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Effects of Omega-3 Fatty Acids on Organ Transplantation

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-Based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. This report on Effects of Omega-3 fatty acids on organ transplantation was requested and funded by the Office of Dietary Supplements, National Institutes of Health. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for health care quality improvement projects throughout the Nation. The reports undergo peer review prior to their release.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

We welcome comments on this evidence report. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to **epc@ahrq.gov.**

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Structured Abstract

Context. Laboratory studies and human studies in the non-transplant setting have suggested a potential benefit of omega-3 fatty acid supplementation on several outcome measures, some of which may benefit patients undergoing organ transplantation.

Objectives. To perform a systematic review of the literature and to assess the effects of supplementation with omega-3 fatty acids (eicosapentaenoic acid [EPA; 20:5 n-3], docosahexaenoic acid [DHA; 22:6 n-3], commonly referred to as "fish oil", and alpha-linolenic acid [ALA, 18:3 n-3]) on various transplant-related outcomes.

Data Sources. The following electronic databases were searched for potentially relevant studies: MEDLINE, Embase, Cochrane Central Register of Controlled Trials, Biological Abstracts, and Commonwealth Agricultural Bureau databases. Bibliographies of retrieved citations were reviewed to identify additional studies. Members of the Technical Expert Panel, authors of major controlled trials, and experts in the individual areas of transplantation were contacted to identify other sources of data including unpublished studies.

Study Selection. The literature search identified 1,281 abstracts, which (after screening for relevance) led to the retrieval of 78 full-text articles. Of these, 39 were rejected while 8 represented duplicate reports of the same patients, resulting in 31 unique studies. There were 23 kidney transplant studies with a total of 846 patients, 6 heart transplant studies with 233 patients, 1 liver transplant study with 26 patients, and 1 bone marrow study with 17 patients. There were a total of 21 randomized controlled trials (13 of which were in kidney transplantation), 6 prospective cohort studies, 2 non-randomized controlled trials, and 2 case reports.

Data Extraction. Data from each eligible study were extracted related to study design, population demographics, the amount and type of omega-3 fatty acids consumed, and outcomes. Features of methodological quality were also recorded, including (for randomized controlled trials) information about randomization, allocation concealment, and blinding techniques.

Data Synthesis. All but 1 study used fish oil as the source of omega-3 fatty acids. Major concerns in all evaluated studies were their small size and methodological deficiencies. There was variability in the rigor with which endpoints were defined and measured. Important covariates (such as use of antihypertensive agents or the intensity of immunosuppression) were often poorly described or inconsistently applied even when the study considered outcomes that may have been confounded by these factors.

No consistent benefits of fish oil supplementation were observed for any outcome with the exception of a modest benefit on triglycerides in kidney transplantation. Improvement in renal function was described in several studies, although discordant results were also reported. There were no clear patient- or study-related characteristics to account for the heterogeneity. At best, the degree of improvement was modest and did not translate into other clinically important outcomes such as improved graft survival, although the duration of the studies was generally less than one-year.

A meta-analysis of rejection episodes in kidney transplantation found no significant benefit on either early (<6 months post transplant) or late rejection episodes. The overall relative risk of

having at least one rejection episode in those receiving fish oil supplementation was 0.91 (95% CI 0.74, 1.10) in 4 studies with a total of 224 patients, all of which had a follow-up of 1 year (the longest follow-up reported). A meta-analysis of 7 randomized controlled trials (with a total of 470 patients) of graft survival in kidney transplantation found no significant benefit from fish oil supplementation (relative risk 1.00, 95% CI 0.96, 1.05). There was no significant heterogeneity between the studies. No clinically important interactions were observed between fish oil supplementation and the dose or trough-levels of cyclosporin A.

Conclusions. Fish oil supplementation in organ transplant recipients is associated with a modest reduction in triglyceride concentrations, a benefit that has been established in the non-transplant setting. Inconsistent benefits on renal function across studies may suggest a potential benefit in a subset of patients, the characteristics of whom remain unclear. Whether administration of omega-3 fatty acids prior to transplantation would improve its benefits is unclear. Long-term studies are needed to determine whether benefits on renal function translate into improved renal outcomes. Similarly, long-term follow-up in recipients of heart transplants will be required to determine whether fish oil supplementation reduces the risk of post-transplant atherosclerosis. Because of the scarcity of data, the effects of ALA supplementation in the transplant setting cannot be determined.

