

Alimentos funcionales con omega 3 de origen marino

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Responsable del Área de Nutrición de Biosearch Life

Profesor Asociado de Ciencias y Tecnología de los Alimentos de la Universidad de Granada

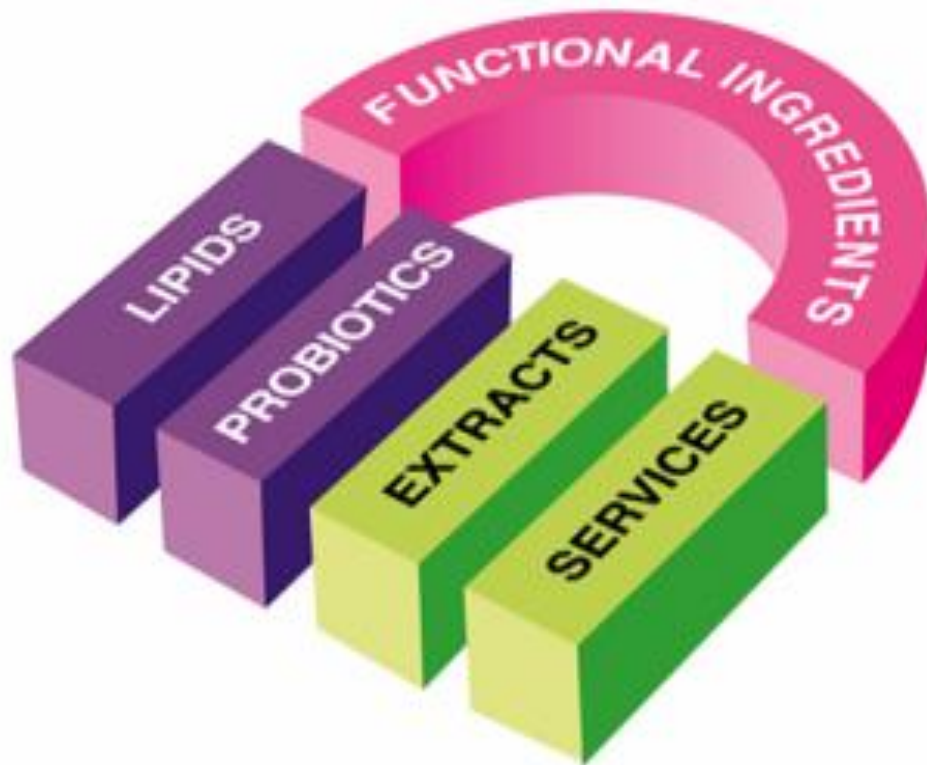
Profesor Asociado de Nutrición Humana y Dietética de la Universidad de Granada

Vigo, 8 de noviembre de 2013

INSTALACIONES

- **Granada:** Centro de I+D, Planta Piloto y Fábricas de producción de Lípidos y Probióticos (60)
- **Madrid:** Oficina de Ventas (20)
- **Cáceres:** Planta de producción de Extractos Vegetales (35)
- **Valladolid:** Planta de producción de Extractos Acuosos y Orgánicos (5)





Biosearch tiene 2 líneas principales de negocio:

- 1. I+D y Servicios de Análisis**
(principalmente para Lactalis)
- 2. Ingredientes funcionales**
(fabricación y comercialización)



“La salud de todo el cuerpo se fragua en la oficina del estómago”

*Miguel de Cervantes Saavedra en
El ingenioso hidalgo don Quijote de la Mancha*

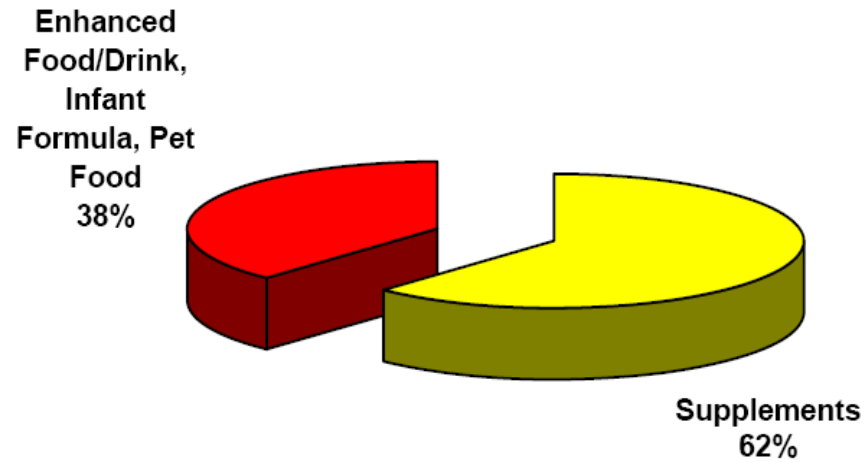
SENC, 2004



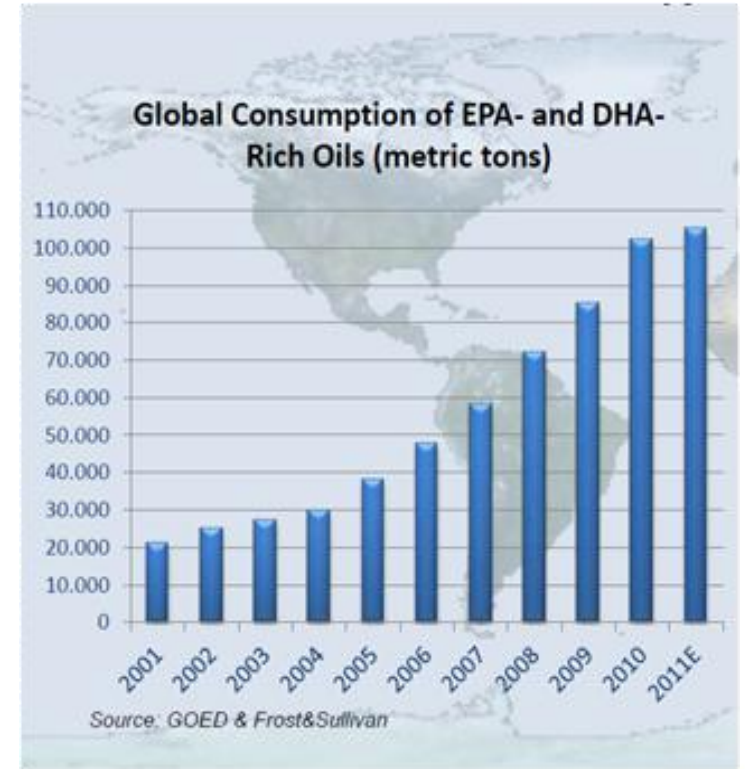
biosearch life



Omega-3 ingredients market share by sector, YE June 2007
(Volume %)



Source: Leatherhead Food International



Son alimentos



No píldoras



*Un **alimento** puede ser considerado **funcional** si se logra **demostrar** satisfactoriamente que posee un **efecto beneficioso** sobre una o varias funciones específicas en el organismo, que **mejora** el estado de salud y de bienestar, o bien que **reduce** el riesgo de una enfermedad.*

Nutrición + Efecto Saludable

Enfoques prioritarios

Las alegaciones de salud:

- Deben estar científicamente fundamentadas.
- Deben ser válidas para el alimento tal como se lo consume en la actualidad o como se prevé que habrá de consumirse en el futuro para alcanzar una dosis efectiva mínima.
- Deben comunicarse al consumidor en forma clara, comprensible y veraz.

