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Blood omega-3 biomarkers, diabetic retinopathy and retinal vessel status in patients with type 1 diabetes

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BACKGROUND/OBJECTIVES: Clinical research on dietary omega-3 fatty acids and retinal health in type 1 diabetes (T1D) is scarce. In patients with T1D, we examined the associations between blood biomarkers of marine omega-3 (which reflect their dietary intake) and prevalent diabetic retinopathy (DR), and retinal microvascular data obtained through optical coherence tomography angiography (OCTA).

SUBJECTS/METHODS: Exploratory, cross-sectional sub-study of a prospective, consecutive, large-scale OCTA study conducted in a longitudinal cohort (ClinicalTrials.gov NCT03422965). We used baseline data from 188 consecutive patients with T1D and 88 controls. We determined blood omega-3 biomarkers (eicosapentaenoic [EPA], docosapentaenoic [DPA] and docosahexaenoic [DHA] acids) by gas-chromatography. Ocular data included DR grading, and 6 × 6 mm OCTA scans to obtain macular vessel density and perfusion density, and foveal avascular zone area, perimeter, and circularity.

RESULTS: Patients with T1D, regardless of DR stage, showed significantly lower blood levels of EPA, DHA, DHA, and EPA + DHA than non-diabetic controls ($P < 0.001$, all cases). In multivariate models in patients with T1D, higher EPA was associated with a lower prevalence of DR ($P = 0.044$); and increasing proportions of DPA, DHA, EPA + DHA, and total marine omega-3 fatty acids related to a higher vessel and perfusion densities in the macula (P values from 0.014 to 0.050).

CONCLUSIONS: In patients with T1D, higher blood omega-3 status related to lower DR grades and preserved retinal perfusion. Our results, which are consistent with the current model of the pathogenesis of DR and data from experimental models, add to the notion of marine-derived omega-3 fatty acids as a healthy fat.

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INTRODUCTION

Diabetic retinopathy (DR) is the leading cause of blindness in patients with type 1 diabetes (T1D). The retina is particularly vulnerable to microvascular damage due to its high metabolic and oxygen demands and its dependence on an intact blood-retinal barrier [1]. Chronic exposure to elevated blood glucose triggers inflammation and oxidative stress, which are critical in the onset and development of ischaemic microvascular disease of the retina and retinal neurodegeneration. Because damage of retinal capillaries and the ensuing impaired retinal blood flow occurs in a time-dependent manner, early detection of these microvascular changes could lead to modifications in the pharmacological management of patients with T1D, as a way to reduce the risk of incident DR and vision loss.

The retina is rich in long-chain omega-3 (n-3) polyunsaturated fatty acids (LCn-3PUFAs), particularly docosahexaenoic acid (C22:6n-3, DHA) [2]. Once released from cell membranes, these fatty acids are transformed to oxylipins with vasculoprotective properties [3, 4]. Because cell membrane LCn-3PUFA status is modifiable and dependent on intake, dietary LCn-3PUFAs or consumption of its parent food (fatty fish) is suggested to protect against DR [5]. However, to our knowledge, human data are scarce and limited to type 2 diabetes [6, 7]. We hypothesised that increasing dietary intake of DHA and other LCn-3PUFAs such as eicosapentaenoic acid (EPA) and docosapentaenoic acid (DPA) relates to preserved retinal vasculature in patients with T1D. To address this issue, we determined the circulating omega-3 status by gas-chromatography (an objective and valid biomarker of dietary intake of omega-3 [8]) and searched for independent associations with prevalence of DR, and with retinal microvascular data obtained through optical coherence tomography angiography (OCTA), a novel and non-invasive retinal imaging technique that allows detection of perfused and non-perfused areas of the retina to the capillary level without the injection of dye [9] that has shown strong association to the DR grade [10].

