

.....

**Omega-6/Omega-3 Essential Fatty Acid Ratio:
The Scientific Evidence**

.....

World Review of Nutrition and Dietetics

Vol. 92

Series Editor

Artemis P. Simopoulos

The Center for Genetics, Nutrition and Health, Washington, D.C., USA

Advisory Board

Regina C. Casper USA

Cuiqing Chang China

Claudio Galli Italy

Uri Goldbourt Israel

C. Gopalan India

Tomohito Hamazaki Japan

Michel de Lorgeril France

Victor A. Rogozkin Russia

Leonard Storlien Sweden

Ricardo Uauy-Dagach Chile

Antonio Velazquez Mexico

Mark L. Wahlqvist Australia

Paul Walter Switzerland

Bruce A. Watkins USA

KARGER

.....

Omega-6/Omega-3 Essential Fatty Acid Ratio: The Scientific Evidence

Volume Editors

Artemis P. Simopoulos

The Center for Genetics, Nutrition and Health, Washington, D.C., USA

Leslie G. Cleland

Royal Adelaide Hospital, Adelaide, S.A., Australia

24 figures and 37 tables, 2003

The logo for Karger, consisting of the word "KARGER" in a bold, sans-serif font. The letters are white and set against a dark grey rectangular background. The letter "A" has a small triangle above it.

KARGER

Basel · Freiburg · Paris · London · New York ·
Bangalore · Bangkok · Singapore · Tokyo · Sydney

.....
Artemis P. Simopoulos

The Center for Genetics,
Nutrition and Health
Washington, D.C. (USA)

Leslie G. Cleland

Rheumatology Unit
Royal Adelaide Hospital
Adelaide, S.A. (Australia)

Library of Congress Cataloging-in-Publication Data

Omega-6/omega-3 essential fatty acid ratio : the scientific evidence / volume editors,
Artemis P. Simopoulos, Leslie G. Cleland.

p. ; cm. – (World review of nutrition and dietetics, ISSN 0084-2230 ; v. 92)

Includes bibliographical references and index.

ISBN 3-8055-7640-4 (alk. paper)

1. Omega-6/omega-3 fatty acid ratio. 2. Essential fatty acids in human nutrition I.
Simopoulos, Artemis P., 1933- II. Cleland, Leslie G. III. Series.

[DNLM: 1. Fatty Acids, Essential-metabolism. 2. Fatty Acids. Omega-3-metabolism.

3. Linoleic Acids-metabolism. QU 90 O552 2003]

QP752.E84O46 2003

613.2'84-dc22

2003058871

Bibliographic Indices. This publication is listed in bibliographic services, including Current Contents® and Index Medians.

Drug Dosage. The authors and the publisher have exerted every effort to ensure that drug selection and dosage set forth in this text are in accord with current recommendations and practice at the time of publication. However, in view of ongoing research, changes in government regulations, and the constant flow of information relating to drug therapy and drug reactions, the reader is urged to check the package insert for each drug for any change in indications and dosage and for added warnings and precautions. This is particularly important when the recommended agent is a new and/or infrequently employed drug.

All rights reserved. No part of this publication may be translated into other languages, reproduced or utilized in any form or by any means electronic or mechanical, including photocopying, recording, microcopying, or by any information storage and retrieval system, without permission in writing from the publisher.

© Copyright 2003 by S. Karger AG, P.O. Box, CH-4009 Basel (Switzerland)

www.karger.com

Printed in Switzerland on acid-free paper by Reinhardt Druck, Basel

ISSN 0084-2230

ISBN 3-8055-7640-4

.....

Contents

VII Preface

1 Importance of the Ratio of Omega-6/Omega-3 Essential Fatty Acids: Evolutionary Aspects

Simopoulos, A.P. (Washington, D.C.)

23 The Importance of Omega-6/Omega-3 Fatty Acid Ratio in Cell Function.

The Gene Transfer of Omega-3 Fatty Acid Desaturase

Kang, J.X. (Boston, Mass.)