Por tanto, existe la urgente necesidad de establecer directivas sobre la manera de:

- Respalda la fundamentación científica de los efectos como base de las alegaciones.
- Comunicar los beneficios a los consumidores y a los profesionales de la salud.

Conceptos sobre Alimentos Funcionales. ILSI, 2002.

EUROPEAN PARLIAMENT

2004



2009

Proposal for a

**REGULATION OF THE EUROPEAN
PARLIAMENT AND OF THE COUNCIL
on nutrition and health claims made on foods**

eupoly-3[®]

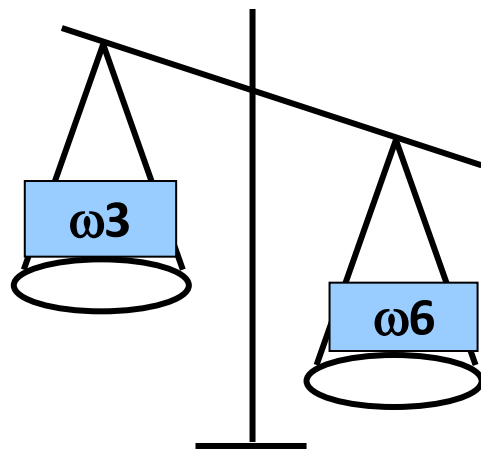
OMEGA-3 EPA+DHA

Passion for **INNOVATION**
Passion for **LIFE**

Innovation | Manufacturing | Quality

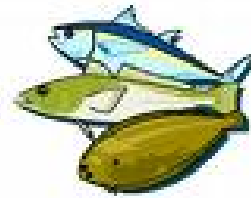


biosearch life

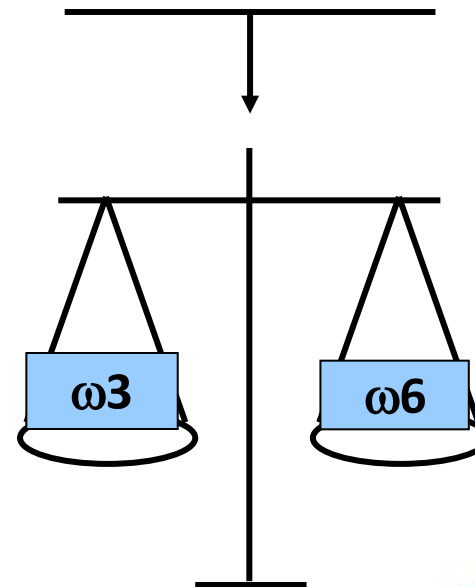


Dieta occidental

Pescado



**Alimentos
funcionales**







Health effects of oleic acid and long chain omega-3 fatty acids (EPA and DHA) enriched milks. A review of intervention studies.

Eduardo López-Huertas

Estación Experimental del Zaidín, Consejo Superior de Investigaciones Científicas (CSIC), Profesor Albareda 1, Granada 18008, Spain

4. Summary of intervention studies

A total of 9 intervention studies reporting CV effects of milks containing EPA and DHA PUFA and/or oleic acid were found using PubMed searches. Out of those, 7 were carried out with healthy subjects or groups with increased CV risk factors, and two studies with CVD patients. In all the studies, milk fat was substituted by EPA and DHA PUFA from refined fish oils with or without other vegetable oils (mainly olive oil and high-oleic sunflower oil). Study design, intervention groups, daily intake of nutrients from the dairy...

- [Romeo J, Wärnberg J, García-Mármol E, Rodríguez-Rodríguez M, Díaz LE, Gómez-Martínez S, Cueto B, López-Huertas E, Cepero M, Fonollá J, Marcos A.](#) Daily consumption of milk enriched with fish oil, oleic acid, minerals and vitamins reduces cell adhesion molecules in healthy children. *Nutr Metab Cardiovasc Dis.* 2011 Feb;21(2):113-20.

- [Martín-Bautista E, Muñoz-Torres M, Fonollá J, Quesada M, Poyatos A, López-Huertas E.](#) Improvement of bone formation biomarkers after 1-year consumption with milk fortified with eicosapentaenoic acid, docosahexaenoic acid, oleic acid, and selected vitamins. *Nutr Res.* 2010; 30 (5) :320-6.

- [Fonollá J, López-Huertas E, Machado FJ, Molina D, Álvarez I, Mármol E, Navas M, Palacín E, García-Valls MJ, Remón B, Boza JJ, Marti JL.](#) Milk enriched with “healthy fatty acids” improves cardiovascular risk markers and nutritional status in human volunteers. *Nutrition.* 2009; 25 (4): 408-14.

- [Carrero JJ, Fonollá J, Marti JL, Jiménez J, Boza JJ, López-Huertas E.](#) Intake of fish oil, oleic acid, folic acid, and vitamins B-6 and E for 1 year decreases plasma C-reactive protein and reduces coronary heart disease risk factors in male patients in a cardiac rehabilitation program. *J Nutr.* 2007; 137 (2): 384-90.

- [Carrero JJ, López-Huertas E, Salmerón LM, Baró L, Ros E.](#) Daily supplementation with (n-3) PUFAs, oleic acid, folic acid, and vitamins B-6 and E increases pain-free walking distance and improves risk factors in men with peripheral vascular disease. *J Nutr.* 2005;135 (6): 1393-9.

- [Carrero JJ, Baró L, Fonollá J, González-Santiago M, Martínez-Férez A, Castillo R, Jiménez J, Boza JJ, López-Huertas E.](#) Cardiovascular effects of milk enriched with omega-3 polyunsaturated fatty acids, oleic acid, folic acid, and vitamins E and B6 in volunteers with mild hyperlipidemia. *Nutrition.* 2004; 20 (6): 521-7.

- [Baró L, Fonollá J, Peña JL, Martínez-Férez A, Lucena A, Jiménez J, Boza JJ, López-Huertas E.](#) n-3 Fatty acids plus oleic acid and vitamin supplemented milk consumption reduces total and LDL cholesterol, homocysteine and levels of endothelial adhesion molecules in healthy humans. *Clin Nutr.* 2003; 22 (2): 175-82.