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MATERIALS AND METHODS

Study design

This is an exploratory, cross-sectional sub-study of a prospective, consecutive, large-scale OCTA study conducted in a cohort of T1D patients undergoing yearly follow-up visits as per routine clinical care at the Diabetes Unit of the Endocrinology service, and in healthy volunteers recruited after social media campaigns supported by the Hospital Clinic Communications department [11]. Exclusion criteria included ocular comorbidities (i.e., macular oedema, previous ocular surgery, macular laser, intravitreal therapies, etc.), media opacities, or inability to perform complete ocular examinations or provide written informed consent. The study was registered in the Clinical Trials website (NCT03422965) and it was approved by the Institutional Review Board of Hospital Clinic of Barcelona (study protocol version 0.2, 23/11/2016). Written informed consent was obtained for all participants. For this sub-study, we collected blood samples in 188 consecutive patients with T1D and 88 controls (all of them recruited between May 2017 and May 2019) at the time of the first OCTA examination.

Fatty acid analysis

We determined fatty acids in a dried blood sample obtained by fingertip prick sampling. Because fasting was not required, we applied a method to determine omega-3 in glycerophospholipids [12], the omega-3 profile of which has been reported to be marginally affected by the fasting state [13]. In brief, participants were asked to clean the tip of the finger with an alcohol wipe. Once alcohol was dried, we pricked the fingertip with a lancet and squeezed the finger to allow the formation of a blood drop, which was let drop off the finger onto a prewashed chromatography strip (Whatman 903 filter paper), which was air-dried for 5 min, placed in an individual plastic bag and stored at −80 °C until fatty acid analysis. One punch of dried blood spot was heated at 100 °C for 45 min in 14% boron trifluoride methanol (Sigma, St. Louis, MO, USA). After cooling, hexane and water were added, and an aliquot of the hexane layer was injected to an Agilent HP 7890 Gas Chromatograph equipped with a 30 m × 0.25 µm × 0.25 mm SupraWAX-280 capillary column (Teknokroma, Barcelona, Spain), an autosampler, and flame ionisation detection. Twenty-two fatty acids were quantified and expressed as a percentage of total fatty acids. Total LCn-3PUFAs was computed as the sum of EPA, DPA, and DHA. As reported [12], the fatty analysis method has been cross-validated against the reference method used in the determination of fatty acids in blood samples [14].

Clinical variables

Collected ocular data included best-corrected visual acuity (BCVA), slit-lamp biomicroscopy, intraocular pressure measurement, retinal fundus exam and biometry (IOL Master, Carl Zeiss Meditec, Dublin, CA, USA). DR stage was graded using the International Scale [15]. A comprehensive battery of OCTA images was obtained using a Cirrus OCT model (Carl Zeiss Meditec, Dublin, CA, USA). OCTA scanning protocols included 6 × 6 mm cube scans centred in the fovea by gaze fixation. Image quality check was performed and scans with presence of artifacts, segmentation errors, or signal strength index (SSI) < 7 (indicating poor image quality in OCTA) were excluded from analysis. OCTA quantifications were performed by the built-in commercial software AngioPlex Metrix (v2017, Carl Zeiss Meditec, Dublin, CA, USA) in the superficial capillary plexus of the study eyes, defined by the internal limiting membrane and the inner plexiform layer boundaries. OCTA measurements included vessel density (VD), perfusion density (PD) and foveal avascular zone area (mm^2), perimeter (mm), and circularity (%). No manual adjustments of the segmentation slab were performed.

Finally, we calculated the 5-y mean HbA1c by using data collected yearly during the previous 5 years from electronic medical records.

Statistical analyses

We expressed categorical variables as frequencies and percentages, whereas quantitative variables following normal distribution were expressed as mean (95% confidence interval [CI]). The normal distribution of continuous variables was assessed by the Kolmogorov–Smirnov test. Due to their skewedness, OCTA variables were rank-transformed for further parametric analyses.

We assessed differences in omega-3 biomarkers among participants from different clinical entities (healthy controls; T1D without DR; T1D with mild DR; and T1D with advanced DR) by Mann-Whitney U-test and Kruskal-Wallis test. We also assessed differences for omega-3 biomarkers among healthy controls, T1D without DR and T1D with DR in gender strata by Mann-Whitney U-test and Kruskal-Wallis test.

