The Associations of Dietary Intake of Polyunsaturated Fatty Acids With Diabetic Retinopathy in Well-Controlled Diabetes

Mariko Sasaki,[1–4] Ryo Kawasaki,[1,5] Sophie Rogers,[1] Ryan Eyn Kidd Man,[1,6] Katsumasa Itakura,[1] Jing Xie,[1] Victoria Flood,[7,8] Kazuo Tsubota,[4] Ecosse Lamoureux,[1,6,9] and Jie Jin Wang[1,10]

[1]Centre for Eye Research Australia, Royal Victorian Eye and Ear Hospital, Department of Ophthalmology, Melbourne University, Victoria, Australia
[2]Department of Ophthalmology, Tachikawa Hospital, Tokyo, Japan
[3]National Institute of Sensory Organs, National Tokyo Medical Center, Tokyo, Japan
[4]Department of Ophthalmology, Keio University, Tokyo, Japan
[5]Department of Public Health, Yamagata University Faculty of Medicine, Yamagata, Japan
[6]Singapore Eye Research Institute, National University of Singapore, Singapore
[7]Faculty of Health Sciences, University of Sydney, Sydney, Australia
[8]St. Vincent's Hospital, Sydney, Australia
[9]Duke-NUS Graduate Medical School, Singapore
[10]Centre for Vision Research, Department of Ophthalmology and Westmead Millennium Institute for Medical Research, University of Sydney, Australia

Correspondence: Jie Jin Wang, Centre for Vision Research, Department of Ophthalmology and Westmead Millennium Institute for Medical Research, University of Sydney, C24, Westmead, NSW 2145, Australia; jiejin.wang@sydney.edu.au.

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Purpose. To assess the associations between dietary intake of polyunsaturated fatty acids (PUFAs) and diabetic retinopathy (DR).

Methods. This was a cross-sectional study of 379 patients (median age: 66.0 years) with diabetes attending a diabetes eye clinic. Daily fatty acid intake was assessed by using a validated Food Frequency Questionnaire and adjusted for energy intake. Diabetic retinopathy was graded from fundus photographs as no DR, nonproliferative DR, or proliferative DR. Patients were categorized as "well-controlled diabetes" ($n = 123$) and "poorly controlled diabetes" ($n = 256$), defined as glycated hemoglobin (HbA1c) level $< 7.0\%$ or $\geq 7.0\%$, respectively.

Results. There were no associations between any fatty acid intake and DR. However, among patients with well-controlled diabetes, increasing daily intake of PUFAs was associated with a reduced likelihood of the presence (odds ratio [OR]: 0.18; 95% confidence interval [CI]: 0.06–0.59) and severity of DR after adjusting for age, sex, HbA1c, mean arterial blood pressure, and duration of diabetes. Moreover, an increased saturated fatty acid (SFA) intake was associated with increased likelihood of the presence (OR: 2.37; 95% CI: 1.15–4.88) and severity of DR. No association was found among those with poorly controlled diabetes.

Conclusions. Increasing PUFA intake was associated with a reduced likelihood of the presence and severity of DR in well-controlled diabetes, whereas increasing SFA intake was associated with an increased likelihood of the presence and severity of DR. Further studies to confirm this observation are warranted to elucidate the underlying mechanisms and potential role of dietary PUFA and SFA intake in the management of DR.

Keywords: diabetic retinopathy, polyunsaturated fatty acids, saturated fatty acid

Diabetic retinopathy (DR), a major cause of vision impairment in working-aged adults,[1] is the most common complication of diabetes. The Meta-Analysis for Eye Disease Study Group has analyzed data from 22,896 individuals with diabetes and reported the prevalence of any DR and vision-threatening DR to be 34.6% and 10.2%, respectively.[1] There are an estimated 93 million people with any DR and 28 million with vision-threatening DR worldwide.[1] Major known risk factors of DR are diabetes duration and poor control of glycemia, blood pressure, and lipids.[1,2] Intensive control of blood glucose and blood pressure and lipid management are essential for effective management of DR.[3] Other modalities of treatments and modifying risk factors to reduce the risk of DR remain the focus of ongoing research.

