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Omega-3 index in patients with severe diabetic ocular complications

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Summary

Background The aim of the study was to assess the omega-3 index and the proportions of other relevant fatty acids (FAs) in patients undergoing vitrectomy due to severe diabetic ocular complications. According to evidence, an optimal omega-3 index range is 8–11% and a high level of saturated FAs correlate with advanced diabetic retinopathy (DR).

Methods Patients with diabetes mellitus (DM) undergoing vitrectomy due to diabetic macular edema or vitreous hemorrhage secondary to proliferative DRP were recruited for this study. Prior to surgery, the omega-3 index, defined as the proportion of omega-3 FAs in the membranes of erythrocytes, and the proportions of omega-6, omega-9, saturated and trans FAs were assessed using "high-sensitivity" gas chromatography with flame ionization detection.

Results In total, 12 patients with DM type 1 ($n=2$) and type 2 ($n=10$) were enrolled. Their age was 69 ± 12 years and their HbA_{1c} averaged 7.6 ± 1.2%. The omega-3 index was 4.5 ± 1.2%. There was a moderate negative correlation between HbA_{1c} and the omega-3 index ($r=-0.51$, $p=0.09$). The proportions of other FAs were within the normal ranges. However, the proportions of omega-6 and saturated FAs were in the upper range (33.3 ± 2.2% and 41.1 ± 1.3%, respectively).

Conclusion Patients with severe diabetic ocular complications who require vitreoretinal surgery are generally under-supplied with omega-3 FAs and over-supplied with omega-6 and saturated FAs. Patients with diabetes might consequently benefit from early omega-3 FA supplementation and a reduction of saturated FAs in order to prevent or at least slow down the development of DRP and ultimately preserve vision.

Keywords Supplementation · Fatty acids · Erythrocytes · Diabetes mellitus · Vitrectomy

Omega-3-Index bei Patient*innen mit schweren diabetischen Augenkomplikationen

Zusammenfassung

Hintergrund Ein optimaler Omega-3-Index beträgt 8–11 %, und ein hoher Anteil an gesättigten Fettsäuren korreliert mit einer fortgeschrittenen diabetischen Retinopathie (DR). Das Ziel der Studie ist es, den Omega-3-Index sowie die Anteile anderer relevanter Fettsäuren (FS) bei Patient*innen, die sich aufgrund schwerer diabetischer Augenkomplikationen einer Vitrektomie unterziehen, zu erheben.

Methoden Für diese Studie wurden Patient*innen mit Diabetes mellitus (DM) rekrutiert, bei denen aufgrund eines diabetischen Makulaödems oder einer Glaskörperblutung infolge einer proliferativen DR eine Vitrektomie erfolgte. Vor der Operation wurden der Omega-3-Index, definiert als das Verhältnis der Omega-3-FS in den Membranen der Erythrozyten, und die Anteile der Omega-6-, Omega-9-, gesättigten und trans-FS mithilfe einer hoch sensiblen Gaschromatographie mit Flammenionisationsdetektion bestimmt.

Ergebnisse In die Studie wurden 12 Patient*innen mit DM Typ 1 ($n=2$) und Typ 2 ($n=10$) eingeschlossen. Ihr Alter betrug 69 ± 12 Jahre, und ihr HbA1c-Wert lag im Durchschnitt bei 7,6 ± 1,2 %. Der Omega-3-Index lag bei 4,5 ± 1,2 %. Es bestand eine mäßige negative Korrelation zwischen dem HbA1c und dem Omega-

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3-Index ($r = -0{,}51$, $p = 0{,}09$). Die Anteile der anderen FS lagen innerhalb der Normbereiche. Die Omega-6- und gesättigten FS-Anteile lagen jedoch im oberen Bereich (33,3 ± 2,2 % bzw. 41,1 ± 1,3 %).
Schlussfolgerung Patient*innen mit schweren diabetischen Augenkomplikationen, die eine vitreoretinalen Operation benötigen, sind im Allgemeinen mit Omega-3-FS unter- und mit Omega-6-FS sowie gesättigten FS überversorgt. Diabetiker*innen könnten daher von einer frühzeitigen Supplementierung mit Omega-3-FS und einer Reduzierung gesättigter FS profitieren, um die Entwicklung einer DR zu verhindern bzw. zumindest zu verlangsamen und letztlich das Sehvermögen zu erhalten.

