Inverse Association Between Fish Intake and Risk of Glucose Intolerance in Normoglycemic Elderly Men and Women

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Objective: To examine the association of fish intake with the subsequent risk of impaired glucose tolerance and diabetes mellitus (glucose intolerance). Research Design and Methods: In 1971, information about food intake was obtained by the cross-check dietary history method on 175 men and women aged 64–87 yr who were normoglycemic and free of clinical diabetes. During the follow-up period from 1972 to 1975, an oral glucose tolerance test was performed annually, and in 59 of 175 elderly people a diagnosis of glucose intolerance was made at least once. Results: In 1971, ~60% of the subjects usually ate fish, with a mean daily intake of 24.2 g. In fish eaters, the incidence of glucose intolerance was significantly lower compared with nonfish eaters (odds ratio [OR] 0.40, 95% confidence interval [CI] 0.21–0.77). With logistic regression analysis, this inverse association could not be explained by taking into account age and sex or possible confounding baseline characteristics, such as the prevalence of myocardial infarction, body mass index, energy intake per kilogram body weight, or intake of carbohydrates (OR 0.47, 95% CI 0.23–0.93). Baseline characteristics of the oral glucose tolerance test and serum triglyceride levels could also not account for this result. Conclusions: These results suggest that, in an elderly population, the habitual consumption of a small amount of fish may protect against the development of impaired glucose tolerance and diabetes mellitus. ***Diabetes Care*** **14:935–41, 1991**

Apart from the effect on energy balance, the role of nutritional factors in the onset of non-insulin-dependent diabetes mellitus (NIDDM) and glucose intolerance remains unclear (1,2). Since the beginning of this century it has been repeatedly suggested that a high-fat intake is responsible for an increased risk of diabetes (3,4). However, the source of fat may be more important, and a protective effect of ω-3 fatty acids, mostly found in fish, has been hypothesized (5). Beneficial effects of fish oil intake on glucose metabolism and diabetes incidence have been observed in animals (6,7). Results from intervention studies on glucose homeostasis in NIDDM patients are inconclusive, but are mostly not supportive of a beneficial effect on glycemic control (8,9). However, the effect of fish oil on glucose metabolism in normoglycemic subjects may differ from the effect in NIDDM patients (8,10–12). The result of increased fish or fish oil intake on the development of glucose intolerance in normoglycemic humans has not been studied.

Therefore, we investigated the relationship between fish intake and incidence of impaired glucose tolerance and diabetes during 4 yr of follow-up. For this purpose, we studied an elderly population, which is generally prone to a high incidence of derangements in glucose metabolism and is likely to benefit most from a possible preventive effect.

RESEARCH DESIGN AND METHODS

From 1971 to 1975, a longitudinal health survey was conducted among patients of one of the authors (C.H.B.) who had a general practice in Rotterdam, Netherlands (13). All noninstitutionalized men and women born be-

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fore 1907 and able to participate were invited to take part in the study. Of 394 eligible subjects, 340 (86.6%) agreed to enter the study. Due to limitations of laboratory facilities, 292 subjects were medically examined in 1971. Between 1971 and 1975, men and women were examined annually. For this study, the analyses were restricted to the 257 subjects who participated in the baseline examination and in at least one examination during the follow-up period from 1972 to 1975. Furthermore, only the subjects with normal glucose tolerance and no clinical diagnosis of diabetes mellitus at baseline (n = 183) were taken into account. Finally, the study was restricted to 175 men and women for whom complete information about risk factor status in 1971 was available.

In 1971, food and beverage intake data were collected by the cross-check dietary history method as used in the Zutphen study, the Dutch contribution to the Seven Countries study (14,15). For this purpose, the method was adapted to the Dutch situation (15,16) and provided information about the usual food consumption pattern during the 14 days preceding the interview. The interviews were conducted by one dietitian who was trained by the nutritional staff of the Zutphen study. The interviews were structured and standardized with the dietary sheets from the Zutphen study. The interviews were conducted during home visits from January to December 1971 in the same month the medical examination took place.