Applicability of the results to contemporary transplantation procedures is uncertain since most of the studies were performed several years ago, with some more than a decade old. The technology for all transplantation procedures continues to improve with a larger choice of immunosupressive agents, a better understanding of how to use them, and means to address the known complications of transplantation including some of the important outcomes (such as hyperlipidemia and hypertension).

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Summary

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Introduction

This evidence report has been prepared by the Tufts-New England Medical Center (Tufts-NEMC) Evidence-based Practice Center (EPC) concerning the health benefits of omega-3 fatty acids on organ transplantation. These reports are among several that address topics related to omega-3 fatty acids, and that were requested and funded by the Office of Dietary Supplements, National Institutes of Health (NIH), through the EPC program at the Agency for Healthcare Research and Quality (AHRQ). Three EPCs—the Tufts-NEMC EPC, the Southern California EPC (SCEPC), based at RAND, and the University of Ottawa EPC—each produced evidence reports. To ensure consistency of approach, the three EPCs collaborated on selected methodological elements, including literature search strategies, rating of evidence, and data table design.

The aim of the reports is to summarize the current evidence on the health effects of omega-3 fatty acids (eicosapentaenoic acid [EPA; chemical abbreviation: 20:5 n-3], docosahexaenoic acid [DHA; 22:6 n-3], alpha-linolenic acid [ALA, 18:3 n-3], and docosapentaenoic acid [DPA, 22:5 n-3]) on the following: cardiovascular disease, cancer, child and maternal health, eye health, gastrointestinal diseases, kidney diseases, asthma, autoimmune diseases, immune-mediated diseases, organ transplantation, mental health, and neurological diseases and conditions. In addition to informing the research community and the public on the effects of omega-3 fatty acids on various health conditions, it is anticipated that the findings of the reports will also be used to help define the agenda for future research.

Reporting the Evidence

This evidence report on omega-3 fatty acids and organ transplantation is based on a systematic review of the literature. The Tufts-NEMC EPC held meetings and teleconferences with technical experts including a technical expert panel (TEP), as well as individual experts in relevant areas of transplantation, to identify specific issues central to this report. A comprehensive search of the medical literature was conducted to identify studies addressing the key questions. Evidence tables of study characteristics and results were compiled, and the methodological quality of the studies was appraised. Study results were summarized with qualitative reviews of the evidence, summary tables, and meta-analyses, as appropriate.

A number of individuals and groups supported the Tufts-NEMC EPC in preparing this report. The TEP served as our science partner. It included technical experts, representatives from AHRQ, and institutes at NIH to work with the EPC staff to refine key questions, identify important issues, and define parameters to the report. Additional domain expertise was obtained through local experts who joined the EPC.

The Tufts-NEMC EPC also worked in conjunction with EPCs at the University of Ottawa and the SCEPC. The three EPCs coordinated efforts to produce evidence reports

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on 10 topics related to omega-3 fatty acids over a 2-year period, with the goal of producing evidence reports with a uniform format. Evidence table layout and study quality assessment were standardized. In addition, literature searches for all evidence reports were performed by the University of Ottawa EPC, using identical search terms for studies of omega-3 fatty acids. The three EPCs agreed on a common definition of omega-3 fatty acids; however some variation that reflected different topics and key questions was permitted in definitions and study eligibility criteria.

Key Questions

Nine key questions, which fall under five major categories, are addressed in this report.

Graft-Related Outcomes

Question 1. What is the evidence that omega-3 fatty acid supplementation reduced rejection episodes or graft failure in patients (adults or children) who received an organ transplant?

Question 2. What is the evidence that omega-3 fatty acid supplementation is renoprotective (improves glomerular filtration rate or increases kidney size) or is protective against primary kidney disease recurrence following kidney transplantation?

Cardiovascular Disease-Related Outcomes

Question 3. What is the evidence that omega-3 fatty acid supplementation lowers cardiovascular disease risk factors or events in organ transplant recipients (adults or children)?

Infectious Outcomes

Question 4. What is the evidence that omega-3 fatty acid supplementation reduces serious infectious complications following organ transplantation?

All Outcomes

Question 5. What is the evidence that any benefits to organ transplant recipients from omega-3 fatty acid supplementation differ in different subsets of patients?