Polyunsaturated fatty acids (PUFAs), consisting of mainly n-3 PUFA and n-6 PUFA, are one of the nutritional factors that have beneficial effects on health, having consistently been found to be associated with lower likelihood of having cardiovascular diseases (CVDs) and dyslipidemia.[4,5]

Recently, there has been increasing evidence supporting the protective effect of PUFA intake on diabetes complications. The Nurses' Health Study cohort[6] has shown that a high consumption of n-3 PUFA is associated with lower coronary heart disease (CHD) incidence among 5103 women with type 2 diabetes,

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after adjusting for established coronary risk factors. A randomized controlled trial has shown that administration of n-3 PUFA supplements improves albuminuria in patients with non–insulin-dependent diabetes and diabetic nephropathy.[7] The National Health and Nutrition Examination Survey in the United States has further reported that dietary intake of n-6 PUFA is inversely associated with having peripheral neuropathy among 1062 adults with known diabetes, after adjusting for potential confounders.[8] However, the association between dietary intake of PUFAs and the risk of DR has not been investigated previously.

We therefore aimed to examine the cross-sectional associations between dietary intake levels of PUFAs and the prevalence of DR in sample of patients with diabetes. A secondary aim was to investigate the relationship between PUFA intake and DR, depending on the state of diabetes control in the sample.

Methods

Study Population

We used data collected in the Diabetes Management Project (DMP), details of which have been previously described.[9] In brief, 609 English-speaking adults with diabetes, aged 18 years or older, were recruited from general and specialized eye clinics at the Royal Victorian Eye and Ear Hospital (Victoria, Australia) from March 2009 to July 2010. Diabetes status was derived from medical records. Of the 609 participants, 433 (71.1%) had completed a Food Frequency Questionnaire (FFQ) (protocol described below). The participants who completed the FFQ had significantly lower albumin to creatinine ratio than those who did not (median: 1.85, interquartile range [IQR]: [0.70–7.20] vs. 2.85 [0.90–17.00], $P = 0.008$). However, the proportion of the participants with well-controlled diabetes, mean value of glycated hemoglobin (HbA1c), and duration of diabetes did not differ between the groups with and without the FFQ.

Among the 433 participants, 33 were excluded owing to missing fundus images or suboptimal fundus image quality (i.e., poor focus, lashes, uneven illumination) and 21 were excluded owing to missing demographic data or other variables (e.g., HbA1c or duration of diabetes). The remaining 379 participants (61.8% of the 613) (median age: 66 years, IQR: 57.0–74.0) were included in this analysis.

Written informed consent was obtained from all DMP participants. The study was approved by the Human Research and Ethics Committee of Royal Victorian Eye and Ear Hospital (08/815H) and adhered to the tenets of the Declaration of Helsinki.

Assessment of Diabetic Retinopathy

Diabetic retinopathy was graded at the Retinal Vascular Imaging Centre, Centre for Eye Research Australia, by experienced graders masked to participants' clinical details, according to the modified Early Treatment of Diabetic Retinopathy Study [ETDRS], from two-field, 45° fundus photographs (CR6-45NM; Canon, Inc., Tokyo, Japan). The presence of any DR was defined as ETDRS levels ≥ 20 in either eye. The severity of DR was categorized as "no DR" (levels $<$ 20), "nonproliferative DR" (NPDR; 20 $\leq$ level $\leq$ 60), and "proliferative DR" (PDR; levels $>$ 60).

Dietary Assessment

Dietary intake was assessed by using a semi-quantitative FFQ modified from an early version of FFQ by Willett et al.[10] for the Australian diet and vernacular, which was validated and used in the Blue Mountains Eye Study.[11] Dietary data collected included portion sizes, frequency estimates, and details about margarines, butters, and oils to permit more detailed analysis of fatty acid intake.[11,12] Glycemic index (GI) values were assigned to individual food items in the FFQ from methods published previously and have been found to have reasonable validity among middle aged and older people as compared to 12 days of weighed food records.[13] After checking all 444 FFQ data, 11 participants considered to have unreliable FFQ data were excluded on the basis of the following criteria defined by a nutrition epidemiologist/accredited dietician (VF): returned FFQs with more than 12 missing values or missing responses on an entire page, or daily energy intakes of either less than 2500 kJ or greater than 18,000 kJ.[11] As a result, 433 completed FFQs were considered usable. The 2010 electronic version of the Australian Tables of Food Composition, NUTTAB2010,[14] was used to calculate the nutrient value of each food group.