In patients with T1D, we constructed a logistic regression model to search for associations between each omega-3 biomarker of interest (EPA, DPA, DHA, EPA + DHA, and LCn-3PUFAs—predictors) and the prevalence of DR in patients with T1D (outcome), adjusting for age, gender, duration of T1D, and 5-year mean HbA1c. This analysis was repeated after stratifying for gender, adjusting for age, duration of T1D, and 5-year mean HbA1c. We also constructed a multinomial regression model to search for associations for prevalence of mild DR and advanced DR as separate entities, adjusting for the variables previously listed.

We next determined the associations between omega-3 biomarkers and data from OCTA, namely VD and PD, as well as foveal avascular zone measurements (area, perimeter, and circularity). We constructed a linear regression model for each biomarker and outcome, adjusting for age, gender, duration of T1D, 5-year mean HbA1c, prevalence of DR (yes/no), and SSI. For each outcome we used data from the eye with the most advanced DR stage. In the event that both eyes were valid, and with the same DR stage, we randomly selected data from one eye. Detailed information on this matter is displayed in each Table from "Results". For VD and PD, analyses were repeated after stratifying for gender, adjusting for age, duration of T1D, 5-year mean HbA1c, prevalence of DR (yes/no), and SSI.

For all regression analyses, standard diagnostic checks on the residuals from the fitted models showed no evidence of any failure of the assumptions of normality and homogeneity of the residual variance. Statistical significance was set at the $P < 0.05$ level in all cases. Analyses were performed using SPSS software, release 22.0 (IBM Corp.). Figures were built using R software (R Foundation for Statistical Computing; http://www.r-project.org/).

RESULTS

The characteristics of the study population by clinical categories are shown in Table 1. There were 150 women and 126 men, with a mean age of 41 ± 13 y (range, 19 to 73). All patients with T1D were treated with insulin, roughly 20% of them being on insulin pump therapy. No dietary restrictions were indicated. Detailed information on the blood fatty acid status by clinical categories can be found in Supplementary Table 1. As depicted in Fig. 1, patients with T1D, regardless of DR stage, showed significantly lower blood levels of EPA, DPA, and DHA than non-diabetic controls (panels A-C; $P < 0.001$, all cases). Accordingly, statistically significant differences between controls and patients with T1D were also observed for EPA + DHA (panel D) and LCn-3PUFAs (data not shown). For all biomarkers, differences were more marked in women than in men (Supplementary Fig. 1 and 2).

We then focused on the 188 patients with T1D. When exploring the association with prevalent DR, each 1-SD increase of EPA (0.250%) was associated with a lower 36% prevalence of DR (Odds Ratio [OR] = 0.639; 95% CI: 0.413 to 0.989, $P = 0.044$ – Table 2). After stratifying for gender, statistically significant associations were limited to women (OR = 0.494; 95% CI: 0.273 to 0.892, $P = 0.019$ – Supplementary Table 2). Each 1-SD increase of EPA (0.250%) was also associated with a lower 71% prevalence of advanced DR (OR = 0.295; 95% CI: 0.103 to 0.846, $P = 0.023$ – Supplementary Table 3). No statistically significant associations were observed for other explored omega-3 biomarkers.

However, all omega-3 biomarkers except for EPA showed significant, direct associations with both VD and PD (Table 3), although statistical significance for many associations vanished after stratification for gender (Supplementary Table 4). None of the omega-3 biomarkers showed significant associations with foveal avascular zone area (mm^2), perimeter (mm), or circularity (%) (Supplementary Table 5).

DISCUSSION

In this cross-sectional, exploratory study conducted in 188 consecutive patients with T1D undergoing regular visits as per

Table 1. Demographic and clinical data of the study population (n = 276).