37 Omega-6/Omega-3 Ratio and Brain-Related Functions

Yehuda, S. (Ramat Gan)

57 Dietary Prevention of Coronary Heart Disease: Focus on Omega-6/Omega-3 Essential Fatty Acid Balance

de Lorgeril, M.; Salen, P. (Grenoble)

74 Effects of an Indo-Mediterranean Diet on the Omega-6/Omega-3 Ratio in Patients at High Risk of Coronary Artery Disease: The Indian Paradox

Pella, D. (Kosice); Dubnov, G. (Jerusalem); Singh, R.B. (Moradabad);

Sharma, R. (New York, N.Y.); Berry, E.M.; Manor, O. (Jerusalem)

81 Omega-6/Omega-3 Fatty Acid Ratio: The Israeli Paradox

Dubnov, G.; Berry, E.M. (Jerusalem)

92 Linoleic Acid to Alpha-Linolenic Acid Ratio. From Clinical Trials to Inflammatory Markers of Coronary Artery Disease

Zampelas, A.; Paschos, G. (Athens); Rallidis, L. (Piraeus); Yiannakouris, N. (Athens)

- 109 The Japan Society for Lipid Nutrition Recommends to Reduce the Intake of Linoleic Acid.** A Review and Critique of the Scientific Evidence
Hamazaki, T. (Toyama); Okuyama, H. (Nagoya)
- 133 Omega-6/Omega-3 Polyunsaturated Fatty Acid Ratio and Cancer**
Chajès, V.; Bougnoux, P. (Tours)
- 152 Omega-6/Omega-3 Fatty Acids and Arthritis**
Cleland, L.G.; James, M.J.; Proudman, S.M. (Adelaide, SA)
- 169 Author Index**
- 170 Subject Index**

.....

Preface

Several sources of information suggest that human beings evolved on a diet with a ratio of omega-6 to omega-3 essential fatty acids of ~ 1 whereas in Western diets the ratio is 15/1–16.7/1, and in India ratios in urban areas range between 38/1 and 50/1 whereas in rural areas the ratios range from 5/1 to 6.1/1. Western diets are considered ‘relatively deficient’ in omega-3 fatty acids, because they contain excessive amounts of omega-6 fatty acids compared with the diet on which human beings evolved and their genetic patterns were established. Excessive amounts of omega-6 polyunsaturated fatty acids (PUFA) and a very high omega-6/omega-3 ratio, as is found in today’s Western and Indian diets, promote the pathogenesis of many diseases, including cardiovascular disease, cancer, and inflammatory and autoimmune diseases, whereas increased levels of omega-3 PUFA (a lower omega-6/omega-3 ratio), exert suppressive effects. In the secondary prevention of cardiovascular disease, a ratio of omega-6/omega-3 of 4/1 was associated with a 70% decrease in total mortality. The same ratio of omega-6/omega-3 of 4/1 appears to be the optimal ratio for brain-mediated functions. A ratio of omega-6/omega-3 of 2.5/1 reduced rectal cell proliferation in patients with colorectal cancer, whereas a ratio of 4/1 with the same amount of omega-3 PUFA had no effect. The lower omega-6/omega-3 ratio in women with breast cancer was associated with decreased risk. A ratio of omega-6/omega-3 of 2–3/1 suppressed inflammation in patients with rheumatoid arthritis, and a ratio of 5/1 had a beneficial effect on patients with asthma, whereas a ratio of 10/1 had adverse consequences.

These studies indicate that the optimal ratio may vary with the disease or condition under consideration. This is consistent with the fact that chronic diseases are multigenic and multifactorial. Furthermore, genetic polymorphisms interact with the nutritional environment to define the phenotype. Therefore, it is quite possible that the therapeutic dose of omega-3 fatty acids will depend on the degree of severity of disease resulting from the genetic predisposition. A lower ratio of omega-6/omega-3 fatty acids is more desirable in reducing the risk of many of the chronic diseases of high prevalence in Western societies, as well as in the developing countries.

This volume on *Omega-6/Omega-3 Essential Fatty Acid Ratio: The Scientific Evidence* in the series *World Review of Nutrition and Dietetics* considers the scientific evidence of the importance of the omega-6/omega-3 essential fatty acid ratio in the prevention and management of a number of chronic diseases. Because the first person to consider the ratio was Ralph Holman, who also suggested the omega (ω) nomenclature, the 'omega (ω)' nomenclature was selected for this volume instead of the 'n-' nomenclature.

The volume begins with the paper on the 'Importance of the Ratio of Omega-6/Omega-3 Essential Fatty Acids: Evolutionary Aspects' by Artemis P. Simopoulos. The author considers the evidence and the factors that led to the excessive increases in the omega-6/omega-3 ratio. During evolution, the ratio of 18:2 ω 6 (linoleic acid, LA) to 18:3 ω 3 (α -linolenic acid, ALA) was 0.70/1 and the longer chain omega-6/omega-3 ratio was 1.79/1, just under 2. Therefore, from the evolutionary standpoint, the total omega-6/omega-3 ratio has a range of 1-2/1. Two countries' diets come close to the ratio of evolution: the traditional diet of Crete (Greece) and the traditional diet of Japan. In both countries, the rate of death due to cardiovascular disease is the lowest. It is now recognized that there is a need to return the omega-3 fatty acids into the food supply, both for normal growth and development and for the prevention and management of chronic diseases. In doing so, caution must be exercised to return the omega-3 fatty acids in type and amounts consistent with data obtained from: (1) studies on the evolutionary aspects of diet; (2) studies at the molecular level, and (3) data obtained from clinical intervention trials.