The participants were interviewed, with their spouses in attendance, concerning their usual food consumption pattern during weekdays and weekends. As a first check, the average consumption of food during 1 day or 1 wk was estimated. If necessary, portions were weighed on a postal scale. For a second check, the results were checked with information on the quantities of food bought during 1 wk for the entire household. From this information, the usual food consumption during an average day was calculated. It was also recorded whether the participant followed a special diet prescribed by the family physician or specialist.

In 1988, the food intake data were uniformly coded by one experienced dietitian. The data were converted into energy and nutrients with the uniform food-encoding table, an extended computerized version of the Netherlands food table (17). This table contained the energy and nutrient composition of Dutch foods in 1970, including the ω-3 polyunsaturated fatty acids eicosapentaenoic acid (C20:5ω3) and docosahexaenoic acid (C22:6ω3) (18).

Physical examinations took place yearly and were conducted by an experienced general practitioner who was the principal investigator of the study (C.H.B.). Information about the history of cardiovascular and pulmonary diseases was obtained from the Dutch translation of the questionnaire from the London School of Hygiene and Tropical Medicine (19). The use of drugs was determined by searching the patient's records. Weight and height were measured with subjects wearing underwear and socks only. Body mass index (BMI) was calculated by dividing body weight by height squared (kg/m^2). A fasting blood sample was obtained by venipuncture and analyzed for serum lipids. Serum total cholesterol and triglycerides were analyzed at the Gaubius Institute/TNO (Leiden, Netherlands) by thin-layer chromatography (20). Information about smoking habits was obtained through standardized questions asked by the physician during the medical examination.

At every yearly examination, a complete oral glucose tolerance test (OGTT) was conducted according to the 1965 guidelines of the World Health Organization (WHO) (21). The OGTT was taken in the morning after an overnight fast. A capillary blood sample was obtained from the subjects in the fasting state and at 30, 60, and 120 min after an oral load of 50 g glucose. Whole-blood glucose analyses were conducted with the glucose oxidase method (test kit Boehringer Mannheim). Blood sampling and chemical analyses were conducted at the Rotterdam Ophthalmological Hospital. The methods used were identical at every annual examination. From the glucose measurements a summarizing index, the area under the curve (AUC), was derived. This area was calculated with the trapezoidal rule

$$AUC = \Sigma_i[(x_i - x_{i-1}) \cdot (y_{i-1} + y_i)/2]$$

where x_i denotes the time (min) at the ith measurement and y_i denotes the glucose value at the ith moment. When subjects were found to be diabetic according to the WHO criteria from 1965 for OGTT (21), they were given dietary advice or treatment. For this study, the results were reclassified with the WHO criteria from 1985, dividing the subjects into three categories: normoglycemia, impaired glucose tolerance, and diabetes mellitus (1). The diagnoses of impaired glucose tolerance or diabetes mellitus from the 1985 criteria corresponded with the diagnosis of diabetes mellitus from the 1965 criteria.

For this investigation, 175 subjects, normoglycemic since 1971, were eligible. Weight, height, and dietary habits were comparable with those reported for other free-living Dutch elderly people studied in that period (13). In 59 participants, a diagnosis of impaired glucose tolerance or diabetes mellitus, based on the results of the OGTT, was made during follow-up. These subjects were referred to as incident cases of glucose intolerance. Seventy-seven percent of the 175 subjects participated in all four follow-up examinations.

The SPSS/PC+ package programs were used for statistical analyses (22). For analyses of baseline characteristics by disease outcome and fish intake, Student's t test was used. When the risk factor distributions were skewed, the Mann-Whitney U test was preferred. For sex, prevalence of myocardial infarction, smoking, drug use, and alcohol drinking proportions were compared with the χ^2-statistic. Cumulative incidence rates were calculated, and from this information a crude risk ratio for fish intake in relationship to glucose intolerance was calculated, as well as a crude odds ratio (OR). There-

after, logistic regression analyses were used to provide ORs after adjustment for different confounders. Analysis of person-years or multivariate proportional hazard (Cox) regression analysis was not used. The time of diagnosis was less reliable for the 40 subjects not participating in all four follow-up examinations. Also, regarding Cox regression analysis, the proportional hazard assumption was not satisfied for all determinants, as judged from the log minus log plot (23). Besides sex and prevalence of myocardial infarction, age (<70, ≥70 yr) and alcohol intake (no/yes) were entered as categorical variables. All other confounders were entered as continuous variables. Stepwise logistic regression analysis was used to determine which aspects of OGTT at baseline were the strongest predictors of incidence of glucose intolerance during follow-up. The AUC and 120-min glucose concentration were selected with this procedure. Therefore, only these two indicators of baseline glucose tolerance were used in the subsequent analyses. All *P* values were based on two-sided tests of statistical significance.

