Polyunsaturated Fatty Acid Consumption May Play a Role in the Onset and Regression of Microalbuminuria in Well-Controlled Type 1 and Type 2 Diabetic People

A 7-year, prospective, population-based, observational multicenter study

THE DIABETES AND NUTRITION STUDY GROUP OF THE SPANISH DIABETES ASSOCIATION (GSEDNU)*

The risk of developing microalbuminuria at some point in the life of a diabetic patient has been estimated to be >60% (1,2). The main risk factors associated with the presence of microalbuminuria have already been identified (3–9). Recently, 32–58% regression of microalbuminuria in type 1 diabetic patients has been reported (10–13). Modifiable factors associated with regression, such as low blood pressure, low cholesterol and triglyceride levels, and HbA_{1c} <8%, suggest that diet can play a relevant role in reducing the risk of microalbuminuria (14–18).

The Diabetes and Nutrition Clinical Trial (DNCT) is a prospective, population-based, observational multicenter study designed to evaluate the nutritional pattern (based on 7-day food diaries) of diabetic patients in Spain and its relation with the development of diabetes complications. In this study, we report changes in nephropathy status and their connection with nutritional patterns that occurred during the 7-year follow-up in a sample of Spanish people with diabetes.

RESEARCH DESIGN AND METHODS — A total of 192 diabetic patients (93 type 1 diabetic and 99 type 2 diabetic patients) attended the four centers between 1993 and 2000 and completed the study. Selection criteria and a wide description of the experimental design have been previously reported (19,20). Diabetic nephropathy was defined by the albumin-to-creatinine ratio in the three first-morning urine samples.

Nephropathy progression was considered when diabetic patients were normoalbuminuric in 1993 and were micro- or macroalbuminuric in 2000 or if they had microalbuminuria in 1993 and macroalbuminuria in 2000. Patients were considered to have nephropathy regression if they presented with microalbuminuria in 1993 and normoalbuminuria in 2000 or if they presented with macroalbuminuria in 1993 and micro- or normoalbuminuria in 2000.

RESULTS — At baseline, 37 (19.3%) diabetic patients had diabetic nephropathy, 23 (12.0%) microalbuminuria, and 14 (7.3%) macroalbuminuria. After a median follow-up period of 6.5 years, 3 type 1 diabetic patients (nephropathy progression rate 3.9%, 0.6%/year) and 12 type 2 diabetic patients (nephropathy progression rate 15.2%, 2.3%/year) progressed to microalbuminuria and 2 type 1 diabetic patients (nephropathy progression rate 2.6%, 0.4%/year) progressed to macroalbuminuria. Two type 2 diabetic patients (nephropathy progression rate 16.7%, 2.6%/year) progressed from microalbuminuria to macroalbuminuria. Seven type 1 diabetic patients (nephropathy regression rate 63.6%, 9.8%/year) and two type 2 diabetic patients (nephropathy regression rate 16.7%, 2.6%/year) regressed from microalbuminuria to normoalbuminuria, whereas one type 1 diabetic patient (nephropathy regression rate 16.7%, 2.6%/year) and four type 2 diabetic patients (nephropathy regression rate 50%, 7.7%/year) passed from macroalbuminuria to microalbuminuria. One type 2 diabetic patient (nephropathy regression rate 12.5%, 1.9%/year) regressed from macroalbuminuria to normoalbuminuria. Table 1 shows the nutrient intake, clinical characteristics, and laboratory data of the study subjects by nephropathy status. The nutritional pattern of patients with nephropathy regression was characterized by greater polyunsaturated fatty acid (PUFA) and smaller saturated fatty acid (SFA) intakes than those of patients with nephropathy ($P < 0.05$), whereas the PUFA-to-SFA and monounsaturated fatty acid (MUFA)-to-SFA ratios were significantly greater ($P < 0.001$). The opposite pattern is associated with progression of nephropathy.

CONCLUSIONS — Different factors that can confuse the interpretation of

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*A list of the members of the GSEDNu Study Group can be found in the APPENDIX.