Blood and Urine Chemistry

Fasting (>8 hours) blood samples were collected to assess blood glucose, HbA1c, and serum lipids (triglycerides, total and high-density lipoprotein [HDL] cholesterol levels). "Well-controlled diabetes" was defined as HbA1c level less than 7.0% (53 mmol/mol), and "poorly controlled diabetes" was defined as HbA1c level 7.0% or more (53 mmol/mol).

Fasting plasma glucose and serum lipids were estimated with a chemistry analyzer (Modular P; Roche Diagnostics, Mannheim, Germany). The Friedewald formula was used to calculate low-density lipoprotein (LDL) cholesterol levels when plasma triglyceride concentrations were less than or equal to 4.5 mM (400 mg/dL). In participants with triglyceride concentrations $>$ 4.5 mM, LDL cholesterol measurements were not calculated. In eight participants with triglyceride concentrations greater than 4.5 mM, LDL cholesterol measurements were not calculated.

A midstream urine sample was collected in 50-mL specimen containers to determine the albumin to creatinine ratio. All blood and urine analyses were performed at Melbourne Pathology (Melbourne, Australia), with individual results electronically delivered by using a password-protected program. This laboratory is accredited to the International Standard ISO15189 (Medical Laboratories) and is certified by National Association of Testing Authorities.

Assessment of Other Risk Factors

Each participant underwent a comprehensive face-to-face interview using validated questionnaires.[9] Information collected included a range of socioeconomic, clinical, biochemical, and anthropometric measurements, medications used, and lifestyle factors. Key covariables relevant to risk of DR were included in the analyses and these included age; sex; duration of diabetes (years); use of insulin or oral diabetes medications, antihypertensive medications, lipid-lowering medications, and omega-3 fatty acid supplements; HbA1c level (percentage and mmol/mol); blood pressure (BP; mm Hg); body mass index (kilograms divided by height in meters squared); waist circumference (centimeters); albumin to creatinine ratio; and smoking status (current smoker, past smoker, or never smoked).

Statistical Analysis

Dietary intakes of total fat, saturated fatty acids (SFAs), monounsaturated fatty acids (MUFAs), PUFAs, protein, carbohydrate, and vitamins (Vitamin C, Vitamin E, and β-carotene)

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Table 1. Baseline Characteristics by Diabetes Control Status

