Efectos antioxidantes / antiinflamatorios de un suplemento a base de triglicéridos de DHA altamente concentrado: beneficios a corto, medio y largo plazo en los Estudios Clínicos Aleatorizados Oftalmológicos

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Antioxidant/anti-inflammatory effects of a highly-concentrated DHA triglyceride supplement: short, medium and long-term benefits in ophthalmology RCTs

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ABSTRACT

STUDY OBJECTIVES: Docosahexaenoic acid (DHA) is the dominant fatty acid of retinal phospholipids and has a key role in maintaining retinal integrity. It was hypothesized that oral supplementation with a highly-concentrated DHA formulation might be beneficial in ocular diseases with pathophysiological mechanisms susceptible to be influenced by the pleiotropic effects of DHA. The studies aimed to assess whether a food supplement based on a highly-rich DHA triglyceride plus vitamins and minerals resulted not only in clinical benefits, but also in improvement of biochemical serum biomarkers of antioxidant and anti-inflammatory activity.

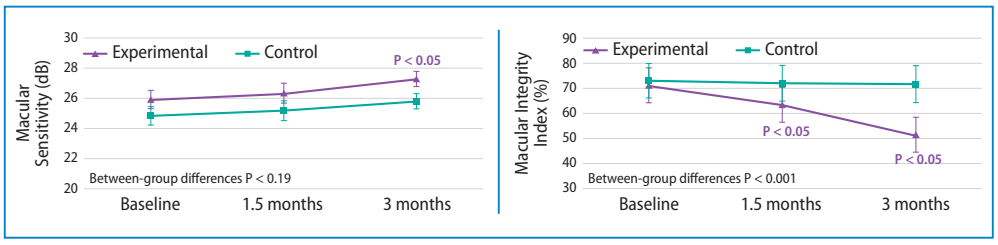
METHODS: Between 2014 and 2017, four RCTs were conducted in patients with diabetic retinopathy (DR), diabetic macular edema (DME) and pseudoexfoliative glaucoma (PEX). Patients assigned to the intervention arm (DHA group) received a nutraceutical formulation (DHA 1,050 mg/day) (Brudyretina or Brudypio 1.5 g, Brudy Lab, Barcelona, Spain) for different time periods depending on each RCT. Patients were consecutively randomized (1:1) to DHA supplementation or to the control group. Outcomes were best-corrected visual acuity (BCVA), central subfield macular thickness (CSMT), macular function (microperimetry), serum HbA1c, DHA erythrocyte membrane content, plasma total antioxidant capacity (TAC), malondialdehyde (MDA) and serum interleukin-6 (IL-6) levels.

RESULTS: In 24 asymptomatic patients with non-proliferative DR (12 patients, 24 eyes in each group) treated for 90 days, there were improvements in macular sensitivity (from 25.9±2.4 to 27.3±2.3 dB, P=0.03) and macular integrity index (71.2±33.2 to 51.6±35.9, P=0.002) in the DHA group only. In 47 patients with PEX treated for 6 months, intraocular pressure (IOP) decreased from 15.1±4.9 mmHg at baseline to 12.2±2.4 mmHg (P=0.007). In the two RCTs of DME, study arms included treatment with 0.5 mg intravitreal ranibizumab plus the nutraceutical supplementation versus intravitreal ranibizumab alone. In 62 patients (DHA group: 29 patients, 34 eyes; controls: 33 patients, 42 eyes) treated for 24 months, the difference between groups in the decrease of CSMT was significant (95% CI 7.20-97.656; P=0.024) as well as the difference in the percentage of patients with >10 ETRDS letters gain (66.7% vs 40%, P=0.044). In the 36-month extension study of this trial with 55 patients (DHA group: 26 patients, 31 eyes; controls: 29 patients, 38 eyes), mean decrease of CSMT was higher in the DHA group than in controls (275 ± 50 µm vs 310 ± 97 µm) with significant differences (P<0.01) at months 25, 30, 33, and 34. The percentages of patients with ETRDS gains > 5 and > 10 letters were also higher in the DHA group. In all RCTs, differences between the study groups in BCVA were not found. Biochemical findings in the DHA groups included significant differences versus controls in increases of the erythrocyte membrane content of ω-3 DHA and plasma TAC levels as well as decreases of serum HbA1c, MDA and IL-6 levels.