Nutrition 25 (2009) 408–414

NUTRITION[®]

www.nutritionjml.com

Applied nutritional investigation

Milk enriched with “healthy fatty acids” improves cardiovascular risk markers and nutritional status in human volunteers

Juristo Fonollá, Ph.D.^{a,*}, Eduardo López-Huertas, Ph.D.^a, Francisco J. Machado, Ph.D.^b,
Diego Molina, M.D.^c, Ignacio Álvarez, M.D.^d, Enrique Mármol, M.D.^e,
Mónica Navas, M.D.^f, Eduardo Palacín, M.D.^g, María J. García-Valls, Ph.D.^h,
Begoña Remón, Ph.D.^c, Julio J. Boza, Ph.D.^a, and José L. Marti, Ph.D.ⁱ

^a *Nutrition and Health Department, Puleva Biotech S.A., Granada, Spain*

^b *Medical Service of Granada University, Granada, Spain*

^c *Medical Service of El Corte Inglés-Granada, Granada, Spain*

^d *Medical Service of Alcampo-Granada, Granada, Spain*

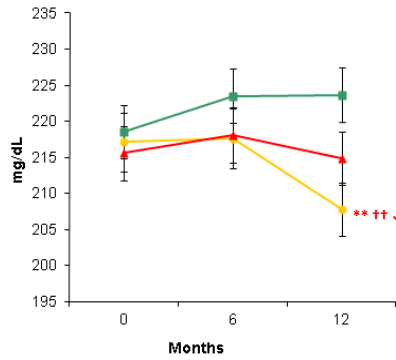
^e *Medical Service of Hipercor-Granada, Granada, Spain*

^f *Medical Service of Puleva Food S.A., Granada, Spain*

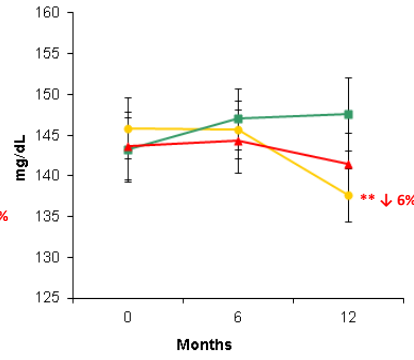
^g *Medical Service of INAGRA S.A., Granada, Spain*

^h *Medical Service of Cervezas Alhambra S.A., Granada, Spain*

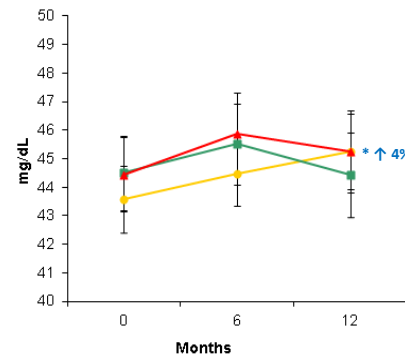
ⁱ *Department of Cardiology, University Hospital “San Cecilio”, Granada, Spain*