The second paper 'The Importance of Omega-6/Omega-3 Fatty Acid Ratio in Cell Function: The Gene Transfer of Omega-3 Fatty Acid Desaturase' by Jing X. Kang, is a confirmatory study at the molecular level of the omega-6/omega-3 ratio that supports the knowledge obtained from studies on the evolutionary aspects. In this paper Dr. Kang shows how the insertion of the missing delta-3 desaturase in cardiac myocytes and cancer cells in culture, leads to the production of 18:3 ω 3 from 18:2 ω 6, and eicosapentaenoic acid (EPA) formation from arachidonic acid (AA) proceeds until the ratio between omega-6 and omega-3 equals 1/1.

The next paper 'Omega-6/Omega-3 Ratio and Brain-Related Functions' by Shlomo Yehuda is a very extensive review of the evidence from experimental studies carried out in humans and rodents. Dr. Yehuda begins by discussing the evidence for the importance of the ratio and the relationship of essential fatty acids to the blood-brain barrier and the brain. He then describes the role of PUFA in brain neurotransmitters, membrane fluidity and myelin, prostaglandins, cholesterol and fatty acids and their influence on the fluidity index. Subsequently, he discusses the experimental studies on omega-3 fatty acid deficiency, PUFA and early development, the role of essential fatty acids in aging, Alzheimer's disease, fatty acid metabolism, and seizure control and multiple sclerosis. The effects of essential fatty acids on sleep showed that a ratio of 18:2 ω 6 to 18:3 ω 3 of 4/1 had beneficial effects in a group of students. The same ratio of 4/1 reduced the elevated levels of cortisol in rodents. Dr. Yehuda's review relates mainly to LA and ALA. The author concludes that a ratio of 18:2 ω 6 to 18:3 ω 3 of 4/1 is the optimal ratio of brain mediated functions.

Similarly, the paper 'Dietary Prevention of Coronary Heart Disease: Focus on Omega-6/Omega-3 Essential Fatty Acid Balance' by Michel de Lorgeril and Patricia Salen indicates that a ratio of 18:2 ω 6 to 18:3 ω 3 of 4/1 is associated with a decrease of 70% in total mortality from cardiovascular disease in a dietary pattern consistent with the diet of Crete in patients with one episode of myocardial infarction. The authors describe in detail the components of the diet, which is a modified diet of Crete, and their physiologic functions. Epidemiological studies as well as randomized dietary trials including moderate amounts of omega-3 fatty acids in the experimental diet suggest that these fatty acids, despite their low concentrations in blood and tissues, may be important in relation to the pathogenesis (and prevention) of coronary heart disease. Whereas a striking protective effect of an ALA-rich modified diet of Crete was reported with a 50–70% reduction of the risk of recurrence after 4 years of follow-up, it is still not known whether ALA is cardioprotective by itself only or also through its conversion into very long-chain omega-3 fatty acids (EPA and DHA) and then into the corresponding eicosanoids and prostaglandins. The authors state that, 'According to our current knowledge, dietary ALA should represent about 0.6–1% of total daily energy or about 2 g per day in patients following a Mediterranean type of diet, whereas the average intake of LA should not exceed 7 g per day. Supplementation with very long chain omega-3 fatty acids (about 1 g per day) in patients following a Mediterranean type of diet was shown to decrease the risk of cardiac death by 30% and of sudden cardiac death by 45%. Thus, in the context of a diet rich in oleic acid and poor in saturated and omega-6 fatty acids, even a small dose of very long chain omega-3 fatty acids (1 g in the form of capsules) might be very protective. These data underline the importance of the omega-6/omega-3 ratio in the prevention of coronary heart disease.'