RESULTS

At the baseline examination in 1971, the subjects were between 64 and 87 yr of age. About 57% of the subjects consumed fish: 60% of the men and 53% of the women. The mean ± SD daily fish intake of the habitual fish consumers amounted to 24.2 ± 18.7 g, of which ~89% consisted of lean fish (e.g., cod, plaice), 6% of fatty fish (e.g., mackerel, herring), and 5% of canned fish (e.g., sardines).

The 4-yr cumulative incidence of impaired glucose tolerance and diabetes mellitus in the total study population amounted to 33.7% (Table 1). No significant difference in incidence was observed between men and women. In 34 of 75 nonfish eaters and 25 of 100 fish eaters, glucose intolerance was diagnosed during follow-up. This resulted in a risk ratio for fish intake of 0.55 (95% confidence interval [CI] 0.36–0.84) and an OR of 0.40 (95% CI 0.21–0.77).

TABLE 1
Cumulative incidence of glucose intolerance during 4 yr of follow-up in 175 elderly men and women free of diabetes who were normoglycemic at baseline (Rotterdam, 1971–1975)

	Population (*n*)	Cases (*n*)	Cumulative incidence (%)
Total	175	59	33.7
Men	98	30	30.6
Women	77	29	37.7
Nonfish eaters	75	34	45.3
Fish eaters	100	25	25.0*

Impaired glucose tolerance or diabetes mellitus, as diagnosed from oral glucose tolerance test.
*$P < 0.01$ significantly different from fish eaters.

TABLE 2
Baseline intake of selected dietary variables to incidence of glucose intolerance in 175 elderly men and women who were normoglycemic and free of diabetes at baseline (Rotterdam, 1971–1975)

Dietary variable	Incidence of glucose intolerance	
	No (*n* = 116)	Yes (*n* = 59)
Fish intake (g)	16.0 ± 19.9	9.6 ± 14.7*
Energy intake (MJ)	9.05 ± 2.48	8.60 ± 2.20
Energy intake/body weight (kJ/kg)	131.2 ± 41.3	120.6 ± 33.3
Total protein (% energy)	12.5 ± 2.6	12.9 ± 2.7
Total fat (% energy)	44.4 ± 6.7	43.0 ± 5.6
Saturated fat (% energy)	17.4 ± 3.2	16.9 ± 2.7
Polyunsaturated fat (% energy)	8.1 ± 2.9	8.1 ± 2.4
Total carbohydrates (% energy)	40.2 ± 7.1	42.1 ± 5.4*
Monosaccharides + disaccharides (% energy)	18.6 ± 6.0	20.0 ± 5.7
Alcohol use (%)	56.9	54.2

Values are means ± SD. Impaired glucose tolerance or diabetes mellitus, as diagnosed from oral glucose tolerance test.
*$P < 0.05$.

At baseline, future glucose intolerance cases were characterized by a lower mean fish intake and a higher intake of carbohydrates (Table 2). A lower energy intake per kilogram body weight was also found in future cases, but this was of borderline statistical significance ($P < 0.10$). No significant differences in the intake of other nutrients were noted. Future cases of glucose intolerance had a higher mean BMI at baseline and higher 120-min glucose and AUC levels (Table 3). The difference in mean serum triglyceride concentrations was statistically significant at $P < 0.10$. No differences in age, smoking habits, prevalence of myocardial infarction, and the use of medications, e.g., diuretics, were observed.