	All Subjects	(A) Well-Controlled*	(B) Poorly Controlled*	*P* for Difference Between (A) and (B)
N	379	123	256	
Age, y	66.0 (57.0, 74.0)	67.0 (59.0, 75.0)	65.0 (56.0, 72.5)	**0.030**
Sex, % male	66.0	69.1	64.5	0.37
Type II diabetes, %	86.3	89.9	84.5	0.16
Duration of diabetes, y	13.0 (7.0, 21.0)	9.0 (4.0, 15.0)	15.0 (10.0, 23.0)	**<0.001**
No DR, *N* (%)	150 (39.5)	77 (62.6)	73 (28.5)	**<0.001**
NPDR, *N* (%)	142 (37.5)	30 (34.4)	112 (43.8)	
PDR, *N* (%)	87 (23.0)	16 (13.0)	71 (27.7)	
Body mass index, kg/m^2	29.6 (25.9, 33.8)	28.9 (25.4, 33.9)	30.0 (26.3, 33.8)	0.21
Waist circumference, cm	104.5 (96.0, 116.0)	101.3 (94.0, 114.0)	106.3 (97.0, 116.0)	0.076
Hypertension, %	81.0	79.7	81.6	0.68
Current smoker, %	9.8	8.1	10.6	0.41
HbA1c, %, mmol/mol	7.4 (6.7, 8.3) 57 (50, 67)	6.5 (6.1, 6.7) 48 (43, 50)	8.0 (7.4, 8.9) 64 (57, 74)	NA
Fasting blood glucose, mM	7.7 (6.2, 9.9)	6.5 (5.5, 7.4)	8.5 (7.2, 11.3)	**<0.001**
Total cholesterol, mM	4.4 (3.8, 5.3)	4.4 (3.6, 5.1)	4.4 (3.8, 5.4)	0.13
HDL cholesterol, mM	1.3 (1.1, 1.6)	1.3 (1.1, 1.7)	1.3 (1.1, 1.6)	0.62
LDL cholesterol, mM	2.3 (1.7, 3.0)	2.2 (1.6, 2.8)	2.3 (1.7, 3.2)	0.18
Triglycerides, mM	1.5 (1.1, 2.3)	1.3 (1.0, 2.1)	1.7 (1.1, 2.4)	**0.030**
Albumin to creatinine ratio	1.9 (0.7, 7.4)	1.6 (0.5, 3.7)	2.2 (0.8, 9.0)	**0.030**
Use of oral hypoglycemic medication, %	69.3	64.9	71.4	0.22
Use of insulin, %	42.4	26.1	50.5	**<0.001**
Use of antihypertensive medication, %	76.1	75.7	76.3	0.89
Use of lipid-lowering medication	65.4	65.8	65.2	0.92
Total energy intake, kcal	1772.9 (1328.7, 2227.7)	1851.5 (1512.6, 2227.7)	1708.1 (1265.2, 2221.9)	**0.020**
Carbohydrate intake, g	176.8 (157.0, 201.8)	183.5 (154.7, 207.2)	174.7 (158.1, 197.6)	0.365
Protein intake, g	91.5 (80.6, 103.5)	88.6 (75.6, 100.2)	92.2 (82.2, 104.8)	0.092
Total fat intake, g	64.4 (55.9, 71.3)	63.0 (55.2, 70.9)	65.3 (56.9, 71.8)	0.20
SFA intake, g	23.6 (19.6, 27.5)	22.6 (18.9, 26.9)	24.2 (19.8, 27.6)	0.057
MUFA intake, g	23.6 (19.9, 26.3)	23.5 (19.3, 25.3)	23.7 (20.0, 26.7)	0.26
PUFA intake, g	9.9 (8.5, 12.5)	9.9 (7.8, 12.8)	10.0 (8.5, 12.3)	0.89
β-Carotene intake, μg	3819.4 (2305.8, 5763.9)	3819.6 (23.16.6, 5774.7)	3806.7 (2296.1, 5702.0)	0.82
Vitamin C intake, mg	125.1 (87.8, 166.7)	132.3 (86.7, 165.8)	124.2 (88.6, 167.4)	0.56
Vitamin E intake, mg	6.4 (5.0, 8.0)	6.4 (5.0, 7.8)	6.4 (5.1, 8.0)	0.54
Glycemic index	50.4 (4.3)	50.6 (4.2)	50.1 (4.3)	0.286
Higher alcohol intake, % intake > 10 g	18.5	22.0	16.8	0.23

Values in table are mean (standard deviation) for normally distributed variables, median (interquartile range) for continuous variables without normal distribution, or percentages for categorical variables. Fatty acid, micronutrient, and macronutrient intake are expressed as energy-adjusted values. Hypertension: use of antihypertensive medication or blood pressure ≥ 140/90. NA, not applicable.

* Well-controlled: HbA1c < 7.0% (53 mmol/mol), poorly controlled: HbA1c ≥ 7.0% (53 mmol/mol).

were adjusted for total energy intake (kilocalories) by using the residuals method described by Willett and Stampfer,[15] and the median energy intake was 1772.9 kcal in the study sample.