CONCLUSIONS: In four RCTs in ophthalmology, results obtained in the DHA supplemented groups versus non-supplemented controls showed clear and significant benefits in clinical outcomes and biochemical parameters. Consistency of the findings across all RCTs with different duration of treatments supports the clinical advantage of DHA supplementation.

SHORT-TERM EFFECTS (3 MONTHS) OF DHA SUPPLEMENTATION NON-PROLIFERATIVE DIABETIC RETINOPATHY

- Prospective controlled study (EudraCT 2017-00856-25)
- 24 asymptomatic patients with NPDR (24 eyes in each group)
- DHA supplement (Brudyretina 1,050 mg/day) for 90 days
- Main outcome: macular function (microperimetry, MAIATM CenterVue)

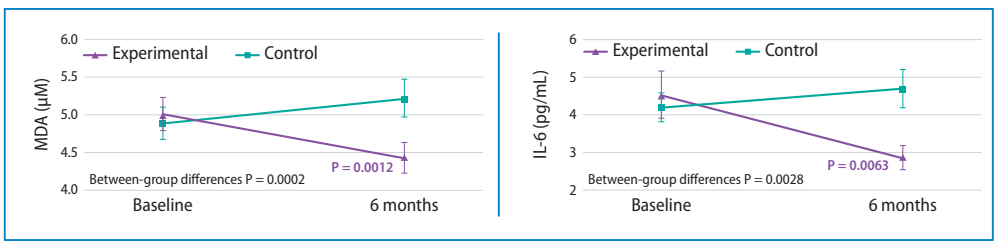


Significant improvement of macular sensitivity, decrease of macular integrity index (lower values higher probability of normal findings), significant increase of TAC and decrease of IL-6, in the DHA group only; between-group differences P < 0.05. Differences in BCVA and CSMT (OCT) were not found.

CONCLUSION: In early stage DR, dietary supplementation with DHA for 90 days was associated with a progressive and significant improvement of macular function. Biochemical changes supported the favourable effect of DHA.

MID-TERM EFFECTS (6 MONTHS) OF DHA SUPPLEMENTATION PSEUDOEXFOLIATIVE GLAUCOMA

- Open-label randomized controlled trial (EudraCT 2014-001104-21)
- 47 patients with early to moderate PEX glaucoma (DHA group 23, controls 24)
- DHA supplementation (1.5 g/day) (Brudypio) for 6 months
- Main outcomes: plasma malondialdehyde (MDA), TAC and IL-6

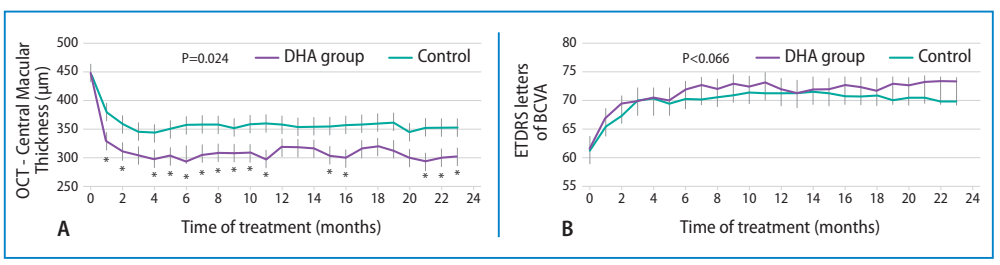


Significant improvement in MDA, TAC and IL-6 in the DHA group; between group differences P < 0.01. IOP decreased significantly in both eyes in the DHA group. Changes in BCVA and retinal nerve fiber layer thickness (OCT) were not observed.

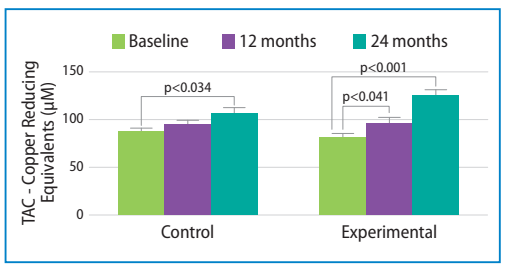
CONCLUSION: Targeting pathophysiological mechanisms of PEX glaucoma by reducing oxidative stress and inflammation with a high-rich DHA food supplement may be an attractive therapeutic approach.