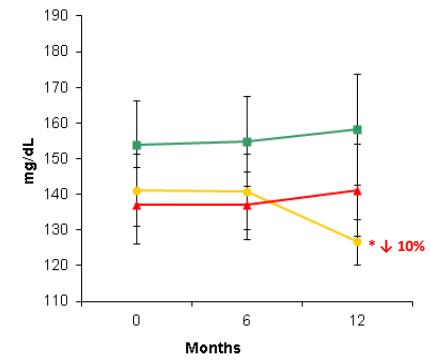
Total cholesterol



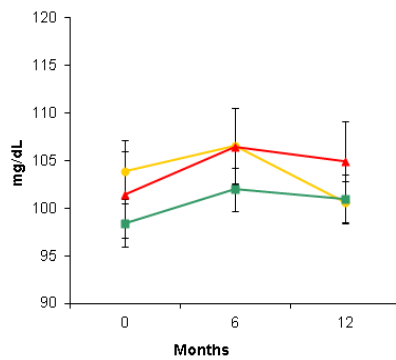
LDL-cholesterol



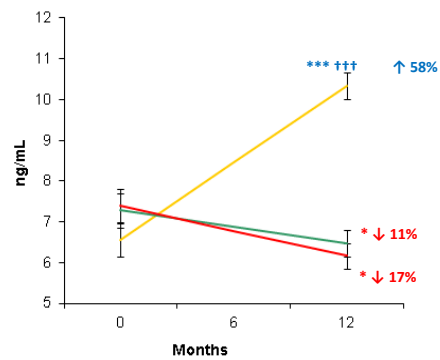
HDL-cholesterol



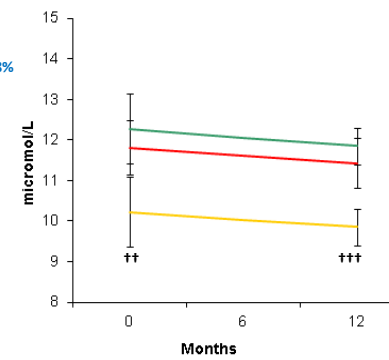
Triglycerides



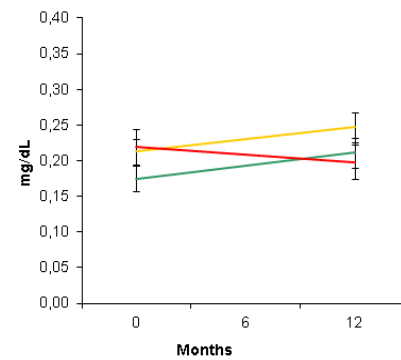
Serum glucose



Serum folate



Homocysteine

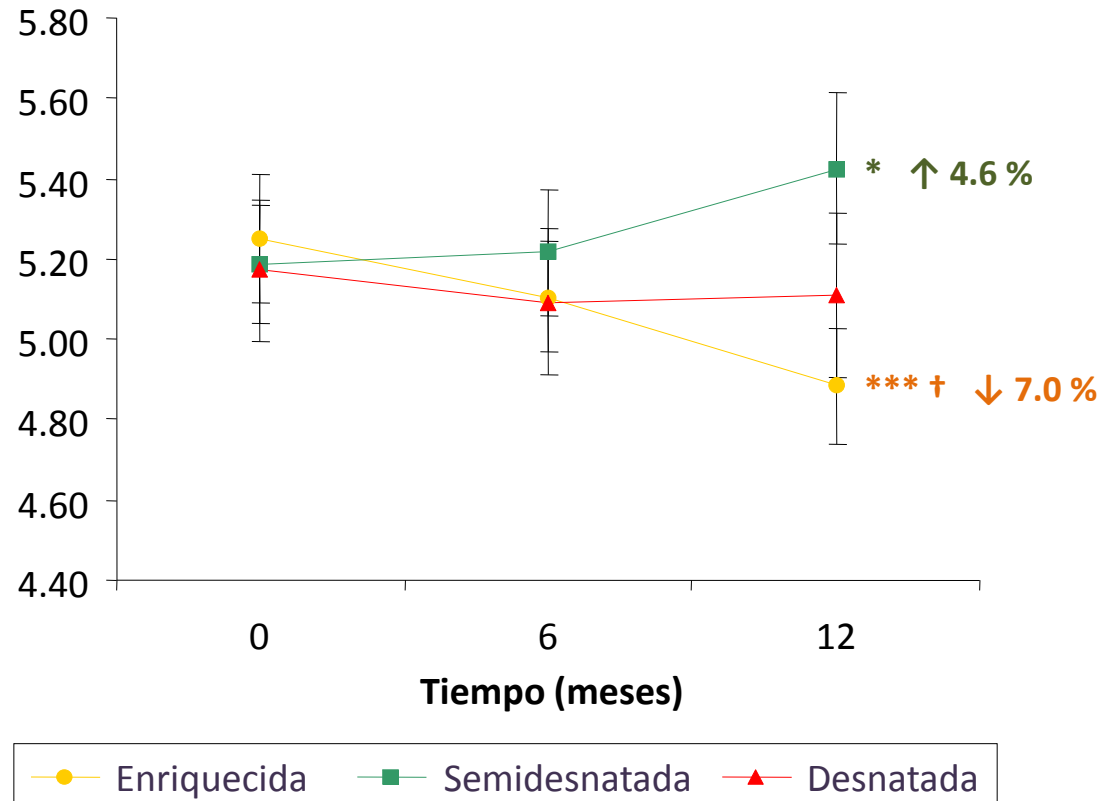


C-reactive protein

— Enriched — Semi-skimmed — Skimmed

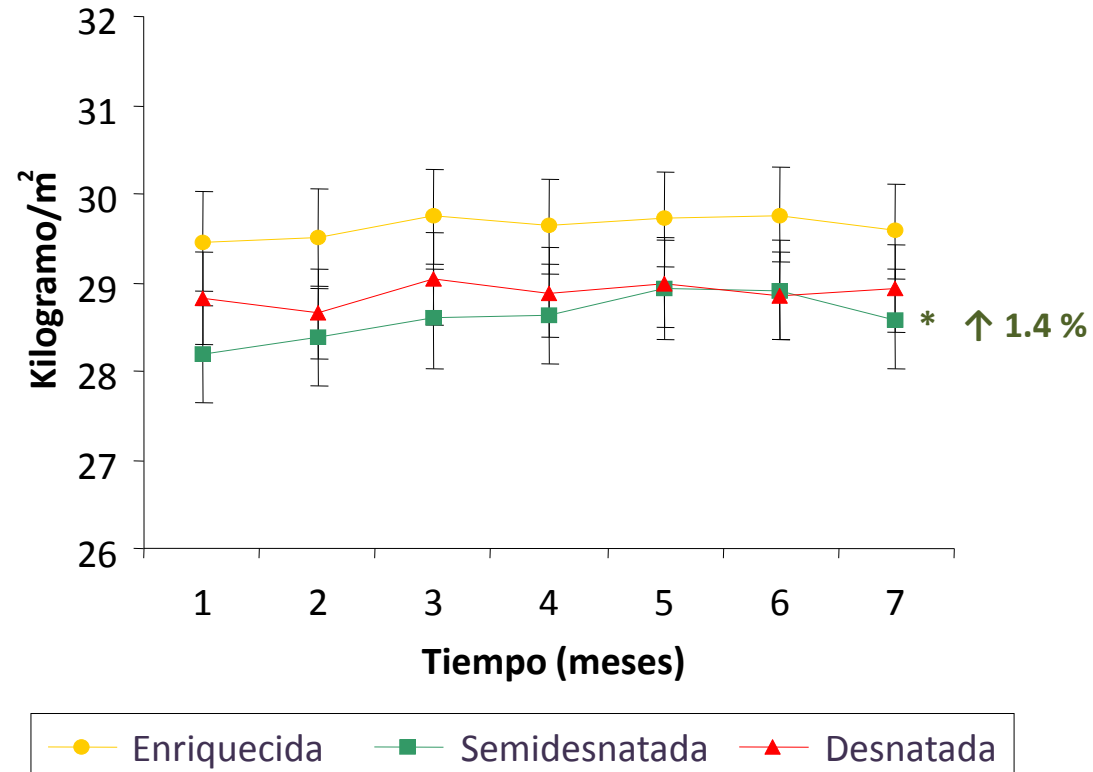
* $p > 0.05$, ** $p > 0.01$, *** $p > 0.001$ vs T0; † $p > 0.05$, †† $p > 0.01$, ††† $p > 0.001$ vs semi-skimmed; $p > 0.05$, $p > 0.01$, $p > 0.001$ vs skimmed

Colesterol total/HDL

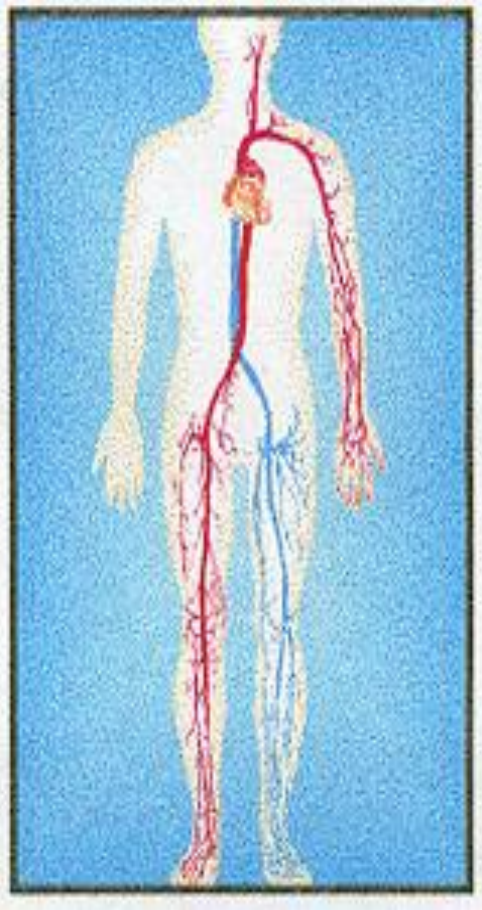


* $p > 0.05$, ** $p > 0.01$, *** $p > 0.001$ vs T0; † $p > 0.05$, †† $p > 0.01$, ††† $p > 0.001$ vs semidesnatada; $p > 0.05$, $p > 0.01$, $p > 0.001$ vs desnatada