Baseline characteristics are presented for overall sample and also for subgroups stratified by diabetes control status. Continuous variables with a skewed distribution are presented as median (IQR). Differences in basic characteristics between well-controlled and poorly controlled patients with diabetes were assessed by using Wilcoxon rank-sum test for continuous variables and χ^2 test for categorical variables.

The association between energy-adjusted fatty acid intake and presence of DR was assessed by using logistic regression models. The association between energy-adjusted fatty acid intake and the severity of DR was assessed by using multinomial logistic regression models. Both associations were expressed as odds ratios (ORs) with 95% confidence intervals (CIs). The multivariable-adjusted models included age, sex, HbA1c (%), mean arterial pressure [⅓(SBP − DBP) + DBP], and duration of diabetes (years). Interactions between the exposure variable (energy-adjusted fatty acid intake) and other significant predictors of DR (e.g., diabetes control status) were tested. Possible interactions between fatty acid intake and HbA1c-derived diabetes control groups were assessed by quantifying the average marginal effects, calculating and graphing the differences in probability of presenting with DR across a range of fatty acids intake.[16] Further analyses were performed separately for the two subgroups of well-controlled and poorly controlled diabetes. The adjusted likelihoods of having DR by energy-adjusted PUFA intake levels and by subjects with well- and poorly controlled diabetes were plotted.

We also examined the associations between PUFA intake and serum lipid levels by using simple linear regression models. All analyses were undertaken with Intercooled Stata 12.1 for Windows (StataCorp, College Station, TX, USA).

Results

Characteristics of the 379 patients with diabetes are presented in Table 1. There were 52 (13.7%) and 327 (86.3%) patients with type 1 and type 2 diabetes, respectively. The median of duration of diabetes was 13.0 years (IQR: 7.0–21.0). The median of daily total PUFA and SFA intake was 9.8 g (IQR: 8.4–

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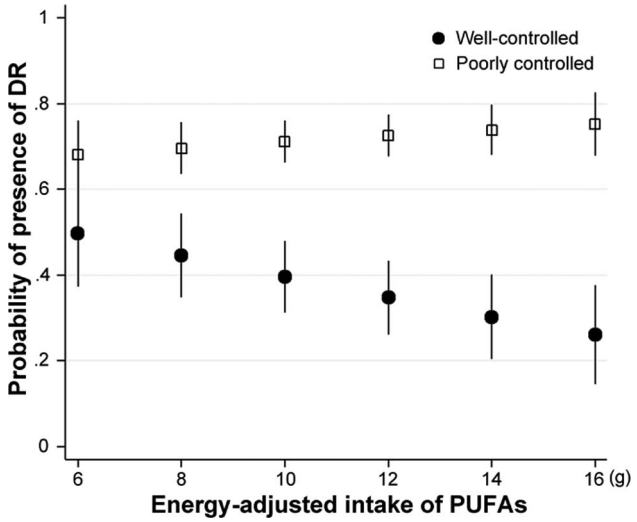

FIGURE. Estimated probabilities of presenting with diabetic retinopathy by PUFA intake in two stratified diabetes-controlled groups. Logistic regression models were adjusted for age, sex, HbA1c, mean arterial pressure, and diabetes duration. *Black circles*: Well-controlled diabetes with HbA1c < 7.0% (53 mmol/mol). *White squares*: Poorly controlled diabetes with HbA1c ≥ 7.0% (53 mmol/mol).

12.4) and 23.6 g (IQR: 19.6–27.5), approximately 5% and 12% of daily energy intake, respectively. We found no correlations between PUFA intake and serum LDL, HDL, or total cholesterol. A weak, inverse correlation between PUFA intake and triglycerides was found in the whole study sample ($R = -0.131$, $P = 0.012$).

After adjusting for age, sex, HbA1c, mean arterial pressure, and duration of diabetes, we found no significant associations between the presence of DR and intake levels of any fatty acids in the whole sample. There was also no association between GI, micronutrient (Vitamin C, vitamin E, or β-carotene) or macronutrient (carbohydrate, protein) intake levels and the presence of DR in the whole sample (data not shown).