Variable	No diabetes, controls (n = 88)	Type 1 diabetes		
		No DR (n = 110)	Mild DR (n = 63)	Advanced DR (n = 15)
Age, y	45 (42; 48)	38 (36; 40)	40 (37; 42)	45 (39; 51)
Women, N (%)	56 (63.6)	58 (52.7)	31 (49.2)	5 (33.3)
Diabetes duration, y	--	16.1 (14.5; 17.8)	25.2 (22.7; 27.7)	31.1 (26.2; 35.9)
5-y mean HbA1c, %	5.38 (5.30; 5.46)	7.76 (7.31; 8.20)	7.64 (7.45; 7.83)	7.76 (7.37; 7.14)
Insulin requirements, IU/kg/day	--	0.62 (0.57; 0.66)	0.60 (0.55; 0.66)	0.83 (0.65; 1.01)
Insulin pump, N (%)	--	21 (19.1)	15 (23.8)	3 (20.0)
Body mass index, kg/m^2	23.7 (22.9; 24.5)	24.4 (23.7; 25.1)	25.0 (24.2; 25.8)	26.7 (24.3; 29.0)
Smoking status				
Never, N (%)	60 (68.2)	64 (58.2)	42 (66.7)	9 (60.0)
Current, N (%)	7 (8.0)	28 (25.5)	13 (20.6)	0 (0.0)
Former, N (%)	21 (23.9)	18 (16.4)	8 (12.7)	6 (40.0)
Hypertension, N (%)	9 (10.3)	10 (9.1)	8 (12.7)	3 (20.0)
ACEI or ARB treatment, N (%)	7 (8.0)	12 (10.9)	7 (11.1)	3 (20.0)
Dyslipidaemia, N (%)	37 (42.0)	36 (32.7)	24 (38.1)	11 (73.3)
Statin treatment, N (%)	3 (3.4)	18 (16.4)	8 (12.7)	9 (60.0)
Antiplatelet treatment, N (%)	1 (1.1)	3 (2.8)	0 (0.0)	2 (13.3)
Laboratory tests				
Total cholesterol, mg/dL	196 (189; 204)	177 (172; 182)	180 (172; 189)	188 (177; 199)
LDL-c, mg/dL	117 (110; 124)	101 (97; 106)	105 (99; 111)	112 (102; 122)
HDL-c, mg/dL	58 (54; 61)	60 (58; 63)	60 (55; 65)	55 (44; 67)
Triglycerides, mg/dL	112 (98; 126)	78 (68; 87)	79 (69; 89)	103 (81; 125)
Haemoglobin, g/L	138 (135; 141)	142 (140; 145)	142 (139; 146)	143 (134; 152)
Platelets, 10^9/L	251 (238; 264)	251 (237; 265)	258 (244; 273)	269 (229; 309)

Otherwise stated, data are expressed as mean (95% confidence interval).
DR diabetic retinopathy, *ACEI* angiotensin-converting enzyme inhibitors, *ARB* angiotensin II receptor blocker, *HbA1c* glycated haemoglobin, *IU* insulin units, *LDL-c* low-density lipoprotein-cholesterol, *HDL-c* high-density lipoprotein cholesterol.
Advanced DR includes moderate Non-proliferative DR (NPDR) + severe NPDR + proliferative DR.

routine clinical care at a Diabetes Unit, and in 88 healthy control individuals, we observed that compared to healthy controls, patients with T1D display a lower status of marine omega-3 blood biomarkers; that increasing proportions of EPA are associated with a lower risk of prevalent DR, particularly in women; and that increasing proportions of DPA, DHA, EPA + DHA, and LCn-3PUFAs independently relate to a higher vessel and perfusion densities in the macula, as assessed by OCTA, a novel and non-invasive retinal imaging technique.

Three findings deserve to be highlighted. The first one is the lower blood status of examined omega-3 biomarkers in patients with T1D in comparison to healthy controls. Although the cross-sectional nature of this study precludes us from establishing any causality, there is increasing experimental evidence about the beneficial effects of LC-n3PUFA intake in the prevention of T1D (reviewed in [16]), mechanistically explained by the anti-inflammatory action and the reduction of islet autoimmunity by LC-n3PUFAs [17]. In this regard, our results are consistent with previous observational studies in paediatric populations using either blood biomarkers [18–20] or self-reported data [18, 21], all of them supporting the view of a protective effect of LCn-3PUFAs in lowering the risk of T1D. Further clinical research is warranted to firmly establish causality.