Schlüsselwörter Supplementierung · Fettsäuren · Erythrozyten · Diabetes mellitus · Vitrektomie

Abbreviations

BCVA	Best-corrected visual acuity
DM	Diabetes mellitus
DME	Diabetic macular edema
DR	Diabetic retinopathy
FA	Fatty acid
IL	Interleukin
LDL	Low-density lipoprotein
OCT	Optical coherence tomography
VEGF	Vascular endothelial growth factor
VH	Vitreous hemorrhage

Introduction

Diabetes mellitus (DM) can lead to various ocular complications including diabetic macular edema (DME) and/or vitreous hemorrhage (VH) due to proliferative diabetic retinopathy (DR; [1]). These complications represent one of the leading causes of legal blindness, especially in working-age adults [1]. The pathophysiology of diabetic ocular complications is complex; however, two essential factors have been identified including the hypoxia-driven upregulation of vascular endothelial growth factor (VEGF) and a chronic retinal inflammation [2–5].

Omega-3 fatty acids (FA) were found to play a more significant role in this context than previously thought [6]. Specifically, a high intake of omega-3 FAs reduces the risk of developing DR in individuals with well-controlled DM ($HbA_{1c} < 7.0\%$; [6]). The reason for this is assumed to be anti-VEGF and the anti-inflammatory effect of omega-3 FAs [7–14]. In particular, omega-3 FAs suppress the VEGF pathway by activating the transcription factor peroxisome proliferator-activated receptor-α [14]. Omega-3 FAs further suppress the transcription factor nuclear factor-κB, which consecutively leads to less production of pro-inflammatory cytokines including tumor necrosis factor-α and interleukins (IL)-1 and IL-6 [11, 12]. In addition, omega-3 FAs represent the main structural lipids in photoreceptor membranes and are thus essential for their regeneration and vision in general [15].

The saturation of the body with omega-3 FAs is generally lower in the diabetic than in the non-diabetic population [16]. However, we could not find any evidence regarding omega-3 FA saturation in patients with severe DR undergoing vitrectomy. This subset of patients is of particular interest because the surgical outcomes often do not meet expectations. Since omega-3 FAs partly modulate the course of DR, patients with DM might generally benefit from omega-3 FA supply. The World Health Organization recommends an intake of polyunsaturated FAs including omega-3 FAs of 6–11% of the total energy intake to improve health in general, but the majority of the population, especially those with DM, do not follow this recommendation [17, 18]. Moreover, the amount of saturated FAs should be concomitantly decreased, since a high intake of these FAs promotes the developments of severe DR and cardiovascular diseases [6, 19].

The aim of this study was to assess the proportion of omega-3, saturated, and other relevant FAs in the erythrocytes of patients undergoing vitrectomy due to severe diabetic ocular complications.

Methods

This study was approved by the local ethics committee of the Medical University Graz and adhered to the tenets of the Declaration of Helsinki. We recruited patients scheduled for vitrectomy for diabetic complications including chronic DME or VH secondary to proliferative DR at the Department of Ophthalmology, Medical University Graz, between March 2020 and February 2021. The patients were included in this study after they gave their informed consent. For all patients, a complete ophthalmic examination including best-corrected visual acuity (BCVA) measurement, slit-lamp examination, indirect ophthalmoscopy, and optical coherence tomography (OCT) was performed prior to surgery. Patients with VH additionally underwent ocular ultrasound to assess whether the retina was attached. On the day of surgery, a fasting venous blood sample was taken using a 2-mL ETDA tube and sent to a highly specialized laboratory for FA analysis (Omegametrix®, Martinsried, Germany). A complete assessment of the proportion of FAs was made including omega-3, omega-6, monounsaturated (omega-9), saturated, and trans FAs in the membranes of erythrocytes using a standardized and patented "high-sensitivity" gas chromatography with flame ionization detection described elsewhere [20]. In detail, FA methyl esters were extracted from erythrocytes by acid transesterification and analyzed with the GC-2010 gas chromatograph (Shimadzu, Duisburg, Germany) with an SP2560, 100-m capillary column (Supelco®, Bellefonte, PA, USA) using hydrogen as carrier gas. In total, 26 FAs were identified and quantified. The results

Table 1 List of identified fatty acids (FA) (lipid number)