A significant interaction was observed between subgroups of diabetes control status and the daily intake of PUFAs (PUFAs ≥ 14 energy-adjusted g) on the likelihood of having DR ($P = 0.035$). Owing to the presence of the above interactions, further subgroup analyses were undertaken, stratified by well-controlled and poorly controlled diabetes.

Patients with well-controlled diabetes were significantly older ($P = 0.031$) and had a shorter duration of diabetes ($P < 0.001$), higher total energy intake ($P = 0.020$), lower likelihood of using insulin ($P < 0.001$), lower mean levels of fasting blood glucose (<0.001) and serum triglycerides ($P = 0.031$), and lower albumin to creatinine ratio ($P = 0.031$) than patients in the poorly controlled group. Waist circumference; blood pressure; total, LDL, and HDL cholesterol; GI; the proportion with higher alcohol intake (intake > 10 g); energy-adjusted intake of any fatty acids; and mean consumption levels of micronutrients (Vitamin C, vitamin E, or β-carotene) or macronutrients (carbohydrate, protein) did not differ between the two groups (Table 1).

In patients with well-controlled diabetes, increasing intake of PUFAs was associated with reduced odds of having DR (for each 10 energy-adjusted g/d increase, OR: 0.18, 95% CI: 0.06–0.59), whereas increasing intake of SFAs was associated with increased odds of having DR (for each 10 energy-adjusted g/d increase, OR: 2.37, 95% CI: 1.15–4.88) (Fig.; Table 2). Among poorly controlled patients, there was no association between any fatty acid intake and the presence of DR (Fig.; Table 2).

When the association between energy-adjusted fatty acid intake and the severity of DR was analyzed among patients with well-controlled diabetes, increasing intake of PUFAs was associated with reduced odds of NPDR (for each 10 energy-adjusted g/d increase, OR: 0.21, 95% CI: 0.06–0.77) and PDR (OR: 0.13, 95% CI: 0.02–0.74) (Table 3). On the other hand, increasing intake of SFAs was associated with increased odds of NPDR (for each 10 energy-adjusted g/d increase, OR: 2.20, 95% CI: 1.02–4.77) and PDR (OR: 2.85, 95% CI: 1.07–7.59) (Table 3). Among poorly controlled patients, there was no association between any fatty acid intake and the severity of DR (Table 3).

Only 7.8% of patients reported taking supplements containing PUFAs (omega-3 fatty acid supplements), and there was no statistically difference in the proportion of participants taking omega-3 supplements between the well-controlled and poorly controlled diabetes groups (12 vs. 16, $P = 0.22$). The inclusion of supplement use in the multivariable-adjusted model did not alter the association between dietary PUFA intake and DR in both diabetic control groups (data not shown).

DISCUSSION

We found no association between dietary intake of any fatty acids and DR in the whole sample or in those with poorly controlled diabetes (HbA1c ≥ 7.0% [53 mmol/mol]). However, we found that an increased PUFA intake was associated with reduced likelihood of the presence, and also severity, of DR in patients with well-controlled diabetes (HbA1c < 7% [53 mmol/mol]). Moreover, an increased SFA intake was associated with increased likelihood of the presence and severity of DR.

Polyunsaturated fatty acids are one of the nutritional factors that have been reported to have various biological roles as well as beneficial effects on health. Dyslipidemia is an important risk factor in the pathogenesis of DR and diabetic macular edema.[2,17] Polyunsaturated fatty acids have a suppressive effect on lipogenesis in the liver by repressing the sterol regulatory element–binding protein (SREBP)-1.[18] Besides, PUFAs are one of the ligands responsible for the activation of peroxisome proliferator-activated receptor α (PPAR-α),[19] a nuclear receptor protein that has inhibitory effects on the vascular endothelial growth factor (VEGF) pathway. Implicated in angiogenesis, inflammation, and cell migration,[20] VEGF should have a role in

TABLE 2. The Association Between Dietary Fatty Acid Intake and the Presence of Diabetic Retinopathy by Diabetes Control Status