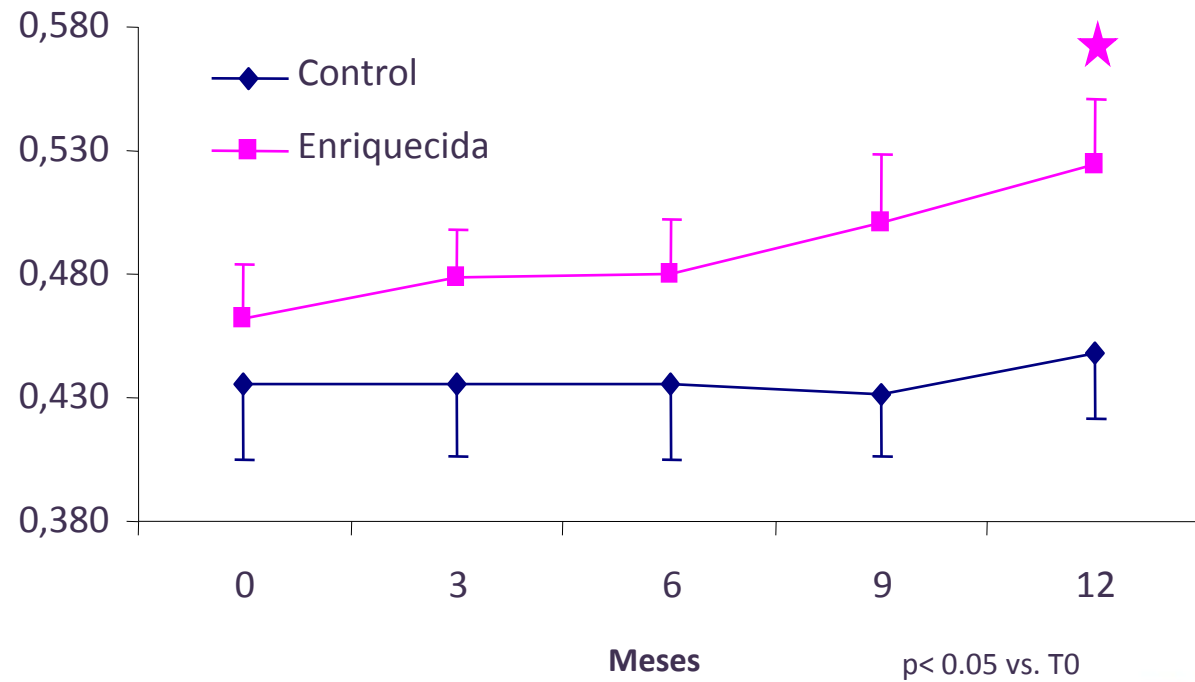
Índice de Masa Corporal



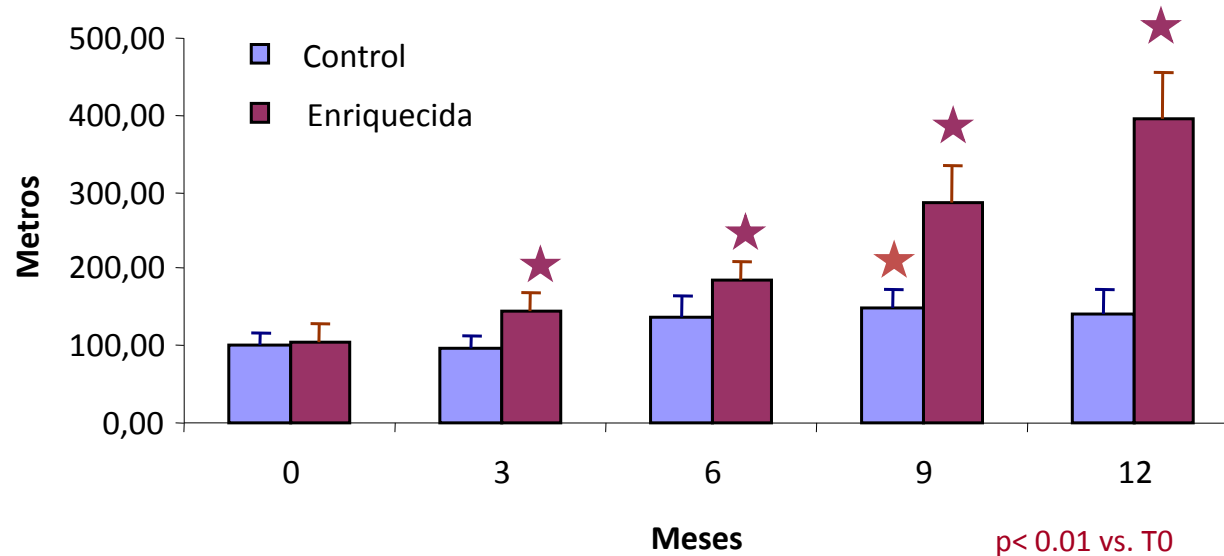
* $p > 0.05$, ** $p > 0.01$, *** $p > 0.001$ vs T0; † $p > 0.05$, †† $p > 0.01$, ††† $p > 0.001$ vs semidesnatada; $p > 0.05$, $p > 0.01$, $p > 0.001$ vs desnatada



Índice ABI




Tapiz rodante



p < 0.01 vs. T0

Tiempo (meses)	0	3	6	9	12
Enriquecida	105 ± 22	146 ± 22	184 ± 26	288 ± 46	394 ± 61
Control	99 ± 17	97 ± 16	137 ± 27	148 ± 26	143 ± 28

 The Journal of Nutrition
Nutrient Requirements and Optimal Nutrition

Intake of Fish Oil, Oleic Acid, Folic Acid, and Vitamins B-6 and E for 1 Year Decreases Plasma C-Reactive Protein and Reduces Coronary Heart Disease Risk Factors in Male Patients in a Cardiac Rehabilitation Program¹

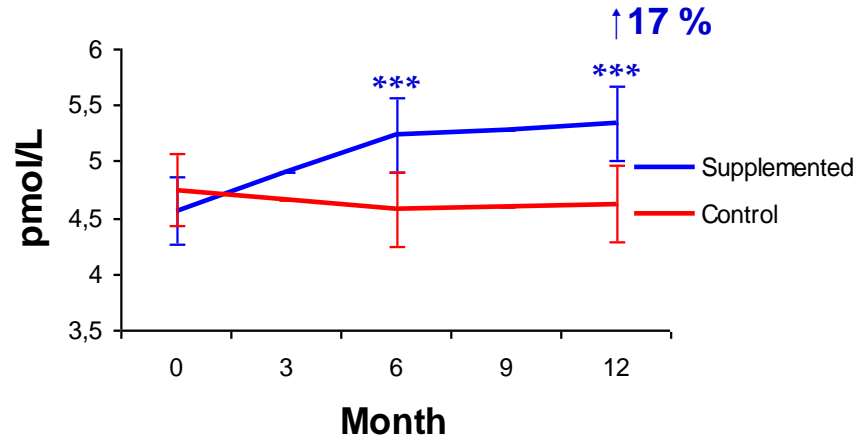
Juan Jesús Carrero,² Juristo Fonollá,³ José Luis Martí,⁴ Jesús Jiménez,³ Julio J. Boza,³ and Eduardo López-Huertas^{3*}