Type of FA	Result in %	Reference range in %[a]
Omega-3 (polyunsaturated) FAs in total	*6.8 ± 1.6*	3.1–20.8
Alpha-linolenic acid (C18:3n3)	0.1 ± 0.05	
Eicosapentaenoic acid (C20:5n3)	0.5 ± 0.03	
Docosapentaenoic acid (C22:5n3)	2.2 ± 0.5	
Docosahexaenoic acid (C22:6n3)	4.02 ± 0.9	
Omega-6 (polyunsaturated) FAs in total	*33.3 ± 2.2*	18.6–39.6
Linoleic acid (C:18:2n6)	10.7 ± 2.7	
Gamma-linoleic acid (C18:3n6)	0.06 ± 0.03	
Dihomo-gamma-linoleic acid (C20:3n6)	1.5 ± 0.4	
Arachidonic acid (C20:4n6)	16.4 ± 2.3	
Docosatetraenoic acid (C22:4n6)	3.6 ± 0.8	
Eicosadieonic acid (C20:2n6)	0.25 ± 0.05	
Docosapentaenoic acid (C22:5n6)	0.8 ± 0.2	
Omega-9 (monounsaturated) FAs in total	*18.3 ± 2.0*	11.6–29.3
Palmitoleic acid (C:16:1n7)	0.4 ± 0.3	
Oleic acid (C:18:1n9)	16.3 ± 2.0	
11-eicosenoic acid (C20:1n9)	0.25 ± 0.04	
Nervonic acid (C:24:1n9)	1.3 ± 0.3	
Saturated FAs in total	*41.1 ± 1.3*	31.0–43.7
Myristic acid (C14:0)	0.5 ± 0.4	
Palmitic acid (C16:0)	22.3 ± 1.6	
Stearic acid (C18:0)	16.5 ± 1.6	
Arachidic acid (C20:0)	0.2 ± 0.05	
Behenic acid (C22:0)	0.5 ± 0.1	
Lignoceric acid (C24:0)	1.1 ± 0.2	
Trans FAs in total	*0.52 ± 0.14*	0.1–2.1
Trans-palmitoleic acid (C16:1n7t)	0.1 ± 0.04	
Elaidic acid (C18:1n9t)	0.32 ± 0.1	
Linoleic acid (C:18:2n6t)	0.014 ± 0.006	
Others (C18:2n6tc, C18:2n6tt)	0.09 ± 0.02	

FAs fatty acids
[a]The reference range is displayed in the assessment of Omegametrix® and is based on measurements in 2000 unselected healthy probands

were provided as percentage of total identified FAs after response factor correction. The coefficient of variation was 5%. The quality of analyses was controlled in accordance with DIN EN ISO 15189. Details of the FAs assessed are listed in Table 1. The omega-3 index is defined as the proportion of eicosapentaenoic and docosahexaenoic acid in the membranes of erythrocytes. The omega-6/omega-3 ratio is defined as $\frac{omega\,6}{omega\,3}$.

Statistical analysis

The statistical analysis was performed using SPSS (IBM, SPSS Statistics 26, Armonk, NY, USA). The proportion of FAs is displayed in percentage ± standard deviation (range). Metric data are presented as mean ± standard deviation (range). The BCVA was converted into logMAR for statistical reasons. The distribution of the data was assessed with the Kolmogorov–Smirnov test. Correlations and the difference between datasets were analyzed depending on the distribution of the data. The statistical significance was defined as $p < 0.05$.

Results

Overall, 12 patients (5 female; 7 male) were enrolled in the study. Their average age was 69 ± 12 years (50–87). Two patients had type 1 DM and 10 patients type 2 DM. Of those with type 2 DM, seven patients were insulin-dependent. The HbA1c averaged 7.6 ± 1.2% (5.5–9.6) in general. HbA1c ≥ 7% was noted in eight patients and HbA1c < 7% was observed in four patients.

Seven eyes of seven patients underwent vitrectomy due to chronic DME resistant to intravitreal therapy and five eyes of five patients were vitrectomized due to VH secondary to proliferative DR. Of those, three had an additional traction related to DR verified with ultrasound. The preoperative BCVA of patients with DME was 0.52 ± 0.3 logMAR (0.2–1). Three of these patients were lost to follow-up postoperatively due to unknown reasons. The postoperative BCVA of the remaining patients ($n = 4$) averaged 0.3 ± 0.1 logMAR (0.1–0.4). In eyes with VH, the preoperative and postoperative BCVA was 1.2 ± 0.9 logMAR (0.2–2) and 0.6 ± 0.4 logMAR (0.2–1.1), respectively.

Overall, the omega-3 index averaged 4.5 ± 1.2% (2.8–7.2). The omega-6/omega-3 ratio was 5.2 ± 1.4:1. Detailed results of the FA assessment are listed in Table 1.