Daily Intake of Fatty Acids	All Subjects, $N = 379$ Odds Ratio (95% CI)	Well-Controlled,* $N = 123$ Odds Ratio (95% CI)	Poorly Controlled,* $N = 256$ Odds Ratio (95% CI)
Total fat, per 10 energy-adjusted g	1.07 (0.88, 1.31)	1.01 (0.70, 1.45)	1.09 (0.84, 1.40)
Saturated fatty acids, per 10 energy-adjusted g	1.35 (0.91, 2.01)	2.37 (1.15, 4.88)	1.03 (0.60, 1.75)
Monounsaturated fatty acids, per 10 energy-adjusted g	1.19 (0.74, 1.92)	0.94 (0.37, 2.37)	1.17 (0.65, 2.11)
Polyunsaturated fatty acids, per 10 energy-adjusted g	0.67 (0.37, 1.20)	0.18 (0.06, 0.59)	1.55 (0.67, 3.56)

Logistic regression models were adjusted for age, sex, HbA1c, mean arterial pressure, and diabetes duration.
* Well-controlled: HbA1c < 7.0% (53 mmol/mol), poorly controlled: HbA1c ≥ 7.0% (53 mmol/mol).

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TABLE 3. The Association Between Dietary Fatty Acid Intake and the Severity of DR by Diabetes Control Status

	All Subjects, $N = 379$, Odds Ratio (95% CI)			Well-Controlled,* $N = 123$, Odds Ratio (95% CI)			Poorly Controlled,* $N = 256$, Odds Ratio (95% CI)		
Daily Intake of Fatty Acids	No DR	NPDR	PDR	No DR	NPDR	PDR	No DR	NPDR	PDR
Total fat, per 10 energy-adjusted g	1	1.09 (0.88, 1.35)	1.03 (0.80, 1.32)	1	0.99 (0.66, 1.48)	1.02 (0.60, 1.75)	1	1.12 (0.86, 1.46)	1.03 (0.76, 1.40)
Saturated fatty acids, per 10 energy-adjusted g	1	1.32 (0.87, 2.00)	1.40 (0.85, 2.31)	1	2.20 (1.02, 4.77)	2.85 (1.07, 7.59)	1	1.01 (0.58, 1.76)	1.07 (0.56, 2.04)
Monounsaturated fatty acids, per 10 energy-adjusted g	1	1.29 (0.78, 2.14)	1.00 (0.55, 1.81)	1	0.91 (0.34, 2.48)	1.01 (0.24, 4.25)	1	1.30 (0.70, 2.40)	0.93 (0.46, 1.91)
Polyunsaturated fatty acids, per 10 energy-adjusted g	1	0.76 (0.41, 1.42)	0.48 (0.21, 1.09)	1	0.21 (0.06, 0.77)	0.13 (0.02, 0.74)	1	1.76 (0.74, 4.18)	1.11 (0.38, 3.27)

Multinomial logistic regression models were adjusted for age, sex, HbA1c, mean arterial pressure, and diabetes duration.

* Well-controlled: HbA1c $< 7.0\%$ (53 mmol/mol), poorly controlled: HbA1c $\geq 7.0\%$ (53 mmol/mol).

the development and progression of DR.[21] For that reason, PPAR-α agonist is expected to have an inhibitory effect on DR. For example, fenofibrate, a lipid-lowering drug also known as a PPAR-α agonist, has reduced the need for laser treatment for DR in patients with type 2 diabetes and prevented the progression of DR in patients with preexisting DR in the Fenofibrate Intervention and Event Lowering in Diabetes study.[22] The Action to Control Cardiovascular Risk in Diabetes eye study has evaluated the effect of simvastatin plus fenofibrate versus simvastatin on the progression of DR in patients with type 2 diabetes who have cardiovascular disease or cardiovascular risk factors, and confirmed that fenofibrate reduces the progression of DR.[23] Not appearing to relate to serum lipid concentration,[23] the beneficial effect of fenofibrate on DR could be partially attributed to the role of PPAR-α.[22] Similarly, improving dyslipidemia and increased activation of PPAR-α by PUFAs may partly explain why increased PUFA intake is associated with a reduced likelihood of having DR, as observed among patients with well-controlled diabetes in our study sample.

