confidence intervals (CIs). We used linear regression to explore the association between dietary intake of fish and difference in urinary ACR between the 2 examinations as continuous outcomes. The regression coefficient (β) represented the amount of change in urinary ACR in participants with dietary intake of fish in each category of the distribution, as compared with those in the lowest category of intake. The logistic regression analysis was used to explore the association between dietary intake of fish and renal function as binary outcomes (renal impairment vs. normal renal function). When modeling the differences in eGFR between the 2 examinations as continuous outcomes, we used linear regression to explore the association between dietary intake of fish and change in eGFR.

We included covariates in multivariable models if they were of *a priori* clinical relevance or if they were associated with outcomes in unadjusted analyses at $P \leq .1$. Covariates included

age, gender, center, diabetes status, systolic blood pressure, fasting serum triglycerides, waist-hip ratio (WHR), smoking, alcohol consumption, and dietary intake of energy, protein, and sodium. In analyses on the prospective association between fish consumption and albuminuria or renal impairment, we also included urinary ACR or eGFR measured at baseline as covariates. We analyzed age, systolic blood pressure, fasting serum triglycerides, WHR, urinary ACR, eGFR, and dietary intake of energy, protein, and sodium as continuous variables. The smoking and diabetes status was coded as yes or no. We tested the interaction between dietary intake of fish and diabetes status on albuminuria and renal function. In sensitivity analyses, we adjusted additionally for the use of angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers to assess whether these treatments altered associations between exposures and outcomes. All the statistical analyses were performed using STATA 9.1 (Stata Corporation, College Station, TX).

Results

In an average follow-up of 5.4 years, 2,261 participants attended both baseline and follow-up examinations. Of these, 416 (18%) reported no intake of fish and 290 (13%) consumed >15 g of fish/day (approximately 1 portion of fish per week). A total of 1,555 (69%) participants consumed ≤15 g of fish/day. At baseline, the average age was 38 years and 38% were men. Of these 2,261 participants, 22% had diabetes and 7% had impaired fasting glucose. The prevalence of microalbuminuria, macroalbuminuria, and renal impairment was 13%, 3%, and 4%, respectively. Participants who consumed more fish were older, more likely to drink alcohol, have a higher educational level and energy intake, and were less likely to smoke, as compared with those who consumed less fish. In addition, participants who consumed more fish had higher values of body mass index, WHR, systolic blood pressure, hemoglobinA1c, urinary ACR, serum triglycerides, but a lower level of eGFR (Table 1).

Dietary intake of fish was significantly associated with an increased risk of albuminuria present at follow-up, comparing >15 g/day versus 0 g/day, in unadjusted generalized ordinal logistic regression (OR: 1.59; 95% CI: 1.09, 2.33; $P = .02$). However, this association diminished after adjusting for potential confounders (OR: 1.20; not significant) (Table 2). Dietary intake of fish and change in urinary ACR showed no association (Table 4).

Dietary intake of fish was not associated with renal impairment present at follow-up in logistic regression analysis (Table 3). Modeling the difference in eGFR as a continuous outcome revealed a significant association between dietary intake of fish and decreased eGFR (worsening) in unadjusted linear regression (β: −3.67; 95% CI: −6.42, −0.92; $P = .007$). However, the estimate of association decreased and was no longer statistically significant in multivariable-adjusted analysis (Table 4). No interaction between dietary intake of fish and diabetes status existed on the risk of nephropathy present at follow-up. In sensitivity analyses, when including the use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in the regression models, we observed minimal change in the magnitude of the association between fish consumption and albuminuria or renal impairment.

Discussion

In the family cohort of the SHS, which averaged 38 years of age and where dietary intake of fish was assessed by FFQ, it was observed that the fish items consumed among the participants were predominantly deep-fried. Only 25% of all participants reported consuming nonfried fish and among these, >99% consumed <1 portion per week. Consuming 1 portion or more of fish weekly, as compared with not consuming any fish, was

associated with a higher risk of nephropathy present at follow-up. However, these associations were subject to confounding and were no longer statistically significant after adjusting for demographic, clinical, lifestyle, and dietary factors.

Previous studies have demonstrated protective associations between dietary intake of fish or n-3 LC-PUFAs in fish and albuminuria. In the Diabetes Control and Complication Trial, individuals with type 1 diabetes who had a higher intake of n-3 LC-PUFAs (approximately 1 portion of oily fish per week) had lower urinary albumin excretion rate, as compared with those with low intake.[11] In the European Prospective Investigation of Cancer–Norfolk population-based study, fish consumption (≥2 portions vs. <1 portion per week) was associated with a lower risk of macroalbuminuria in individuals with existing diabetes.[10] This association was related to the content of n-3 LC-PUFAs present in fish.[18] Biological mechanisms have shown that n-3 LC-PUFAs decrease each of blood pressure[7] and serum triglycerides,[8] which increase the risk of nephropathy. Because fried fish tends to be made from lean fish (with little n-3 LC-PUFAs), rather than fatty fish, it would be less likely to lower triglycerides and blood pressure. As such, the fried fish that our participants frequently consumed may not have provided significant quantities of n-3 LC-PUFAs.