There was no correlation between the preoperative or postoperative BCVA and the omega 3 index ($r = -0.28$, $p = 0.38$ and $r = -0.18$, $p = 0.63$, respectively; Spearman correlation). The omega 3 index was 4.8 ± 1.3% (2.8–7.2) in patients with DME and 3.8 ± 0.8% (2.9–4.8) in those with VH. This difference was not statistically significant ($p = 0.21$, Mann–Whitney *U* test). In patients with type 1 DM ($n = 2$) the omega-3 index was 5.04 ± 0.3% (4.8–5.3) and in those with type 2 DM ($n = 10$) it was 4.4 ± 1.3% (2.8–7.2). Among those with type 2 DM, the omega-3 index averaged 3.8 ± 0.7% (2.9–4.5) in patients with insulin dependency ($n = 7$) and 5.8 ± 1.3% (4.6–7.2) in those with non-insulin-dependent DM ($n = 3$); this difference was statistically significant ($p = 0.017$, Mann–Whitney *U* test). There were also substantial differences in the omega-3 index depending on the HbA1c. In general, the omega-3 index correlated with HbA1c (Fig. 1; $r = -0.51$, $p = 0.09$; Spearman correlation). In patients with well-controlled DM, defined as HbA1c < 7%, and poorly controlled DM (HbA1c ≥ 7%), the omega-3 index was 5.02 ± 1.6% (2.9–7.2) and 4.1 ± 0.7% (2.8–4.8), respectively ($p = 0.27$, Mann–Whitney *U* test).

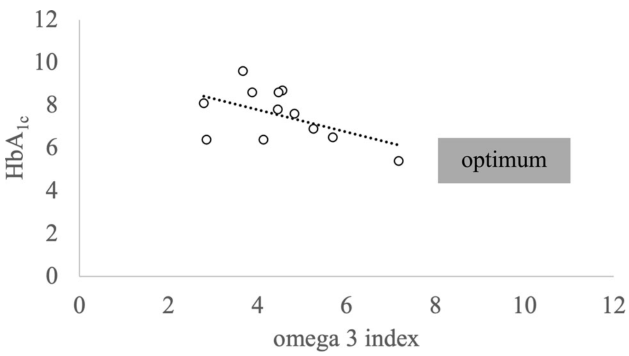

Fig. 1 The omega-3 index in relation to HbA_{1c}. The *gray bar* indicates the optimum for the omega-3 index and HbA_{1c}

The proportion of other FAs including omega-9, saturated, and trans FAs were within the normal range (Table 1). Solely the proportion of saturated FAs was slightly below the threshold. There was a negative correlation between omega-3 index and omega-6 FAs ($r=-0.66$, $p=0.02$; Spearman correlation). There were no correlations between omega-3 index and omega-9 FAs ($r=-0.31$, $p=0.33$; Spearman correlation), saturated FAs ($r=0.39$, $p=0.2$; Spearman correlation), and trans FAs ($r=0.44$, $p=0.15$; Spearman correlation).

Discussion

Our study shows that the omega-3-index in diabetic patients with severe ocular complications requiring vitreoretinal surgery is significantly lower than the recommended optimum of 8–11% [16]. Moreover, in patients with poorly controlled DM (HbA1c ≥ 7.0%), the omega-3 index was even lower compared to patients with well-controlled DM (HbA1c < 7.0%). Omega-3 FAs play a significant role in the regulation of inflammatory reactions in general [7–17]. First, omega-3 FAs suppress the pro-inflammatory transcription factor NF-κB and thus reduce the production and attenuate the effect of pro-inflammatory cytokines including tumor necrosis factor-α, IL-1, and IL-6 [11, 12]. Especially IL-6 plays a significant role in the development and maintenance of DME [3]. Second, omega-3 FAs metabolites including resolvin, protectin, and maresins promote resolution of inflammation processes [8]. Third, omega-3 FAs immanently reduce the level of omega-6-derived pro-inflammatory arachidonic acid, since both omega-3 and omega-6 FAs are metabolized by the same enzymes [9]. This aspect is particularly important since the diet in developed countries has become deficient in omega-3 and excessive in omega-6 FAs over the past few decades [9, 16]. The oversupply in omega-6 FAs consequently leads to an accumulation of arachidonic-acid-derived pro-inflammatory prostaglandins (H2, I2, F2, D2, E2-3, A1), leukotrienes, and lipoxins [9, 16]. The level of omega-6 FAs was 33.2% and thus relatively high according to the reference range of 18–39.6%. In addition to the anti-inflammatory aspect of omega-3 FAs, they also promote an anti-VEGF effect by activation of peroxisome proliferator-activated receptor-α, which subsequently inhibits the VEGF production [14].