²Department of Biochemistry and Molecular Biology, University of Granada, Spain; ³Department of Human Nutrition, Puleva Biotech, Granada, Spain; and ⁴Service of Cardiology, University "San Cecilio" Hospital, Granada, Spain

Abstract

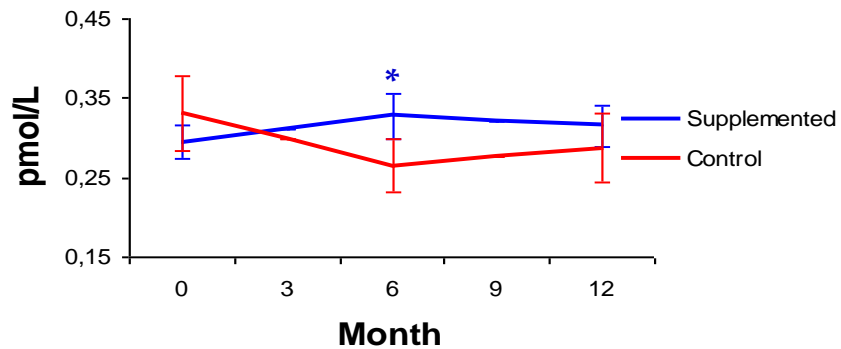
Certain nutrients have been shown to be effective in preventing coronary heart disease. We hypothesized that a daily intake of low amounts of a number of these nutrients would exert beneficial effects on risk factors and clinical variables in patients that suffered from myocardial infarction (MI) and were following a cardiac rehabilitation program. Forty male MI patients were randomly allocated into 2 groups. The supplemented group consumed 500 mL/d of a fortified dairy product containing eicosapentaenoic acid, docosahexaenoic acid, oleic acid, folic acid, and vitamins A, B-6, D, and E. The control group consumed 500 mL/d of semi-skimmed milk with added vitamins A and D. The patients received supervised exercise training, lifestyle and dietary recommendations, and they were instructed to consume the products in addition to their regular diet. Blood extractions and clinical examinations were performed after 0, 3, 6, 9, and 12 mo. Plasma concentrations of eicosapentaenoic acid, docosahexaenoic acid, oleic acid, folic acid, vitamin B-6, and vitamin E increased after supplementation ($P < 0.05$). Plasma total and LDL-cholesterol, apolipoprotein B, and high-sensitivity C-reactive protein concentrations decreased in the supplemented group ($P < 0.05$), and plasma total homocysteine decreased in both groups. There were no changes in heart rate, blood pressure, or cardiac electrocardiographic parameters in either group. Therapeutic lifestyle changes, effected through a CR program comprising regular exercise and the intake of a combination of dietary nutrients, reduced a variety of risk factors in MI patients, which supports the rationale for nutritional programs in the secondary prevention of coronary heart disease. *J. Nutr.* 137: 384–390, 2007.

OPG



*** $p < 0,001$ vs T0

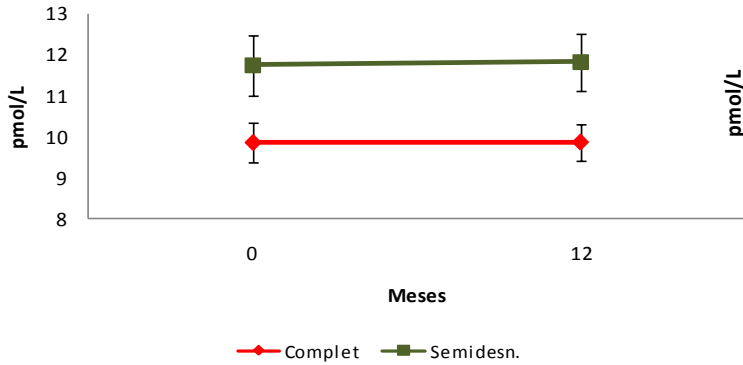
RANKL



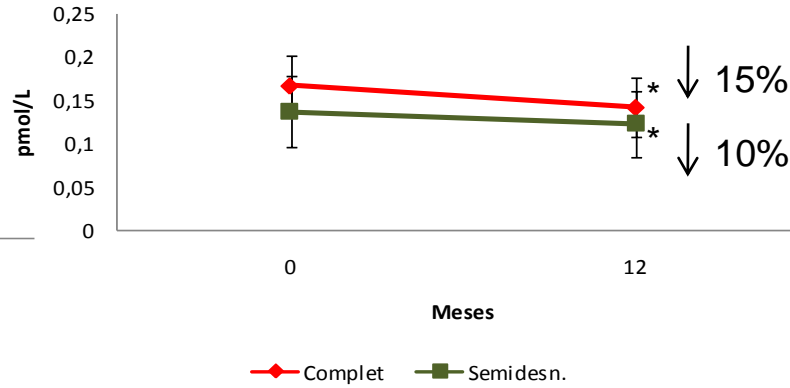
* $p < 0,05$ vs T0

Voluntarios sanos jóvenes

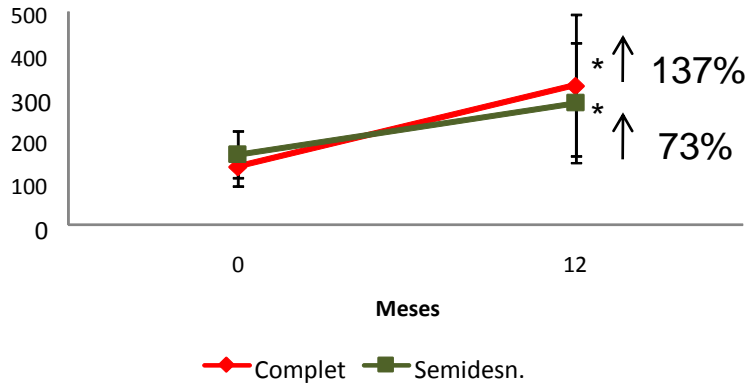
Osteoprotegerina



RANKL



OPG / RANKL



Voluntarias perimenopáusicas

*p > 0.05, ** p > 0.01, *** p > 0.001 vs T0



Denosumab for Prevention of Fractures in Postmenopausal Women with Osteoporosis

Steven R. Cummings, M.D., Javier San Martin, M.D., Michael R. McClung, M.D., Ethel S. Siris, M.D., Richard Eastell, M.D., Ian R. Reid, M.D., Pierre Delmas, M.D., Ph.D., Holly B. Zoog, Ph.D., Matt Austin, M.S., Andrea Wang, M.A., Stepan Kutilek, M.D., Silvano Adami, M.D., Ph.D., Jose Zanchetta, M.D., Cesar Libanati, M.D., Suresh Siddhanti, Ph.D., Claus Christiansen, M.D., for the FREEDOM Trial