Second, in patients with T1D we observed a set of significant, independent associations between blood omega-3 biomarkers and better retinal status at different stages, as expanded below. Given the clinical and economic burden of vascular complications of diabetes, there is a need to identify factors contributing to the vascular health of patients with diabetes, in particular, in those with a long duration of the disease (i.e., T1D). Besides a tight glycaemic control and other cardiovascular risk factors, whether consumption of specific foods, nutrients, and food groups might affect the risk of DR has deserved increasing attention, with beneficial associations for dietary LC-n3PUFAs (or fish) documented in many (but not all) observational studies (reviewed in [22]). We add to the evidence on the topic, by reporting data from an objective biomarker of dietary intake, measured in patients with T1D, who have been less investigated than those with type 2 diabetes [22]. In addition, the use of high-resolution imaging of the retinal microvasculature (OCTA) allowed us to uncover novel associations with vascular metrics that change across the DR *continuum*, as reported for diabetic kidney disease [23] or systemic glycaemic control [24]. To the best of our knowledge, a single clinical study focused on diet and OCT, reporting preserved retinal neurovasculature in those participants with higher self-reported consumption of vegetables, fruits, fish, and olives and vegetable oil [25].

Finally, associations differed by omega-3 species. On the one hand, significant lower prevalence of DR (and advanced DR when considered separately from mild DR) was restricted to EPA, particularly in women. This is of interest because a gender-based analysis of retinal microvascular alterations in patients with type 1 diabetes using OCTA reported that women may have earlier and more microvascular damage than men [26]. On the other