Other FAs including omega-9, saturated, and trans FAs were within the reference range (Table 1). However, the proportion of saturated FAs was 41.1% and thus slightly below threshold of 43.7%. This finding is consistent with the evidence that a high intake of saturated FAs is associated with advanced DR [6]. The reason for this is the fact that a high intake of saturated FAs leads to increased levels of triglycerides and low-density-lipoprotein (LDL) cholesterol, which migrate into the retinal vasculature and oxidate and consequently contribute to the progression of DR [6, 21–24].

The implication of our study is that patients with DM might benefit from supplementation of omega-3 FAs. It has already been shown that an increased daily intake of omega-3 FAs (> 500 mg) over the years reduces the risk of DR-related vison loss by 48% by slowing down the progression of DR and improving DME [25]. Recently, a randomized controlled trial showed that patients with DME undergoing intravitreal anti-VEGF injections had a significantly better outcome when supplementation of omega-3 FAs was additionally given over 24 months compared to the control group receiving intravitreal anti-VEGF injections alone [26]. Based on this evidence, omega-3 FA supplementation might also optimize the outcome in patients with severe diabetic ocular complications undergoing vitreoretinal surgery. In this context, it is of interest that omega-3 FA intake did not prove to be beneficial in patients with poorly controlled DM (HbA1c ≥ 7.0%; [6]). The reason for this is not fully understood; however, it is assumed that small LDL particles, which are more prevalent in individuals with poorly controlled DM, interact with omega-3 FAs and thus diminish their effect [6]. In our study the omega-3 index was evidently lower in patients with poorly controlled DM. This finding might be attributable to a less balanced diet and omega-3-FA-deficient nutrition of patients with poorly controlled DM.

Limitations

This study has several limitations. The relatively low number of patients certainly limits the validity of this study from the statistical perspective. For example, the correlation between HbA1c and the omega-3 index was slightly above the level of statistical significance ($p=0.09$). In addition, the substantial differences in omega-3 index between patients with poorly controlled and well-controlled DM or between patients with DME and VH were not statistically significant. The relatively high costs for the FA assessment limited the number of patients in this study. Nevertheless, our study clearly indicates that patients with severe diabetic ocular complications are generally under-supplied with omega-3 FAs, especially those with poorly controlled DM.

The strength of this study is the assessment of the omega-3 index, which most reliably provides information about the saturation of the body with omega-3 FAs [27]. The serum level of omega-3 FAs, for example, is not a reliable marker due to confounding factors including fasting state, use of drugs, etc. [28] Some studies even evaluated the omega-3 FA intake by assessing a food-frequency questionnaire, which is inexpensive but poorly reliable [25]. Another strength of this study is the additional assessment of other FAs including omega-6, omega-9, saturated, and trans FAs, which gives a good overview of the patients' nutrition habits.

Conclusion

The saturation of the body with omega-3 fatty acids (FAs) is considerably low in patients with severe diabetic ocular complications who require vitreoretinal surgery, especially in those with poorly controlled diabetes mellitus (DM). Conversely, the levels of omega-6 and saturated FAs were relatively high. Our study emphasizes that this subset of patients is generally under-supplied with omega-3 FAs and over-supplied with omega-6 and saturated FAs, which have disadvantageous effects on diabetic retinopathy (DR) development. Consequently, patients with DM might benefit from omega-3 FA supplementation and reduction of saturated FAs in order to prevent or at least slow down the development of DR and ultimately preserve vision.

Author Contribution AG: draft of the work, interpretation of data; FW: interpretation of data, substantive revision; LH: substantive revision; CP: substantive revision; ML: substantive revision; AW: substantive revision; EL: substantive revision; DI: draft and design of the work, interpretation of data.

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Availability of data and material The datasets generated and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Declarations

Conflict of interest A. Guttmann, F. Wallisch, L. Hoeflechner, C. Pahljina, M. Lindner, A. Wedrich, E. Lindner and D. Ivastinovic declare that there is no conflict of interest.

Ethical standards This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of the Medical University Graz (Date: 03.10.2019/No.: 33-488 ex 18/19). *Consent to participate*: Informed consent was obtained from all individual participants included in the study.

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