ABSTRACT

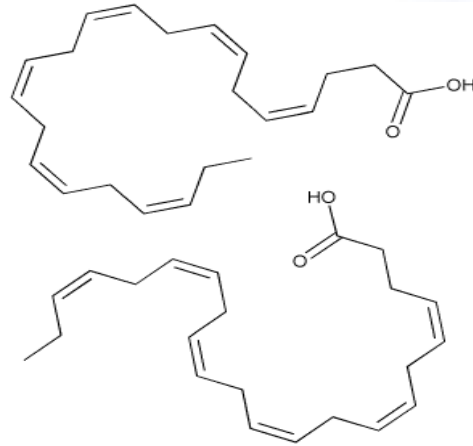
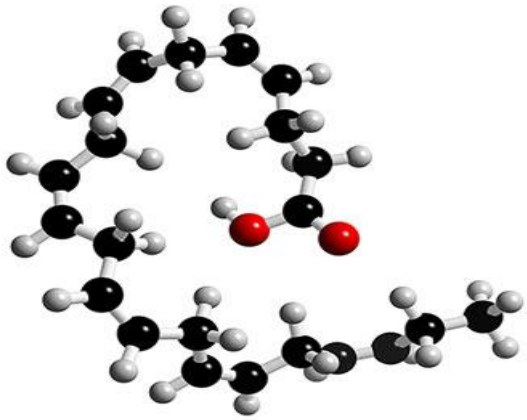
Background Denosumab is a **fully human monoclonal antibody to the receptor activator of nuclear factor- κ B ligand (RANKL) that blocks its binding to RANK, inhibiting the development and activity of osteoclasts, decreasing bone resorption, and increasing bone density.** Given its unique actions, denosumab may be useful in the treatment of osteoporosis.

Methods We enrolled 7868 women between the ages of 60 and 90 years who had a bone mineral density T score of less than -2.5 but not less than -4.0 at the lumbar spine or total hip. Subjects were randomly assigned to receive either 60 mg of denosumab or placebo subcutaneously every 6 months for 36 months. The primary end point was new vertebral fracture. Secondary end points included nonvertebral and hip fractures.

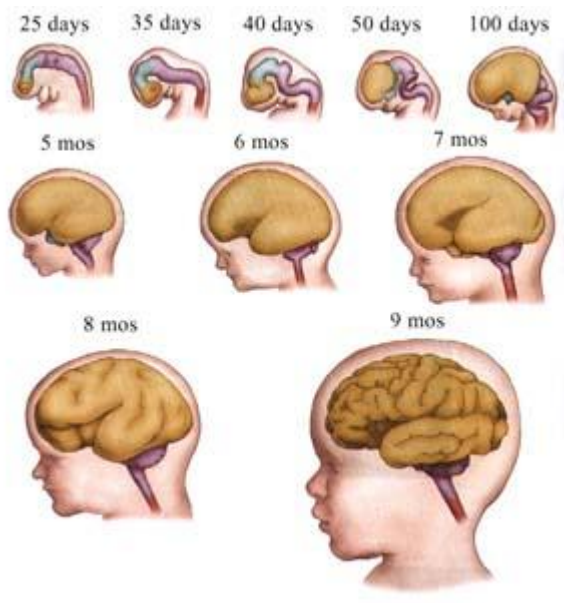
Results As compared with placebo, denosumab reduced the risk of new radiographic vertebral fracture, with a cumulative incidence of 2.3% in the denosumab group, versus 7.2% in the placebo group (risk ratio, 0.32; 95% confidence interval [CI], 0.26 to 0.41; $P < 0.001$) — a relative decrease of 68%. Denosumab reduced the risk of hip fracture, with a cumulative incidence of 0.7% in the denosumab group, versus 1.2% in the placebo group (hazard ratio, 0.60; 95% CI, 0.37 to 0.97; $P = 0.04$) — a relative decrease of 40%. Denosumab also reduced the risk of nonvertebral fracture, with a cumulative incidence of 6.5% in the denosumab group, versus 8.0% in the placebo group (hazard ratio, 0.80; 95% CI, 0.67 to 0.95; $P = 0.01$) — a relative decrease of 20%. There was no increase in the risk of cancer, infection, cardiovascular disease, delayed fracture healing, or hypocalcemia, and there were no cases of osteonecrosis of the jaw and no adverse reactions to the injection of denosumab.

Conclusions Denosumab given subcutaneously twice yearly for 36 months was **associated with a reduction in the risk of vertebral, nonvertebral, and hip fractures in women with osteoporosis.** (ClinicalTrials.gov number, NCT00089791 [ClinicalTrials.gov].) *N Engl J Med.* 2009 Aug 20;361(8):756-65.





DocosaHexaenoic Acid 22:6 ω3



Niños sanos (8 a 12 años)

	<u>Leche entera</u>		<u>Leche enriquecida</u>	
	<u>0 meses</u>	<u>5 meses</u>	<u>0 meses</u>	<u>5 meses</u>
Dígitos	7.92 0.33	8.78 0.37	8.58 0.43	10.02 0.42 ⁺
Letras y Números-Aritmética	7.88 0.51	7.57 0.41	8.29 0.44	8.53 0.48
Memoria de Trabajo	86.90 228	88.45 2.05	89.81 2.38	94.37 2.34
Claves	8.44 0.36	9.73 0.48	9.37 0.42	9.87 0.48
Búsqueda de símbolos-animales	9.30 0.34	9.73 0.37	9.69 0.44	9.92 0.45
Velocidad de procesamiento	95.28 1.70	99.83 1.96	98.69 2.05	100.52 2.23
Velocidad lectora	224.15 17.24	197.11 14.62	243.80 16.38	197.12 12.07⁺
Comprensión lectora	7.60 0.55	9.06 0.40⁺	7.82 0.60	9.31 0.39⁺
Conducta Padres	15.31 0.89	15.58 1.11	13.73 0.82	13.47 0.83
Conducta Profesores	14.71 1.92	16.57 1.44	15.13 1.21	14.86 1.63

n = 102

Media error estándar.