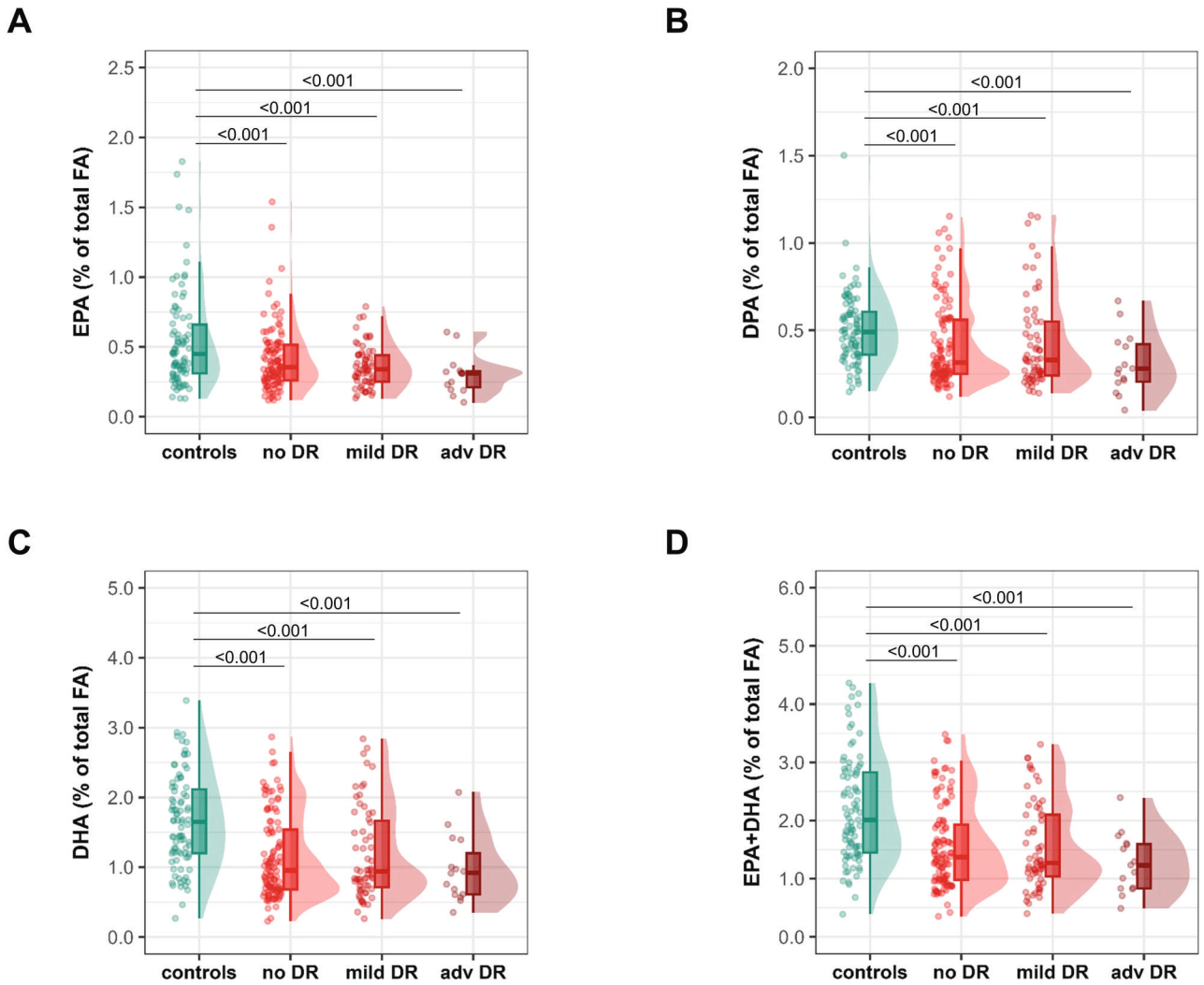

Fig. 1 Comparison of circulating blood omega-3 biomarkers among clinical groups. *FA* fatty acids, *DR* diabetic retinopathy, *adv DR* advanced DR (includes moderate non-proliferative DR + severe NPDR + proliferative DR). P value obtained Mann-Whitney *U*-test and Kruskal-Wallis test; controls (i.e. patients without diabetes), n = 88; patients with Type 1 diabetes without DR, n = 110; patients with Type 1 diabetes with mild DR, n = 63; patients with Type 1 diabetes with advanced DR, n = 15. **A** EPA (eicosapentaenoic acid). Median (interquartile ranges) for the categories are: 0.46 (0.31; 0.67); 0.35 (0.26; 0.52); 0.34 (0.25; 0.44); and 0.31 (0.19; 0.33), respectively. **B** DPA (docosapentaenoic acid). Median (interquartile ranges) for the categories are: 0.49 (0.36; 0.60); 0.32 (0.25; 0.56); 0.33 (0.24; 0.55); and 0.28 (0.20; 0.43), respectively. **C** DHA (docosahexaenoic acid). Median (interquartile ranges) for the categories are: 1.63 (1.19; 2.13); 0.96 (0.68; 1.55); 0.94 (0.69; 1.69), and 0.92 (0.61; 1.39), respectively. **D** EPA + DHA. Median (interquartile ranges) for the categories are: 1.99 (1.43; 2.84); 1.37 (0.98; 1.94); 1.27 (1.00; 2.10); and 1.23 (0.83; 1.62), respectively.

Table 2. Associations between circulating omega-3 fatty acids and prevalence of diabetic retinopathy in patients with T1D (n = 188)[a].

Fatty acid (% of total identified fatty acids)	No DR	DR, OR (95% CI)	P
EPA	1.00 (ref)	0.639 (0.413; 0.989)	0.044
DPA	1.00 (ref)	0.951 (0.665; 1.361)	0.784
DHA	1.00 (ref)	1.060 (0.753; 1.492)	0.740
EPA + DHA	1.00 (ref)	0.956 (0.674; 1.356)	0.801
Total long-chain n-3 PUFA	1.00 (ref)	0.923 (0.649; 1.310)	0.653

Data are presented for 1-SD increase of the omega-3 biomarkers, obtained by logistic regression models, adjusted for age, gender, duration of T1D, and 5-year mean HbA1c.
DR diabetic retinopathy, *OR* Odds Ratio, *CI* confidence interval, *EPA* eicosapentaenoic acid, *DPA* docosapentaenoic acid, *DHA* docosahexaenoic acid.
[a]Participants with measures only for right eye (n = 7), left eye (n = 3) or both eyes (n = 178; in this case, selection of the most advanced DR stage).

Table 3. Associations between circulating omega-3 biomarkers and retinal vessel and perfusion densities in patients with T1D[a].