In the next paper ‘Effects of an Indo-Mediterranean Diet on the Omega-6/Omega-3 Ratio in Patients at High Risk of Coronary Artery Disease: The Indian Paradox,’ Daniel Pella, Gal Dubnov, Ram B. Singh, Rakesh Sharma, Elliot Berry and Orly Manor clearly state that although the Indian diet is low in total fat, it has a high omega-6/omega-3 ratio of about 38/1, which is associated with high rates of cardiovascular disease and diabetes. Changing the cooking oils and increasing the fruit and vegetable intake in the diet brought the ratio down to 9.1/1 and a 40% decrease in cardiovascular disease mortality in both the primary and the secondary prevention of cardiovascular disease.

The paper ‘Omega-6/Omega-3 Fatty Acid Ratio: The Israeli Paradox’ by Gal Dubnov and Elliot Berry similarly points to the fact that nutrition habits in Israel include a low intake of energy, total and animal fat, combined with high levels of the hypolipidemic polyunsaturated fatty acids resulting in a seemingly healthy diet. Nonetheless, the prevalence of coronary artery disease, diabetes mellitus, and cancer in Israel is comparable to other Western countries, despite these dietary differences. The cause for this might be ‘too much of a good thing’, that is, too high levels of omega-6 polyunsaturated fatty acids, which may lead to insulin resistance, increased atherogenesis and thrombosis, coronary events and cancer. ‘This is the Israeli paradox, reflecting the possible dangers of high omega-6 diet.’

Zampelas and co-workers in their paper on ‘Linoleic Acid to Alpha-Linolenic Acid Ratio: From Clinical Trials to Inflammatory Markers of Coronary Artery Disease’ review the protective role of ALA in cardiovascular disease, ALA’s anti-inflammatory function, and their study on the effect of a ratio of LA/ALA of 1/1 in suppressing C-reactive protein (CRP). Their recent research suggests that a LA/ALA ratio of 1/1 could have an anti-inflammatory effect, by reducing interleukin-1 β (IL-1 β), IL-6, tumor necrosis factor- α (TNF- α), and CRP levels. Because the genes for IL-1 β , IL-6, and TNF- α are polymorphic, the effects of ALA on their levels is dependent on the genetic variation of these cytokines.

Tomohito Hamazaki and Harumi Okuyama, in their paper ‘The Japan Society for Lipid Nutrition Recommends to Reduce the Intake of Linoleic Acid: A Review and Critique of the Scientific Evidence’ carried out a most thorough review and critique of the role of omega-6 and omega-3 polyunsaturated fatty acids in the prevention of coronary heart disease and other chronic diseases. The authors explain why 18:2 ω 6 should be reduced in the Japanese diet, which already has an omega-6/omega-3 ratio of 4/1. Their review clearly shows that LA intake should be reduced to 3–4% of energy. The Japanese have an omega-3 fatty acid intake of 0.6% of energy LNA and 0.5% of energy EPA and DHA. Their recommendation is consistent with an omega-6:omega-3 range of 2.7–3.6/1.

There is epidemiological and experimental evidence that EPA and DHA exert protective effects against some common cancers of the breast, colon and perhaps prostate. Veronique Chajès and Philippe Bounoux in their paper 'Omega-6/Omega-3 Polyunsaturated Fatty Acid Ratio and Cancer' review the experimental and epidemiological evidence, and their own clinical intervention studies, and suggest that the most important aspect of PUFA in the prevention of cancer is the ratio of omega-6 to omega-3 PUFA rather than the absolute amount of either. In Western diets, the omega-6/omega-3 PUFA ratio is 15/1 to 16.7/1. Epidemiological and experimental research indicates that an omega-6/omega-3 PUFA ratio of about 1/1–2/1 has a protective effect against the development and growth of breast and colon cancers. Short-term biomarker studies in human beings suggest that omega-3 PUFA supplementation at a ratio of omega-6 to omega-3 PUFA of about 2.5/1 may protect against colorectal carcinogenesis. Little information is yet available on the role of omega-6 PUFA relative to omega-3 PUFA on prostate cancer, and the findings are controversial.