We found a significant interaction between diabetes control status and the effect of PUFAs on DR. Small LDL particles are prevalent in subjects with impaired glucose metabolism, type 2 diabetes and insulin resistance,[24] particularly when these conditions are accompanied by hypertriglyceridemia and abdominal obesity.[25] These small LDL particles have an increased possibility of migrating into the retinal vasculature and increasing susceptibility to oxidation,[26] leading to likely progression of both atherosclerosis[27] and DR.[28] In our sample, patients in the poorly controlled diabetes group had higher levels of triglycerides and a likelihood of greater waist circumference than those in the well-controlled group. Patients with poorly controlled diabetes could have a high prevalence of small LDL particles, compared to those with well-controlled diabetes. In addition, several studies have reported that PUFA intake is inversely associated with LDL particle size[29,30] and that this association could be modified by glucose metabolism status.[30] We speculate that small LDL particles might interact with PUFA intake and increase the risk of DR in the poorly controlled group, which may explain the diminishing beneficial effect of PUFA on DR in this subgroup of patients. Further studies are needed to confirm this observation.

Interestingly, we also found that an increased SFA intake was associated with increased likelihood of having DR in patients with well-controlled diabetes (HbA1c $< 7\%$ [53 mmol/mol]). Dyslipidemia is one of the risk factors for DR and SFA intake raises total and LDL cholesterol.[31] Moreover, a meta-analysis of randomized controlled trials (RCTs)[32] has shown that 5% of energy intake from SFAs that was substituted by PUFAs could reduce 10% of CHD. Decrease in PUFA intake and increase in SFA intake appear to be commonly associated factors for CVD and DR. We also speculate that these effects of fatty acid intake could be counteracted by strong harmful effects of hyperglycemia in patients with poorly controlled diabetes.

Daily intake of PUFAs in our study sample accounted for 5% of daily total energy intake, which was identical to findings from a previous study in an Australian population.[33] The Food and Agriculture Organization of the United Nations and the World Health Organization recommend an intake of PUFA of up to 6% to 11% of total energy intake,[34] mainly for preventing coronary heart disease. Harika et al.[35] have reported that the majority of the population does not adhere to this guideline worldwide. Further increase in the intake of PUFAs should be encouraged.

Strengths of the study included a well-characterized clinical sample of diabetic patients with DR, as well as the use of standardized grading protocols to define DR by trained graders.

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The validated FFQ allowed us detailed analysis of fatty acid intake, with moderate to good validity for fat subtypes.[11] We also recognize several limitations with our study. First, the study was a cross-sectional observation, without temporal information of the associations.[36] Second, we were unable to determine if PUFA intake had a differential association with DR in the two types of diabetes (types 1 and 2) owing to the small sample size of each type. Third, the association between intake of supplements containing PUFAs and DR was not estimated because of small sample size, although inclusion of supplement use in the models did not alter the association between dietary PUFA intake and DR. Fourth, we could not analyze the effect of each component of PUFAs, owing to the limitations of the questionnaire used.[9] Given that each PUFA component, such as n-3 or n-6 PUFA, has been reported to have different effects on various diseases,[4–8] further investigations are warranted to specify the appropriate PUFA components to maximize the benefit of PUFAs. Finally, the proportion of subjects with the FFQ was relatively small (71.1%). However, we compared the basic characteristics and found no substantial differences between the two groups with and without the FFQ, except for the level of albumin to creatinine ratio. We could not exclude the possibility of a chance finding and therefore future studies to validate these findings are needed.

In conclusion, we found that increasing PUFA intake was associated with reduced likelihood of the presence and severity of DR in patients with well-controlled diabetes, and an increased SFA intake was associated with increased likelihood of the presence and severity of DR. On the other hand, no similar association was evident among patients with poorly controlled diabetes. These findings appear to suggest that PUFA and SFA intake could have differential effects depending on diabetes management status. Prospective studies are warranted to confirm this observation and to elucidate the underlying mechanisms and potential role of dietary intake in the management of DR.

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