LONG-TERM EFFECTS (2 YEARS) OF DHA SUPPLEMENTATION WITH OR WITHOUT 0.5 mg INTRAVITREAL RANIBIZUMA IN DIABETIC MACULAR EDEMA

- Prospective randomized controlled trial (EudraCT 2015-001082-74)
- 29 patients (34 eyes) in the DHA group, 33 patients (42 eyes) controls
- DHA supplementation (1,050 g/day) (Brudyretina) for 24 months
- Main outcomes: CSMT, BCVA (ETDRS letters), TAC, HbA1c, ω-3 DHA in the erythrocyte membrane



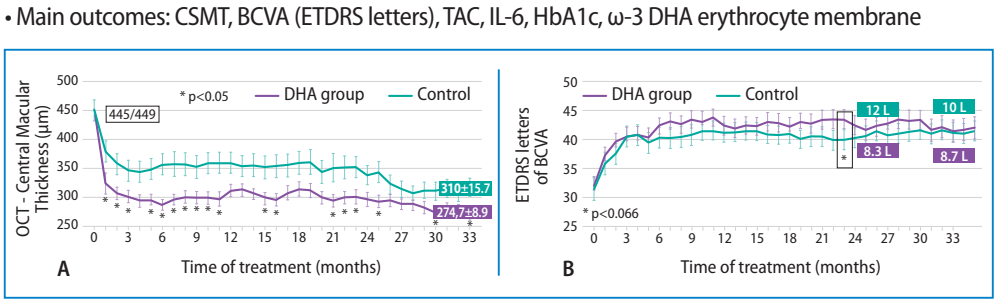
- Significant reductions of CSMT and increase in TAC levels in the DHA group only
- No significant differences in BCVA but better trend in the DHA group
- ω3-DHA erythrocyte membrane increased in the DHA group only
- No differences in HbA1c



CONCLUSION: Intravitreal ranibizumab combined with DHA supplementation reduced Central macular thickness after 2 years of follow-up compared with ranibizumab alone in patients with DME.

LONG-TERM EFFECTS (3 YEARS) OF DHA SUPPLEMENTATION WITH OR WITHOUT 0.5 mg INTRAVITREAL RANIBIZUMAB IN DIABETIC MACULAR EDEMA (EXTENSION TRIAL)

- Prospective randomized controlled trial (EudraCT 2015-001082-74)
- 26 patients (31 eyes) in the DHA group, 29 patients (38 eyes) controls
- DHA supplementation (1,050 g/day) (Brudyretina) for 36 months
- Main outcomes: CSMT, BCVA (ETDRS letters), TAC, IL-6, HbA1c, ω-3 DHA erythrocyte membrane



- Reductions of CSMT, significant differences vs controls at 25, 30, 33 and 34 months
- No differences in BCVA
- Significant differences in TAC and significant decrease in IL-6 levels
- Significant reduction in HbA1c

CONCLUSION: The addition of a high-rich DHA supplement to intravitreal ranibizumab was effective to achieve better sustained improvement of CSMT after 3 years of follow-up compared with ranibizumab alone.

TAKE HOME MESSAGE

- ✓ **A food supplement combining a triglyceride highly-concentrated in DHA plus vitamins and minerals showed clear clinical benefits in patients with NPDR, PEX glaucoma and DME**
- ✓ **The RCT design of studies strengths the validity of results**
- ✓ **Providing DHA supplementation is an important therapeutic intervention in some ocular diseases**

CONFLICTS OF INTEREST: None to be declared.
The DHA food supplement was kindly provided by Brudy Lab, Barcelona, Spain. Brudy Lab had no role in the design, execution, analysis and interpretation of data, writing of the articles and publication decisions.

ABBREVIATIONS: BCVA: best-corrected visual acuity; CSMT: central subfield macular thickness; DHA; docosahexaenoic acid; DME: diabetic macular edema; DR: diabetic retinopathy; HbA1c: glycosylated haemoglobin; IL-6: interleukin-6; MDA: Malondialdehyde; OCT: optical coherence tomography; PEX glaucoma: Pseudoexfoliative glaucoma; RCT: randomized controlled trial; TAC: total antioxidant capacity.