At the baseline examination in 1971, fish eaters were younger and had a lower prevalence of myocardial infarction compared with nonfish eaters (Table 4), but these differences were only borderline significant ($P < 0.10$). No differences in other risk factors were observed. Fish intake was significantly inversely associated with the intake of total carbohydrates and monosaccharides and disaccharides (Table 5). Positive associations were observed between fish intake and the intake of alcohol and energy (also when expressed per kg body wt) and the intake of polyunsaturated fat. The prevalence of prescribed diet was comparable in both groups (18% in fish eaters, 14.7% in nonfish eaters). The change in BMI, serum triglycerides, smoking habits, and myocardial infarction prevalence during follow-up did not differ between fish users and nonfish users.

After adjusting for age and sex, the OR for fish intake amounted to 0.42 (Table 6). In a multivariate model,

that also included energy, carbohydrate and linoleic acid intake, alcohol use, and prescribed diet, only the intake of fish and total carbohydrates was statistically significant. Therefore, only total carbohydrate intake was used as a confounding factor in subsequent analyses. After adjustment for this nutrient and age, sex, BMI, energy intake per kilogram body weight, and myocardial infarction, the protective effect of fish intake on the incidence of glucose intolerance remained statistically significant (OR 0.47, 95% CI 0.23–0.93). When baseline values for serum triglycerides, 120-min glucose, and AUC were taken into account, the result remained essentially unaffected (OR 0.43, 95% CI 0.20–0.91).

Additional analyses showed that the adjusted OR amounted to 0.82 (95% CI 0.30–2.24) in men (n = 98) and 0.28 (95% CI 0.10–0.78) in women (n = 77). However, this difference was not statistically significant (P = 0.24). If the analysis was confined to subjects who had a diagnosis of glucose intolerance at least twice during follow-up (n = 20), the OR amounted to 0.54 (95% CI 0.20–1.47). When the incidence of diabetes mellitus (n = 17) was investigated separately, the OR for fish intake was 0.48 (95% CI 0.16–1.40).

CONCLUSIONS

This study shows that habitual fish intake was inversely associated with the incidence of impaired glucose tolerance and diabetes mellitus in an elderly population. This association was independent of confounding factors such as age, BMI, energy and carbohydrate intake, alcohol use, prescribed diet, prevalence of myocardial infarction, and increased physical activity, as reflected by elevated energy intake per kilogram body weight (24). Also, the association could not be explained by differences in baseline glucose tolerance or serum triglyceride levels. The effect of fish intake appeared to be greater in women than men, but the difference was not statistically significant in this relatively small cohort.

Generally, it is thought that the development of NIDDM and glucose intolerance is affected mainly by genetic factors, age, and obesity (1,2). The role of nutritional factors in the etiology of glucose metabolism disorders, apart from the effect of energy imbalance, is still unclear. However, in many animal and human experiments, specific effects of nutrients on glucose metabolism have been shown, suggesting that these may play a role in the onset of glucose metabolism disorders. In contrast, results from epidemiological investigations are still inconclusive, because in several studies (25–30) but not all (31–33), associations of glucose levels and diabetes incidence with the intake of carbohydrates, fiber, and fat have been observed. These differences in results may be partly explained by methodological problems, such as the quality of the method used for obtaining dietary information, the small heterogeneity in exposure to dietary factors within a population, or the lack of power to detect a presumably small relative risk.

In this study, the cross-check dietary history method was used as the dietary survey method. This method refers to habitual dietary intake and is acknowledged as a valid method in an epidemiological setting (14,34,35). The reproducibility of the version used in this survey was considered very good (36). Regarding the heterogeneity in exposure, there was a clear contrast between two relatively large groups: fish eaters and nonfish eaters. Relatively small CIs for effect estimates could be calculated. This was due to a comparatively high incidence of glucose intolerance (34% in 4 yr) because we did not discern between the diagnoses impaired glucose tolerance and diabetes mellitus from OGTT, and also because we studied subjects >64 yr of age. Regarding the etiology, a separate investigation of impaired glu-

TABLE 3
Baseline levels of selected risk factors to incidence of glucose intolerance in 175 elderly men and women who were normoglycemic and free of diabetes at baseline (Rotterdam, 1971–1975)