Fatty acid (% of total identified fatty acids)	Vessel density[b]		Perfusion density[b]	
	Estimate (95% CI)	P	Estimate (95% CI)	P
EPA	0.051 (−0.141; 0.242)	0.600	0.002 (−0.002; 0.005)	0.408
DPA	0.224 (0.046; 0.402)	0.014	0.004 (0.000; 0.007)	0.032
DHA	0.206 (0.027; 0.385)	0.025	0.004 (0.000; 0.007)	0.042
EPA + DHA	0.191 (0.010; 0.373)	0.039	0.004 (0.000; 0.007)	0.050
Total long-chain n-3 PUFA	0.208 (0.026; 0.391)	0.026	0.004 (0.000; 0.007)	0.039

Data are presented for 1-SD increase of the omega-3 biomarkers, obtained by multiple linear regression analyses, adjusted for age, gender, duration of T1D, 5-year mean HbA1c, prevalence of diabetic retinopathy (yes/no), and signal strength index.
EPA eicosapentaenoic acid, *DPA* docosapentaenoic acid, *DHA* docosahexaenoic acid.
[a]N = 184, with valid measures only for right eye (n = 14) and left eye (n = 19). N = 151 with valid measures for both eyes. Selection of right eye, since it shows more advanced diabetic retinopathy (n = 13). Selection of left eye, since it shows more advanced diabetic retinopathy (n = 8). Random selection for n = 130. As a result, 93 / 91 (right eye; left eye).
[b]Rank-transformed.

hand, increasing proportions of the longer chain counterparts (DPA and DHA) related to a better-perfused macula. In overall, this is an important finding because rather than suggesting divergent effects of omega-3 species, it suggests that different LCn-3PUFAs have a concerted, complementary effect. In addition, it points to a differential mechanism underlying the ocular benefits in T1D, being either closely related to vasculoprotection (prevention of central non-perfusion—DPA and DHA) or less specific (EPA). Future studies should confirm or dispel such hypothesis.

Several limitations may be disclosed. First, OCTA quantifications have been measured with the commercial version of the OCT device, which only allows measurements in the superficial and not in the deep capillary plexus, where some authors have indicated that DR starts [27]. Second, we cannot completely exclude other systemic factors which may have caused a bias in OCT and OCTA measurements. This study has several strengths, as the specific type of patients studied (T1D), the use of objective biomarkers of dietary intake, and the collection of high-quality data in a clinical trial scenario with a full battery of retinal imaging tests in both patients and controls.

In conclusion, in patients with T1D, we found significant associations between biomarkers of dietary omega-3 fatty acids from marine origin and a lower risk of prevalent DR, as well as with preserved microvascular status of the retina (defined by objective OCTA parameters). Our results, which are consistent with the current model of the pathogenesis of DR and data from experimental models, add to the notion of marine-derived omega-3 as a healthy fat in T1D.

SUMMARY

What was known before

- Dietary marine omega-3 fatty acids are linked to retinal health in diabetes, but clinical research in type 1 diabetes is scarce.

What this study adds

- Blood EPA related to a lower risk of prevalent diabetic retinopathy.
- Most omega-3 were directly associated with higher vessel and perfusion retinal densities. We reinforce that marine omega-3 might contribute to retinal health and protection in patients with type 1 diabetes.

DATA AVAILABILITY

The datasets generated during and/or analysed in the current study are available from the corresponding author upon reasonable request.

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AUTHOR CONTRIBUTIONS

AS-V, IV, MC, IL, AA-C, MB, TH, WSH, JZ-V, and EO were involved in the conception, design, and conduct of the study and the analysis and interpretation of the results. AS-V, JZ-V and EO wrote the first draft of the manuscript, and all authors edited, reviewed, and approved the final version of the manuscript. EO is the guarantor of this work and, as such, has full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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COMPETING INTERESTS

Javier Zarranz-Ventura is a member of the Eye editorial board. William S. Harris holds stock in OmegaQuant Analytics, LLC, a laboratory that offers blood fatty acid testing to researchers, healthcare providers and consumers. None of the other authors have any financial interest in the devices employed in this study.

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