The method of preparing fish may determine its health effects. Deep-frying the fish can alter plasma fatty acid profiles and decrease the n-3/n-6 fatty acid ratios.[19] Because the participating tribes live inland, the fish products available were mostly canned or commercially prepared. Commercially prepared fried fish products are frequently deep-fried using partially hydrogenated oils or oils used repeatedly for frying. The *trans* fatty acids and lipid oxidative products from these oils could impair endothelial function and increase the risk of nephropathy.[20–22] Although consuming more nonfried fish has been positively associated with increased plasma levels of n-3 LC-PUFAs[23] and a lower risk of ischemic heart disease and congestive heart failure,[24–26] no similar protective associations are found with dietary intake of fried fish.[24–26]

Clinical and lifestyle factors probably confounded the relationship between fish consumption and nephropathy in this cohort because an association was observed in unadjusted, but not in multivariable-adjusted analyses. Regular intake of fried fish may reflect a lifestyle that increases the risk of nephropathy; this is supported by the observation that adjusting for smoking, alcohol consumption, and dietary intake (protein, energy and sodium) lessened the association. Higher systolic blood pressure and serum triglycerides also confounded the association. However, we could not rule out residual confounding by factors that we did not measure or measured imprecisely.

The strengths of the SHS include the large representative sample of an American Indian population and its comprehensive follow-up. Several potential limitations should be considered. The fish consumption was assessed by FFQ. Although the FFQ was validated for use in American Indians, participants must estimate the frequencies and portion sizes of the fish which can introduce measurement error or reporting bias. Because we analyzed dietary data at baseline only, we could not account for any changes in food intake over time. Finally, urinary ACR and eGFR were ascertained by a single measurement and thus are subjected to daily variability and random errors, which could diminish any association.[27]

In conclusion, this study documented that American Indians participating in the SHS consumed mostly deep-fried fish. Whether consuming fried fish simply reflects an unhealthy lifestyle, or whether frying alters the nutrients of fish increasing the risk of nephropathy, remains unclear. Our findings suggest that regularly consuming fried fish was associated with neither a lower risk, nor a higher risk of nephropathy once we accounted for potential confounders. We support further prospective studies investigating the role of nutrition,

especially dietary intake of n-3 LC-PUFAs and fish, in this population who are at high risk of diabetes and nephropathy.

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Table 1

Characteristics of Participants at Baseline (2001–2003) of the Family Cohort of the Strong Heart Study (n = 2,261) Stratified by Level of Fish Consumption

	Fish Consumption (g/day)			
	0	**0.1–3.7**	**>3.7–15**	**>15**
N (%)	416 (18.4)	775 (34.3)	780 (34.5)	290 (12.8)
Fish consumption (g/day)	0	1.7 (0.9–2.6)	6.9 (4.7–9.5)	23.4 (17.7–34.7) *
Age (years)	33.3 ± 16.3	40.4 ± 16.5	41.3 ± 15.0	40.9 ± 14.3 *
Gender (% male)	32.9	29.3	42.4	53.8 *
Center				
Arizona (%)	31.5	30.7	33.3	33.5
Oklahoma (%)	26.7	35.9	36.3	33.1
North/South Dakota (%)	41.8	33.4	30.4	33.5 *
Education (% more than high school)	47.0	68.6	69.9	68.4 *
Systolic BP (mm Hg)	118 ± 13.8	122 ± 15.4	123 ± 16.6	123 ± 15.4 *
HbA1c (%)	6.4 ± 1.9	6.6 ± 1.9	6.9 ± 2.2	6.8 ± 2.1 *
eGFR (mL/min/1.73 m^2)	107 ± 26.5	99.4 ± 25.1	100 ± 26.0	103 ± 27.0 *
Serum triglycerides (mg/dL)	116 (84–168)	140 (96–197)	141 (102–199)	159 (105–216) *
Urinary ACR (mg/g)	6.9 (4.5–15.2)	7.6 (4.7–16.2)	8.3 (5.0–18.1)	8.6 (4.8–19.7) *
BMI (kg/m^2)	31.4 ± 8.5	32.4 ± 7.4	32.9 ± 7.6	32.8 ± 8.1 *
WHR	0.90 ± 0.07	0.90 ± 0.08	0.92 ± 0.08	0.93 ± 0.08 *
Energy intake (kcal/day)	2515 ± 1361	2006 ± 1064	2557 ± 1247	3469 ± 1486 *
Current alcohol (%)	58.7	58.0	58.7	67.1 *
Current smoker (%)	37.8	33.1	34.6	34.2 *
DM (ADA criteria) (%)	14.5	22.1	23.6	26.4 *

BP, blood pressure; HbA1c, HemoglobinA1c; eGFR, estimated glomerular filtration rate; ACR, albumin–creatinine ratio; BMI, body mass index; WHR, waist–hip ratio; DM, diabetes mellitus; ADA, American Diabetes Association.