Risk factor	Incidence of glucose intolerance	
	No (n = 116)	Yes (n = 59)
Age (yr)	70.0 ± 4.8	70.8 ± 4.9
Body mass index (kg/m²)	25.4 ± 3.3	26.8 ± 4.0*
120-min glucose (mM)	5.39 ± 1.19	6.15 ± 1.11†
Area under the curve (mM/min)	900.8 ± 131.2	1005.7 ± 165.3†
Serum triglycerides (mM)	0.98 ± 0.44	1.15 ± 0.60
Myocardial infarction (%)	6.9	10.2
Smoking (%)	52.6	45.8
Diuretic use (%)	14.7	13.6

Values are means ± SD. Impaired glucose tolerance or diabetes mellitus, as diagnosed from oral glucose tolerance test.
*P < 0.05.
†P < 0.001.

TABLE 4
Baseline levels of selected risk factors to fish intake in 175 elderly men and women who were normoglycemic and free of diabetes (Rotterdam, 1971)

Risk factor	Fish intake at baseline	
	No (n = 75)	Yes (n = 100)
Age (yr)	71.4 ± 5.6	69.5 ± 4.0
Body mass index (kg/m²)	26.2 ± 4.1	25.7 ± 3.1
120-min glucose (mM)	5.72 ± 1.31	5.58 ± 1.13
Area under the curve (mM/min)	955.7 ± 135.1	921.5 ± 161.9
Serum triglycerides (mM)	1.01 ± 0.42	1.06 ± 0.56
Myocardial infarction (%)	12.0	5.0
Smoking (%)	46.7	53.0
Diuretic use (%)	17.3	12.0

Values are means ± SD.

cose tolerance and diabetes mellitus could also be of interest. However, subjects with impaired glucose tolerance were treated as diabetic patients during this study in the 1970s, and it is clear that subjects with impaired glucose tolerance are at a higher risk for developing diabetes (37,38). Therefore, this was not feasible. In the study of impaired glucose tolerance, some misclassification may have occurred (39), and false positives may have been included in the study. However, random misclassification is known to attenuate observed effect estimates (39) and therefore cannot account for these results. Also, when the analysis was confined to cases who were diagnosed at least twice during follow-up, comparable effect estimates were found. This was also true when the incidence of diabetes was analyzed separately.

Interest in the role of fish and ω-3 fatty acids on glucose metabolism arose from the low incidence of diabetes in populations consuming large amounts of fish and marine foods, e.g., Greenland and Alaskan Eskimos and Alaskan Indians (40,41). Apparently, these findings could not be explained by differences in genetic predisposition or obesity (41). Storlien et al. (6) observed an increased insulin sensitivity in liver tissue and skeletal muscle in experiments conducted in rats when dietary ω-6 fatty acids were partially replaced by fish oil. In rats on a fish oil diet, a lower incidence of diabetes was found compared with a control group (7).

Short-term experiments on the effect of fish oil on glucose homeostasis in diabetic patients were not conclusive so far (8,9). Beneficial effects on insulin sensitivity in diabetic patients have been documented (42). However, in most studies, the addition of ω-3 fatty acids was found to increase glucose and glycosylated hemoglobin levels to some extent (8,9,43,44). It is suggested that this may be partly explained by the size of the fish oil dose, mostly 4–10 g ω-3 fatty acids/day, equivalent to 330–830 g fish/day (8,43,44). The fact that, in most experiments, fish oil is supplemented to the diet instead of isocalorically replaced may also play a role (8). Furthermore, in a recent controlled study, the effect appeared to be transient (44). In nondiabetic subjects on a fish oil diet, a reduced islet cell response to mixed meals (11) and an increased insulin sensitivity (11,12) were found. Lardinois et al. (10) observed a beneficial effect of fish and fish oil on insulin secretion in normoglycemic subjects, but not in diabetic patients (10). Due to basic differences in carbohydrates and lipid metabolism, it seems plausible that the intake of fish or fish oil has different effects in normoglycemic subjects compared with diabetic patients.