Question 6. What is the evidence that effects of omega-3 fatty acid supplementation on outcomes of interest vary depending on the time of administration relative to transplantation procedures (pre- or post-transplant)?

Effects on Immunosuppressive Agents and Related Drugs

Question 7. What is the evidence in patients (adults or children) who receive an organ transplant that the benefits of omega-3 fatty acid supplementation interact with the concomitant administration of various immunosuppressive agents/drugs?

Question 8. What is the evidence in patients (adults or children) who receive an organ transplant that serum levels of immunosuppressive agents/drugs are altered by omega-3 fatty acid supplementation?

Question 9. What is the evidence in patients (adults or children) who receive an organ transplant that omega-3 fatty acid supplementation can replace or reduce the need for other more potent anti-inflammatory or immunosuppressive drugs (such as steroids and non-steroidal anti-inflammatory drugs)?

Methods

Patient Population and Settings

The target population included adults or children undergoing any form of organ transplantation.

Search Strategy

We conducted a comprehensive literature search to address the key questions. Relevant studies were identified primarily through search strategies conducted in collaboration with the University of Ottawa EPC. The Tufts-NEMC EPC used the OVID search engine to conduct preliminary searches on the MEDLINE® database. The final searches used six databases including MEDLINE, MEDLINE In Process and Other Non-Indexed Citations, EMBASE, CAB abstracts, BIOSIS abstracts, and Central Cochrane Database of Systematic Reviews from 1966 to week 4, 2003. Subject headings and text words were selected so that the same set could be applied to each of the different databases. Following the initial electronic search, tables of contents of major transplant and clinical specialty journals were hand searched during the period while this report was being completed until preparation of the final manuscript.

Additional sources of published and unpublished data were sought by contacting the TEP as well as authors of controlled trials identified in our initial search. Bibliographies of all retrieved studies (including review articles) were also examined.

Study Selection

All abstracts identified through the literature search were screened manually and in triplicate by three independent investigators. Triplicate screening was performed because the modest number of abstracts allowed us to gather additional data for methodology research pertaining to the most efficient method of abstract screening. Eligibility criteria were defined broadly to include all studies (regardless of language of publication, experimental design, or size) that evaluated any potential source of omega-3 fatty acids in human subjects who underwent organ transplantation, and reported any outcome. Any abstract identified by any independent investigator was retrieved for further review.

The full text of studies selected by the abstract screening process was reviewed by three independent investigators. Studies of any design (including controlled trials, cohort studies, case series, and case reports), size, and language were included provided that they reported any outcome in adults or children undergoing organ transplantation who received omega-3 fatty acids.

Studies were excluded if they focused on nonhuman subjects, were review articles or other articles without primary sources of data, focused on subjects who did not undergo organ transplantation, did not use omega-3 fatty acids, or if the amount of omega-3 fatty acids could not be quantified. Acceptable sources of omega-3 fatty acids included fish oil, vegetable oils containing ALA (i.e., canola, rapeseed, soybean, flaxseed, linseed, walnut, mustard seed), Mediterranean diet, or other sources where the quantity was reported explicitly. Pharmaceutical companies and individuals in relevant countries were contacted when a brand name of a fish oil supplement was provided without a quantitative description of its components.

The authors, study locations, and dates of all retrieved studies were compared to identify duplicate reports of the same subjects. Where there was any ambiguity, an attempt was made to contact authors of the relevant publications. Duplicate reports were included if they provided additional data; however, subjects were included and accounted for only once.

Data Extraction Process

Electronic data extraction forms and a database were created in a multi-step process during which the key study questions were translated into a structure that was applicable to all types of transplants and outcomes of interest. Frequent and regular discussions helped to ensure use of uniform definitions. Thus, multiple versions of the data extraction forms were tested by several investigators on samples of the included studies, until a final version was achieved. All investigators were trained on how to complete the form to assure consistency among extractors.

All studies were extracted by three independent investigators to allow for future methodology research aimed at comparing double versus single data extraction. The extraction team included investigators skilled in foreign languages so that non-English studies could be included.

Study features extracted included the design, blinding, randomization method, allocation concealment method, country, funding source, duration, quantity and type of omega-3 fatty acids, eligibility criteria, control interventions, sample characteristics (and their comparability), reasons for withdrawals, and all reported outcomes. In addition, each study was categorized based on study quality as described below.