Data in means ± standard deviations or percentages or medians (interquartile ranges).

* *P* for trend <.05.

Table 2

Estimated Odds Ratios (95% CI) for the Association Between Fish Consumption Measured at Baseline and the Presence of Albuminuria at Follow-up in the Family Cohort of the Strong Heart Study

	Fish Consumption (g/day)				
Exposure	**0**	**0.1–3.7**	**>3.7–15**	**>15**	***P****
Outcome	Albuminuria vs. Normoalbuminuria				
Unadjusted	1.00	1.22 (0.89, 1.68)	1.30 (0.94, 1.78)	1.59 (1.09, 2.33)	.02
Model 1	1.00	1.06 (0.76, 1.48)	1.05 (0.75, 1.47)	1.28 (0.86, 1.90)	.3
Model 2	1.00	1.04 (0.73, 1.48)	0.97 (0.68, 1.38)	1.12 (0.73, 1.73)	.9
Model 3	1.00	1.05 (0.73, 1.50)	1.01 (0.70, 1.44)	1.21 (0.77, 1.92)	.6
Outcome	Macroalbuminuria vs. Normoalbuminuria				
Unadjusted	1.00	1.51 (0.79, 2.88)	1.50 (0.79, 2.86)	2.54 (1.26, 5.13)	.02
Model 1	1.00	1.14 (0.59, 2.18)	1.10 (0.57, 2.11)	1.80 (0.88, 3.67)	.1
Model 2	1.00	1.20 (0.57, 2.51)	0.95 (0.45, 2.02)	1.66 (0.73, 3.78)	.5
Model 3	1.00	1.23 (0.58, 2.62)	1.06 (0.50, 2.27)	2.04 (0.85, 4.86)	.3

TG, serum triglycerides.

Model 1—adjusted for age, gender, center.

Model 2—model 1 + diabetes status, TG, systolic blood pressure, WHR, urinary ACR at baseline.

Model 3—model 2 + smoking, alcohol consumption, energy intake, protein intake, sodium intake.

*P-value is for a linear trend across distribution of fish consumption.

Table 3

Estimated Odds Ratios (95% CI) for the Association Between Fish Consumption Measured at Baseline and the Presence of Renal Impairment at Follow-up in the Family Cohort of the Strong Heart Study*

Outcome	Renal Impairment vs. Normal Renal function				
	Fish Consumption (g/day)				
Exposure	0	0.1–3.7	>3.7–15	>15	$P^{\dagger}$
Unadjusted	1.00	1.77 (1.08, 2.89)	1.88 (1.15, 3.08)	1.73 (0.97, 3.12)	.06
Model 1	1.00	1.20 (0.69, 2.11)	1.44 (0.82, 2.52)	1.48 (0.76, 2.87)	.2
Model 2	1.00	0.98 (0.52, 1.85)	1.41 (0.75, 2.65)	1.47 (0.69, 3.14)	.1
Model 3	1.00	1.03 (0.54, 1.98)	1.43 (0.75, 2.71)	1.46 (0.65, 3.26)	.1

TG, serum triglycerides.

Model 1—adjusted for age, gender, center.

Model 2—model 1 + diabetes status, TG, systolic blood pressure, WHR, eGFR at baseline.

Model 3—model 2 + smoking, alcohol consumption, energy intake, protein intake, sodium intake.

*Excluded participants with eGFR >130 mL/min/1.73 m^2.

†*P*-value is for a linear trend across distribution of fish consumption.

Table 4

Association Between Fish Consumption and Change in Urinary ACR or eGFR Between Baseline and Follow-up Examinations in the Family Cohort of the Strong Heart Study*

Outcomes	Change in Urinary ACR (mg/g)		Change in eGFR (mL/min/1.73 m^2)	
Fish Consumption	**>15 vs. 0 g/day**	***P***	**>15 vs. 0 g/day**	***P***
Unadjusted	42.2 (−42.4, 126.8)	.5	−3.67 (−6.42, −0.92)	.007
Multivariable-adjusted	46.6 (−43.6, 136.9)	.5	−1.83 (−4.61, 0.95)	.2

Multivariable-adjusted models adjusted for age, gender, center, diabetes status, TG, serum triglycerides; WHR, smoking, alcohol consumption, energy intake, protein intake, sodium intake.

*Results of linear regression models are expressed in regression coefficients (95% CI).