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ABSTRACT

OBJETIVOS: El ácido docosahexaenoico (DHA) es el ácido graso dominante de los fosfolípidos retinianos y tiene un papel clave en el mantenimiento de la integridad de la retina. Se formuló la hipótesis de que la suplementación oral con un aporte de DHA altamente concentrado podría ser beneficioso para las enfermedades oculares con mecanismos fisiopatológicos susceptibles de ser influenciados por los efectos pleiotrópicos del DHA. Los estudios tenían como objetivo evaluar si un complemento alimenticio basado en un triglicérido de DHA altamente enriquecido más vitaminas y minerales no solo resultaba en beneficios clínicos, sino también en la mejora de los biomarcadores bioquímicos séricos de la actividad antioxidante y antiinflamatoria.

MÉTODOS: Entre 2014 y 2017, se realizaron cuatro Estudios Clínicos Aleatorizados (ECA) en pacientes con retinopatía diabetica no proliferativa (RDNP), edema macular diabético (EMD) y glaucoma pseudoexfoliativo (PEX). Los pacientes asignados al brazo de intervención (grupo DHA) recibieron una formulación nutracéutica (DHA 1,050 mg / día) (Brudyretina o BrudyPIO, BrudyLab, Barcelona, España) para diferentes períodos de tiempo dependiendo de cada ECA. Los pacientes se aleatorizaron consecutivamente (1: 1) a la administración de DHA o al grupo de control. Fueron evaluados la agudeza visual mejor corregida (AVMC), el espesor macular del subcampo central (EMSC), la función macular (microperimetría), HbA1c sérica, el contenido en DHA de la membrana eritrocitaria, la capacidad antioxidante total en plasma (CAT), el malondialdehído (MDA) y los niveles séricos de interleucina-6 (IL-6).

RESULTADOS: En 24 pacientes asintomáticos afectos de RD no proliferativa (12 pacientes, 24 ojos en cada grupo) tratados durante 90 días, solo hubo mejoras en la sensibilidad macular (de 25.9 ± 2.4 a 27.3 ± 2.3 dB, P = 0.03) y en el índice de integridad macular (71.2 ± 33.2 a 51.6 ± 35.9, P = 0.002) en el grupo DHA. En 47 pacientes con PEX tratados durante 6 meses, la presión intraocular (PIO) disminuyó de 15.1 ± 4.9 mmHg al inicio a 12.2 ± 2.4 mmHg (P = 0.007). En los dos ECA en pacientes afectos de EMD, los brazos del estudio incluyeron el tratamiento con 0,5 mg de ranibizumab intravítreo más la suplementación nutracéutica versus ranibizumab intravítreo solo. En 62 pacientes (grupo DHA: 29 pacientes, 34 ojos, controles: 33 pacientes, 42 ojos) tratados durante 24 meses, la diferencia entre los grupos en la disminución de EMSC fue significativa (IC 95% 7.20-97.656; P = 0.024), así como la diferencia en el porcentaje de pacientes con ganancia > 10 letras ETRDS (66.7% vs 40%, P = 0.044). En el estudio de extensión a 36 meses de este ensayo con 55 pacientes (grupo DHA: 26 pacientes, 31 ojos, controles: 29 pacientes, 38 ojos), la disminución media de EMSC fue mayor en el grupo DHA que en los controles (275 ± 50 µm vs 310 ± 97 µm) con diferencias significativas (P <0.01) en los meses 25, 30, 33 y 34. Los porcentajes de pacientes con ganancias ETRDS > 5 y > 10 letras también fueron mayores en el grupo DHA. Los estudios no hallaron diferencias entre los grupos de estudio en la AVMC. Los hallazgos bioquímicos en los grupos suplementados con DHA mostraron diferencias significativas versus los hallados en los controles no suplementados, en la elevación del contenido de DHA en la membrana eritrocitaria y en la CAT plasmática, así como en la disminución significativa de los niveles séricos de HbA1c, MDA e IL-6.

CONCLUSIONES: En los cuatro ECA oftalmológicos, al comparar los resultados obtenidos en los grupos suplementados con DHA versus en los controles no suplementados, se muestran beneficios claros y significativos, tanto en los resultados clínicos como en los parámetros bioquímicos. La consistencia de los hallazgos en todos los ECA, que han tenido duraciones de tratamiento variables, respalda la ventaja clínica de la administración de suplementos de DHA.

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