Two investigators compared the results of the triplicate data extraction forms. Discrepancies were resolved by discussion and review of the original study until consensus was achieved for all data points.

Methodological Quality

As part of the overall omega-3 fatty acid project, the three collaborating EPCs agreed to use the Jadad Score and adequacy of random allocation concealment as elements to grade individual randomized controlled trials.[1,2] The EPCs also agreed to permit inclusion of other quality elements that were considered to be appropriate for a generic quality score.

There was consensus among the three EPCs that studies should not be graded using a single, quantitative summary score, since such scores are often arbitrary and unreliable.[3] The Jadad Score assesses the quality of randomized controlled trials using three criteria: adequacy of randomization, double blinding, and dropouts.[1] Studies fulfilling all three criteria receive a maximum score of five points. In addition, adequacy of allocation concealment was assessed using the criteria by Schulz et al., as "adequate," "inadequate," or "unclear."[2]

A limitation of the Jadad and Schulz scores is that they address only some aspects of the methodological quality. These scores do not include other elements of study quality, such as potential biases due to reporting and analytic problems. Furthermore, these scoring systems are applicable only to randomized controlled trials.

Thus, to supplement these scores, a 3-category grading system (A, B, C) was applied to each study. This grading system has been used in most of the previous evidence reports from the Tufts-NEMC EPC as well as in evidence-based clinical practice guidelines.[4] This system defines a generic grading system that is applicable to varying study designs including randomized controlled trials, cohort, and case-control studies. The categories are defined as follows:

A Category A studies have the least bias and results are considered valid. This is a study that adheres mostly to the commonly held concepts of high quality including the following:
- A formal randomized study.
- Clear description of the population, setting, interventions, and comparison groups.
- Clear description of the content of the placebo used.
- Appropriate measurement of outcomes.
- Appropriate statistical and analytic methods and reporting.
- No reporting errors.
- Less than 20 percent dropout and clear reporting of dropouts.
- No obvious bias.

B Category B studies are susceptible to some bias, but not sufficient to invalidate the results. They do not meet all the criteria in category A because they have some deficiencies, but none likely to cause major bias. The study may be missing information, making it difficult to assess limitations and potential problems.

C Category C studies have significant bias that may invalidate the results. These studies have serious errors in design, analysis, or reporting, and have large amounts of missing information, or discrepancies in reporting.

In addition to applying these three grading systems, additional comments relating to potential sources of bias and other study limitations were recorded by each investigator during the data extraction process. Such comments are included in the evidence tables.

Statistical Analysis

Results that are included in this report were determined through discussions with members of the TEP as well as additional experts in transplantation. This process allowed us to focus on the major outcomes of interest (and methods for their measurement) that were relevant to the TEP key questions, were available in the identified literature, and relevant for specific areas of transplantation. The following endpoints are featured in the evidence tables, but all measured endpoints are also included.

- Major outcomes for kidney transplantation included the post-transplant glomerular filtration rate (GFR), blood pressure, lipid profile, patient and graft survival, episodes of rejection, and dose and trough levels of cyclosporine (CsA).
- Major outcomes for heart transplantation included post-transplant hypertension, renal function, lipid levels, rejection episodes (including surrogate markers), and coronary disease (including surrogate markers).
- All outcomes for other forms of transplant (i.e, bone marrow and liver) were included in the evidence tables since, as will be noted below, only one study in each category was identified.

As a general rule, when more than one time point was reported for a specific outcome (e.g., glomerular filtration rate), the result representing the longest time point from study inception was included in the primary analysis. However, additional analyses were performed for questions that were of clinical interest or relevant to the TEP questions (e.g., examining the effects of fish oil supplementation on early versus late rejection).

Studies describing renal function after transplantation frequently described the results of more than one method to assess it. All methods are described in the evidence tables. However, the most rigorous method was highlighted and used for comparison across studies whenever available. In particular, direct measurement of the GFR with a radioisotope study or inulin clearance was considered to provide the best estimate of renal function compared with indirect methods (such as the calculated GFR) or serologic markers, such as the plasma concentration of blood urea nitrogen or creatinine.[5]

Important covariates and study characteristics were also featured. These included, for example, the doses and types of immunosuppressant medications, type of transplant (live donor versus cadaveric), specific time in which the omega-3 fatty acid was introduced relative to the transplant, duration of followup, and concomitant use of antihypertensive medications and lipid lowering agents, all of which may have an influence on the major outcomes of interest.