Abbreviations: DNCT, Diabetes and Nutrition Clinical Trial; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid; SFA, saturated fatty acid.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1 —*Clinical characteristics, nutrient intake, and laboratory data for the diabetic subjects*

	Normoalbuminuria	Change	Nephropathy	Change	Progression	Change	Regression	Change
n (men/women)	121 (47/74)	—	37 (18/19)	—	19 (11/8)	—	15 (7/8)	—
Age (years)	50 (28–64)	—	60 (41–73)[a]	—	67 (55–73)[b]	—	56.5 (37.7–73)[c]	—
Duration of disease (years)	19.8 (10.8–28.6)	—	20.3 (11.6–29.1)	—	19.3 (10.1–26.5)	—	17.8 (9.2–21.5)	—
Diabetic patients (type 1/ type 2)	63/58	—	17/20	—	5/14	—	8/7	—
BMI (kg/m^2)	25.6 (22.6–28.9)	13.8	26.9 (23.8–32.5)[a]	4.6	29.0 (25.3–31.0)[b]	4.7	27.2 (24.0–30.1)	−7.7
Body weight (kg)	69.0 (60.7–75)	10.3	69.4 (62.9–85.4)	4.5	73.8 (66.8–81.6)	4.6	69.1 (66.0–85.3)	−7.5
Waist circumference (cm)	86.2 (74–97.7)	−5.6	98 (80.5–107.0)[a]	4.1	100.5 (88.5–108)[b]	5.7	89 (80–98.2)[c]	−6.1
HbA_{1c} (%)	7.1 (6.0–8.5)	−6.5	7.1 (5.6–9.3)	−6.7	7.0 (5.6–8.3)	−17.5	6.5 (6.0–8.0)[c]	−18.7
Systolic blood pressure (mmHg)	130 (112.5–145)	−3.1	140 (130–162.5)[a]	4.2	140 (130–156.2)[b]	3.7	130 (120–148.7)[c]	−2.1
Diastolic blood pressure (mmHg)	77 (70–80)	−3.5	80 (72.5–88.5)[a]	4.4	80 (78.7–87.7)[b]	1.1	75 (70–80)[c]	−1.1
Cholesterol (mmol/l)	5.17 (4.50–5.78)	−1.2	5.62 (4.66–6.05)[a]	−11.9	5.61 (4.57–6.12)[b]	1.3	4.92 (4.02–5.56)[c]	−17.3
HDL cholesterol (mmol/l)	1.63 (1.40–1.83)	23.0	1.43 (1.23–1.82)[a]	27.0	1.63 (1.42–1.78)	29.3	1.40 (1.14–1.65)	−23.8
LDL cholesterol (mmol/l)	3.03 (2.54–3.54)	−6.6	2.98 (2.44–3.71)	−9.2	3.14 (2.17–3.64)[b]	9.1	2.59 (1.93–3.62)[c]	0.5
Triglycerides (mmol/l)	0.84 (0.62–1.18)	3.4	1.25 (0.78–1.68)[a]	3.5	0.96 (0.78–1.18)[b]	−4.6	0.85 (0.57–1.18)[c]	−12.2
Apolipoprotein A1 (mg/dl)	149 (135–172.5)	NE	151.5 (137.2–170.7)	NE	158 (148–175)	NE	139 (118.2–171.7)	NE
Apolipoprotein B (mg/dl)	87 (70.4–105.5)	NE	99.4 (81.7–116.7)[a]	NE	96 (83.4–111)[b]	NE	81 (60.4–101.1)[c]	NE
Lipoprotein (a) (mg/dl)	12.3 (9.6–28.5)	NE	12.3 (9.6–38.4)	NE	16.7 (9.6–62.6)[b]	NE	15 (9.6–40.9)	NE
Energy (kcal/day)	1,803 (1,577–2,245)	5.3	1,806 (1,492–2,320)	−9.2	1,661 (1,322–1,998)	3.3	1,746 (1,473–2,198)	6.8
Carbohydrate								
Percentage	37.3 (34.0–42.7)	3.9	41.0 (36.7–43.0)[a]	0.8	36.8 (33.4–41.3)	−3.2	37.8 (34.0–41.0)	−5.5
Grams	177 (142–214)	9.0	185 (132–223)	11.7	159 (132–184)	−0.2	161 (120–232)	−4.6
Protein								
Percentage	19.2 (16.9–21.0)	−5.1	19.8 (15.3–23.3)	1.1	20.1 (17.8–24.0)	1.1	21.3 (18.0–23.4)	4.5
Grams	85 (75–103)	−1.8	87 (72–103)	9.3	84 (72–100)	0.6	91 (75–105)	2.6
g/kg body wt	1.23 (1.08–1.49)	−0.4	1.25 (1.03–1.48)	4.3	1.13 (0.97–1.35)	0.3	1.31 (1.08–1.51)	3.2
Total fat								
Percentage	40.5 (36.7–45.1)	8.4	39.5 (34.9–42.0)	1.2	39.4 (36.5–42.6)	11.8	42.2 (37.0–43.5)	18.7
Grams	83 (70–104)	1.8	82 (63–105)	6.2	71 (56–92)[b]	7.7	78 (68–88)	11.1
SFAs (%)	28.9 (22.8–37.3)	−7.7	37.8 (31.7–50.6)[a]	0.5	36.6 (29.5–45.0)[b]	2.5	29.4 (24.3–41.0)[c]	−24.1
MUFAs (%)	54.2 (46.9–68.6)	8.7	51.2 (39.2–63.4)[a]	0.7	52.1 (38.0–67.6)	−21.1	53.8 (46.1–65.4)	49.3
PUFAs (%)	16.8 (13.2–20.4)	12.6	10.9 (8.5–15.8)[a]	−3.7	11.2 (8.4–14.0)[b]	3.9	16.7 (15.3–19.2)[c]	26.8
Cholesterol (mg)	336 (282–431)	−1.2	353 (284–441)	11.3	355 (244–420)	1.2	389 (315–454)	−5.9
PUFA-to-SFA ratio	0.58 (0.35–0.73)	28.7	0.28 (0.21–0.34)[A]	−8.3	0.30 (0.25–0.38)[B]	8.5	0.56 (0.40–0.68)[C]	37.1
MUFA-to-SFA ratio	1.87 (1.55–2.27)	18.5	1.31 (1.12–1.61)[A]	2.3	1.41 (1.15–1.62)[B]	−31.9	1.82 (1.54–2.15)[C]	58.9
Fiber (g)	17 (13–20)	20.0	19 (15–25)	−10.5	18 (13–22)	−5.0	13 (10–20)	−4.2
Alcohol (g)	1.3 (0–7.7)	−0.0	0.5 (0–5.2)	−0.0	0 (0–8.5)	−0.0	0 (0–0.2)	0.1