TABLE 5
Baseline intake of energy and selected nutrients to fish intake in 175 elderly men and women who were normoglycemic and free of diabetes (Rotterdam, 1971)

Nutrient	Fish intake at baseline	
	No (n = 75)	Yes (n = 100)
Energy intake (MJ)	8.30 ± 2.22	9.34 ± 2.42†
Energy intake/body weight (kJ/kg)	120.4 ± 42.3	133.1 ± 35.3*
Total proteins (% energy)	12.4 ± 2.7	12.8 ± 2.7
Total fat (% energy)	43.2 ± 6.6	44.4 ± 6.2
Saturated fat (% energy)	17.5 ± 3.2	17.0 ± 3.0
Polyunsaturated fat (% energy)	7.4 ± 2.4	8.6 ± 2.8†
Linoleic acid (% energy)	6.2 ± 2.3	7.5 ± 2.9†
Total carbohydrates (% energy)	42.2 ± 6.7	39.8 ± 6.4*
Monosaccharides + disaccharides (% energy)	20.3 ± 6.4	18.1 ± 5.4*
Alcohol use (%)	45.3	64.0

Values are means ± SD.
*$P < 0.01$.
†$P < 0.05$.

TABLE 6
Adjusted odds ratios for fish intake on incidence of glucose intolerance in 175 elderly men and women who were normoglycemic and free of diabetes at baseline (Rotterdam, 1971–1975)

Adjustments	Odds ratio	95% Confidence interval
None	0.40	0.21–0.77
Age, sex	0.42	0.22–0.81
Dietary factors*	0.42	0.21–0.86
Risk factors†	0.47	0.23–0.93

Impaired glucose tolerance or diabetes mellitus, as diagnosed from oral glucose tolerance.
*Age, sex, prescribed diet, alcohol use, total energy intake, carbohydrate intake, linoleic acid intake.
†Age, sex, prevalence of myocardial infarction, body mass index, energy intake/kg body wt, carbohydrate intake.

In this study the mean intake of the ω-3 fatty acids, eicosapentaenoic (C20:5ω3) and docosahexaenoic (C22:6ω3) acids, by the fish eaters is only ~140 mg/day. This level is much lower than the dosage generally used in intervention studies. It may be questioned whether such low levels can be responsible for the observed lower incidence of glucose intolerance among fish eaters. Maybe some other constituent in fish is able to affect glucose metabolism, but a clear candidate is not yet available. Note that the protective effect of a low intake of (fatty) fish is in agreement with the observed protective effect of a low fish intake on coronary heart disease (45). In addition, the length of the period of habitual fish intake can be of importance, especially in this elderly study population.

The mechanism by which fish intake could beneficially affect the risk of glucose intolerance is not completely understood. For its characteristic ω-3 fatty acids, several possibilities exist. Incorporation of ω-3 fatty acids in cellular membranes increases the fluidity of the membranes. This may stimulate the activity of insulin receptors and glucose transport and increase insulin sensitivity of the tissues (42). The insulin secretion may

also be affected, because ω-3 fatty acids are known to alter the production of eicosanoids, which are suggested to modulate β-cell activity (46). Finally, the beneficial effect of ω-3 fatty acids may be caused by their known potential to decrease very-low-density lipoprotein triglyceride synthesis (47). This may affect the balance in cellular fuel uptake, possibly leading to enhanced glucose clearance by the so-called Randle cycle (48). Evidence for this mechanism was recently provided by an experimental rat study (49). However, note that in this study, the fish eaters did not have lower levels of serum triglycerides at the baseline examination, despite slightly lower levels of AUC. In addition, multivariate analyses showed that the baseline levels of serum triglycerides could not account for this result. Also, levels of serum triglycerides and other possible intermediating factors, such as BMI measured during follow-up, were not associated with baseline fish intake and cannot explain this result.

In summary, an inverse association between fish intake and the incidence of impaired glucose tolerance and diabetes mellitus was observed in a small cohort of elderly men and women. The possible mechanism of the beneficial effect of long-term intake of small quantitites of fish and ω-3 fatty acids on glucose metabolism in normoglycemic subjects and the possibilities for preventive measures require further investigation.

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