Leslie Cleland, Michael J. James and Susanna M. Proudman in their paper 'Omega-6/Omega-3 Fatty Acids and Arthritis' discuss the importance of omega-3 fatty acids in reducing pain and inflammation in patients with rheumatoid arthritis and osteoarthritis, as well as improving the outcome in patients with Crohn's disease and IgA nephropathy. They state, 'Because ω_6 and ω_3 long chain highly unsaturated fatty acids (HUFA) and their polyunsaturated fatty acid (PUFA) metabolic precursors must be acquired from the diet, diet can have an important influence on the likelihood and response to therapy of inflammatory diseases. Therapeutic strategies that reduce ω_6 HUFA and increase ω_3 HUFA ideally should involve reduced intake of ω_6 PUFA in favor of monounsaturates and ω_3 PUFA, and increased intake of ω_3 HUFA, of which fish oil is a particularly rich source.' There is a strong rationale for reducing symptoms of arthritis based on studies of inhibitory effects of dietary fish oil on production of prostaglandin E₂. Inhibition of thromboxane A₂ (TXA₂), TNF- α , and IL-1 production provide a basis for anticipating better long-term outcomes with omega-3-rich diets. Empirically, strong evidence exists for symptomatic benefit in rheumatoid arthritis. A similar rationale exists for benefit in other arthropathies, although there is little evidence upon which to make an evaluation. Data on effects of dietary omega-3 enrichment on long-term outcomes in rheumatoid arthritis are lacking, although improved outcomes in Crohn's disease and IgA nephropathy provide a basis for optimism.

Between 100 and 150 million people globally suffer from asthma with an annual death toll of over 180,000. Asthma has become more prevalent in much of the developed world since the 1960s, with up to 5% of the population typically affected and is the most common chronic condition of childhood with between 20 and 25% of children experiencing wheezing at some point in their

life. The most rapid increase is occurring in children under the age of 5 with a 74% increase between 1980 and 1997. The events of asthma include the activation of a cell-surface esterase, calcium influx, and phospholipase activation leading to arachidonic acid release from a parent phospholipid. As a result of these processes, numerous mediators of asthma are produced including preformed molecules that provide an immediate response, new molecules generated as a result of degranulation of mast cells, and granule-associated mediators that act for an extended period of time. Leukotrienes (LT) and prostaglandins generated from released arachidonic acid as a result of degranulation are classified as newly generated mediators and are involved in the pathological changes associated with asthma.

Leukotrienes C₄ and D₄ mediate bronchial smooth-muscle contraction, mucosal edema, and mucus secretion, with LTB₄ promoting cellular infiltration. It is possible to modify the pattern of LT biosynthesis through specific lipid modifications of the diet with extensive research having been conducted over the past 3 decades. Interest in the role of specific lipids and their influence in asthma has focused on the role of the omega-6 and omega-3 PUFA in the potential amelioration of asthma symptoms as these two families of lipids have the potential to significantly alter the course of eicosanoid biosynthesis.

Based on initial observations in populations that consume high levels of omega-3 PUFA and display a low incidence of asthma, many studies have been conducted examining if omega-3 PUFA consumption would be an effective means of ameliorating asthma symptoms. While increased consumption of omega-6 fatty acids does not lead to an improvement in asthma symptoms, elicitation scores or respiratory parameters, the benefits associated with omega-3 PUFA ingestion have been equivocal. Several studies have demonstrated a benefit while others have not. Still others have shown no general benefit in the overall asthmatic response while others demonstrate a beneficial effect in the late asthmatic response. Short-term feeding may not be effective unless the omega-6 PUFA in the diet are accounted for and long-term feeding may be ineffective if omega-3 PUFA are not fed at a substantial enough level. The benefit when achieved is lost if consumption of omega-3 PUFA is not maintained. Further, the preformed long-chain omega-3 PUFA of marine origin appear to be more effective than α -linolenic acid found in vegetable oils.

Many of the chronic conditions – cardiovascular disease, diabetes, cancer, obesity, autoimmune diseases, rheumatoid arthritis, asthma and depression—are associated with increased production of TXA₂, leukotriene B₄ (LTB₄), IL-1 β , IL-6, TNF, and CRP. All these factors increase by increases in omega-6 fatty acid intake, and decrease by increases in omega-3 fatty acid intake, either ALA or EPA and DHA. EPA and DHA are more potent, and most studies have been carried out using EPA and DHA.

The optimal range of the ratio of omega-6/omega-3 varies from 1/1 to 4/1 depending on the disease under consideration. Studies show that the background diet, when balanced in omega-6/omega-3, reduces the drug dose. It is therefore essential to decrease the omega-6 intake while increasing the omega-3 in the prevention and management of chronic diseases. Furthermore, the balance of omega-6 and omega-3 fatty acids is very important for homeostasis and normal development. The ratio of omega-6 to omega-3 essential fatty acids is an important determinant of health. In making dietary recommendations, omega-6 and omega-3 PUFA should be distinguished in food labels because they are metabolically and functionally distinct.

This volume should be of interest to a large and varied audience of researchers in academia, industry, and government; cardiologists, geneticists, immunologists, neuroscientists, and cancer specialists; as well as nutritionists, dietitians, food scientists, agriculturists, economists and regulators.

Artemis P. Simopoulos, MD