Data are median (quartile 1 − quartile 3). Change was calculated as (value in year 2000 − value in year 1993) × 100/value in year 1993. [a]$P < 0.05$ and [A]$P < 0.001$, nephropathy versus normoalbuminuria; [b]$P < 0.05$ and [B]$P < 0.001$, progression versus normoalbuminuria; [c]$P < 0.05$ and [C]$P < 0.001$, regression versus nephropathy (Mann-Whitney and Kruskall-Wallis tests). NE, not evaluated in 1993.

these data have been analyzed in this study. Protein consumption could affect nephropathy progression (14–16,21,22). Even though the median of protein consumption in this study is closer to the recommended level (<20%), it is still >0.8 g/kg body wt, which is recommended when microalbuminuria is present. This could explain why no association was found between protein consumption and nephropathy. When regression patients were compared with nonregression patients, both groups were treated with ACE inhibitors and/or angiotensin receptor blockers as expected, and no difference was obtained. We have also evaluated the existence of polymorphisms of different alleles potentially associated with nephropathy. Although the presence of risk polymorphism alleles in this population is greater than that in the nondiabetic population (23), we did not observe any associations with nephropathy progression or regression, indicating that this nonmodifiable factor is not determined in the evolution of nephropathy, as previously described (24).

According to the data obtained in our study, normoalbuminuria and nephropathy regression in well-controlled diabetic patients with long-term diabetes duration are associated with greater PUFA consumption and lesser SFA consumption and specifically with higher PUFA-to-SFA and MUFA-to-SFA ratios, whereas the opposite pattern is associated with the progression of nephropathy.

Various mechanisms that relate to the type of fat intake and microalbuminuria development may explain these findings. The consumption of SFAs induces insulin resistance and a hypercoagulable state and in turn worsens diabetes metabolic control (25,26). PUFAs inhibit platelet aggregation and inflammation, reduce some proatherogenic factors, and reduce triglyceride, chylomicron, and lipoprotein(a) levels, and an increase in MUFA or PUFA consumption favorably modifies lipid profiles and reduces their oxidative capacity (25–29). A strong association between MUFA-to-SFA and PUFA-to-SFA ratios and decreased cardiovascular mortality has recently been described (30). The present study data support this hypothesis. Therefore, both ratios are nutritional variables that allow us to more clearly differentiate the patients who are going to regress or progress.

The present study findings are potentially important: first, because microalbuminuria is associated with an increment in cardiovascular mortality in both type 1 and type 2 diabetic patients and, second, because its prevalence is high. Micro- and macroalbuminuria do not have to inevitably progress to end-stage kidney disease, whereas the regression from both conditions is quite frequent. Strict control of glycemia and blood pressure should be a priority. Treatment with ACE inhibitors and/or angiotensin receptor blockers and cessation of smoking remain the therapeutic objectives for modifiable risk factors. When these objectives are attained, other therapeutic measures, such as encouraging PUFA and MUFA consumption over that of SFA, can help prevent micro- and macroalbuminuria. Keeping in mind that nutritional patterns are the base of integral diabetes care, more efforts should be directed to increase PUFA and MUFA intake and to reduce SFA consumption, particularly in people with diabetes and nephropathy.

APPENDIX

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