Many of the outcomes of interest were continuous variables such as blood pressure, GFR, and lipid levels. For these outcomes, the summary tables describe three sets of data: the mean baseline level in the omega-3 fatty acid arm, the net change of the outcome, and the reported *P* values of the

difference between the omega-3 fatty acid and the control arms. The net change of the outcome is the difference between the change in the omega-3 fatty acid arm and the change in the control arm:

Net change = (Omega-3 $_{Final}$ – Omega-3 $_{Initial}$) – (Control $_{Final}$ – Control $_{Initial}$).

While some studies reported adjusted and unadjusted within-arm and between-arm (net) differences, to maintain consistency across studies, we calculated the unadjusted net change using the above formula for all studies when the data were available. All exceptions and caveats are described in footnotes.

We included only the reported *P* values for the net differences. We did not calculate any *P* values, but, when necessary, used provided information on the 95 percent confidence interval (CI) or standard error of the net difference to determine whether it was less than .05. We included any reported *P* value less than 0.10. Those above 0.10 and those reported as "non-significant" were described as "NS" (non-significant).

For measures expressed using standard or Systeme International units (e.g., lipid levels), the original units reported in the study were included in the evidence tables. However, all such measurements were converted to standard units in the summary and results tables to facilitate comparisons.

Uncontrolled trials were described (e.g., case reports), and, when within-group comparisons were made, the within-group change was reported along with its associated *P* value. For dichotomous or categorical variables, the rates in the treatment and control groups were expressed as relative risk and 95 percent CIs. Among these, there were sufficient, clinically comparable data to combine the results of graft or patient survival and rejection episodes in kidney transplantation. This was accomplished using a random effects model meta-analysis.[6]

Results

Search Results

The literature search identified 1,281 abstracts. From these, and from the articles found in bibliographies, a total of 78 studies were ultimately selected for full-text screening (based upon the initial abstract screening and review of the bibliographies of retrieved studies including review articles). Thirty-nine of these were rejected because they did not fulfill inclusion criteria leaving 39 for inclusion. Careful additional review of these studies revealed 8 that were duplicate reports of the same patients leaving a total of 31 independent reports. There were 23 kidney transplant studies with a total of 846 patients, 6 heart transplant studies with 233 patients, 1 liver transplant study with 26 patients, and 1 bone marrow transplant study with 17 patients. The study designs of the qualifying studies include 21 randomized controlled trials (RCTs), 2 non-RCTs, 6 prospective cohort studies, and 2 case reports. Fish oil supplements were used in all but the heart transplant studies.[7] Since the biological effects of long-chain omega-3 fatty acids (EPA and DHA) are different from ALA, the results should be considered separately. As a result, the findings of this report apply almost exclusively to fish oil supplementation.

Twelve study authors of the largest controlled trials were contacted (by telephone or e-mail or both) and, of them, five responded. None was aware of additional published or unpublished data. Similarly, the final list of included studies was considered to be complete after review by the TEP. One member of the TEP reported that he was involved in a pilot study involving omega-3 fatty acids in kidney transplantation that had not yet been completed.

Quality of the Studies

Studies were generally small, and many had important methodological limitations as indicated by the quality measures in summary tables. Masking and methods of randomization were generally not well described. Even among studies in which masking of patients and caregivers was described, it is likely that patients and caregivers became unmasked since fish oil supplementation was frequently associated with a fishy taste and dyspeptic side-effects in the active intervention arm, especially early in the course of treatment. Many controlled trials did not use isocaloric treatments or fats with comparable fatty-acid profiles in the control group, potentially biasing comparisons, especially for cardiovascular outcomes. Furthermore, there was variability in the degree to which compliance was assessed.

Similarly, there was variability in the rigor with which endpoints were defined and measured. Important covariates (such as use of antihypertensive agents or the intensity of immunosuppression) were often not well described or uniformly applied even when the study considered outcomes that may have been confounded by these factors.

Summary results were potentially underpowered since very few controlled studies analyzed the statistical significance for net differences in effects. Most studies only analyzed differences between groups at various time points during the study.