+ Diferencias significativas entre el punto 0 y a los 5 meses para cada tipo de leche (p<0,05)

RESEARCH ARTICLE

Improved Working Memory but No Effect on Striatal Vesicular Monoamine Transporter Type 2 after Omega-3 Polyunsaturated Fatty Acid Supplementation

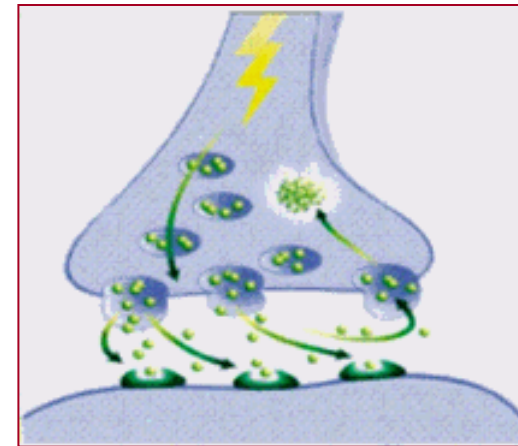
Rajesh Narendran^{1,2*}, William G. Frankle^{1,2}, Neale S. Mason¹,

Matthew F. Muldoon³, Bitu Moghaddam⁴

¹ Department of Radiology, University of Pittsburgh, Pittsburgh, Pennsylvania, United States of America, ² Department of Psychiatry, University of Pittsburgh, Pittsburgh, Pennsylvania, United States of America, ³ Department of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania, United States of America, ⁴ Department of Neuroscience, University of Pittsburgh, Pittsburgh, Pennsylvania, United States of America

Abstract

Studies in rodents indicate that diets deficient in omega-3 polyunsaturated fatty acids (n-3 PUFA) lower dopamine neurotransmission as measured by striatal vesicular monoamine transporter type 2 (VMAT2) density and amphetamine-induced dopamine release. This suggests that dietary supplementation with fish oil might increase VMAT2 availability, enhance dopamine storage and release, and improve dopamine-dependent cognitive functions such as working memory. To investigate this mechanism in humans, positron emission tomography (PET) was used to measure VMAT2 availability pre- and post-supplementation of n-3 PUFA in healthy individuals. Healthy young adult subjects were scanned with PET using [¹¹C]-(+)- α -dihydrotrabenzine (DTBZ) before and after six months of n-3 PUFA supplementation (Lovaza, 2 g/day containing docosahexaenoic acid, DHA 750 mg/d and eicosapentaenoic acid, EPA 930 mg/d). In addition, subjects underwent a working memory task (n-back) and red blood cell membrane (RBC) fatty acid composition analysis pre- and post-supplementation. RBC analysis showed a significant increase in both DHA and EPA post-supplementation. In contrast, no significant change in [¹¹C]DTBZ binding potential (BP_{ND}) in striatum and its subdivisions were observed after supplementation with n-3 PUFA. No correlation was evident between n-3 PUFA induced change in RBC DHA or EPA levels and change in [¹¹C]DTBZ BP_{ND} in striatal subdivisions. However, pre-supplementation RBC DHA levels was predictive of baseline performance (i.e., adjusted hit rate, AHR on 3-back) on the n-back task ($y = 0.19 + 0.07x$, $r^2 = 0.55$, $p = 0.009$). In addition, subjects AHR performance improved on 3-back post-supplementation (pre 0.65 ± 0.27 , post 0.80 ± 0.15 , $p = 0.04$). The correlation between n-back performance, and DHA levels are consistent with reports in which higher DHA levels is related to improved cognitive performance. However, the lack of change in [¹¹C]DBTZ BP_{ND} indicates that striatal VMAT2 regulation is not the mechanism of action by which n-3 PUFA improves cognitive performance.



post 0.80 ± 0.15 , $p = 0.04$). The correlation between n-back performance, and DHA levels are consistent with reports in which higher DHA levels is related to improved cognitive performance. However, the lack of change in [¹¹C]DBTZ BP_{ND} indicates that striatal VMAT2 regulation is not the mechanism of action by which n-3 PUFA improves cognitive performance.

Citation: Narendran R, Frankle WG, Mason NS, Muldoon MF, Moghaddam B (2012) Improved Working Memory but No Effect on Striatal Vesicular Monoamine Transporter Type 2 after Omega-3 Polyunsaturated Fatty Acid Supplementation. PLoS ONE 7(10): e46832. doi:10.1371/journal.pone.0046832

Docosahexaenoic Acid for Reading, Cognition and Behavior in Children Aged 7–9 Years: A Randomized, Controlled Trial (The DOLAB Study)

Alexandra J. Richardson*, Jennifer R. Burton, Richard P. Sewell, Thees F. Spreckelsen, Paul Montgomery

Centre for Evidence-Based Intervention, University of Oxford, Oxford, United Kingdom

Abstract

Background: Omega-3 fatty acids are dietary essentials, and the current low intakes in most modern developed countries are believed to contribute to a wide variety of physical and mental health problems. Evidence from clinical trials indicates that dietary supplementation with long-chain omega-3 may improve child behavior and learning, although most previous trials have involved children with neurodevelopmental disorders such as attention-deficit/hyperactivity disorder (ADHD) or developmental coordination disorder (DCD). Here we investigated whether such benefits might extend to the general child population.

Objectives: To determine the effects of dietary supplementation with the long-chain omega-3 docosahexaenoic acid (DHA) on the reading, working memory, and behavior of healthy schoolchildren.

Design: Parallel group, fixed-dose, randomized, double-blind, placebo-controlled trial (RCT).

Setting: Mainstream primary schools in Oxfordshire, UK (n=74).

Participants: Healthy children aged 7–9 years initially underperforming in reading ($\leq 33^{\text{rd}}$ centile). 1376 invited, 362 met study criteria.

Intervention: 600 mg/day DHA (from algal oil), or taste/color matched corn/soybean oil placebo.

Main Outcome Measures: Age-standardized measures of reading, working memory, and parent- and teacher-rated behavior.

Results: ITT analyses showed no effect of DHA on reading in the full sample, but significant effects in the pre-planned subgroup of 224 children whose initial reading performance was $\leq 20^{\text{th}}$ centile (the target population in our original study design). Parent-rated behavior problems (ADHD-type symptoms) were significantly reduced by active treatment, but little or no effects were seen for either teacher-rated behaviour or working memory.

Conclusions: DHA supplementation appears to offer a safe and effective way to improve reading and behavior in healthy but underperforming children from mainstream schools. Replication studies are clearly warranted, as such children are known to be at risk of low educational and occupational outcomes in later life.

Trial Registration: ClinicalTrials.gov NCT01066182 and Controlled-Trials.com ISRCTN99771026

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