Question 1. What is the evidence that omega-3 fatty acid supplementation reduced rejection episodes or graft failure in patients (adults or children) who received an organ transplant?

Kidney Transplantation

Patient survival: There were seven deaths out of a total of 846 kidney transplant patients, all of which were reported in three studies.8-10 A total of four patients died with a functional graft within 1 year of transplant (one patient in the fish oil group and three patients in the placebo group).8 One patient died of myocardial infarction in the placebo group.9 In a 9-month RCT, two patients in the fish oil group died due to hemorrhagic shock from removal of native polycystic kidney and intestinal infarction.10

Graft survival: A total of 10 RCTs, with 291 patients in the fish oil group and 312 patients in the placebo or control group, described graft survival among kidney transplant recipients.[8-16] However, most studies did not perform quantitative graft survival analyses, underscoring the excellent overall results in kidney transplantation regardless of fish oil supplementation. One exception was a RCT in which 1-year graft survival tended to be better in the fish oil group, although results did not achieve statistical significance.[9] Two other RCTs showed no statistically significant difference in 1-year graft and patient survival rates between fish oil and placebo or control group.[12,14]

Fish oil supplementation was begun 3 days post-transplant in 7 of these 10 reports with a total of 228 and 234 subjects in the fish oil and control groups, respectively. The studies were all of low or intermediate quality. The pooled relative risk of graft survival in those receiving fish oil supplementation was 1.00 (95 percent CI 0.96, 1.05). There was no statistical heterogeneity among studies.

Rejection episodes: Acute rejection episodes were described at varying time points in a total of 11 controlled trials, including 297 patients in the fish oil group and 282 patients in the placebo or control group.[8-12,14-20] The studies were all of low or intermediate quality. In all but two studies (published in three papers[11,19,20]), treatment had been initiated within 3 days following transplantation. To allow for clinically meaningful comparisons across studies, rejection episodes were defined as being "early" (within the first 6 months of transplant) or "late" (after 6 months), corresponding with generally accepted clinical criteria.

One study reported only total episodes of rejection according to treatment (rather than the proportion of patients having a rejection episode), noting a statistically significant reduction in the total number of rejection episodes in the group receiving fish oil.[9] However, it was not possible to tell whether these differences could have been accounted for by multiple episodes of rejection in a small number of patients (or even a single patient). The authors described 6 episodes of rejection in the fish oil group compared with 10 in the control group at 1 month. In the second and third months, there was only 1 acute rejection episode in the fish oil group compared with none in the control group ($P = 0.016$). In months 4 through 6, there were no rejection episodes in either group. Between month 6 and 12, there was 1 rejection episode in each group. Thus, during the year after transplantation, the total number of acute rejection episodes was significantly lower in the fish oil group than in the controls (8 versus 20, $P = 0.029$). These results did not translate into statistically significant improved graft survival at 1 year (97 versus 84 percent, $P = 0.097$).

The other eight reports (in which treatment was started within 3 days post-transplant) described the proportion of patients with at least one rejection episode. The results for "early" and "late" rejection (as defined above) were combined using a random effects model, which showed no significant benefit at any time point examined. Results for two studies that reported rejection episodes between 2 to 9 and 3 to 12 months were not pooled since the time points reported combined "early" and "late" episodes together.[8,10] The pooled relative risk of a rejection episode in those receiving fish oil supplementation was 0.91 (95 percent CI 0.75, 1.11) in four studies with a total of 224 subjects that reported the longest followup (i.e., 1 year). There was no significant heterogeneity among the studies. Overall, either immediate or delayed supplementation with fish oil showed no benefit on graft survival among patients who had kidney transplants. No reduction in either early or late acute rejections was found with fish oil supplementation.

Heart transplantation. Although six studies described a variety of outcomes in a total of 233 heart transplant recipients,[7,21-25] the studies were small, had various designs, and there was little detailed information on rejection episodes or graft survival from which to derive inferences regarding the effect of omega-3 fatty acid supplementation.

Other transplants. A study of liver transplantation focused on the renal effects of fish oil supplementation in those with stable liver graft function (at least 6 months after transplant).[26] The study duration was only 2 months. No effects on rejection or graft survival were described.

A study in bone marrow transplant recipients focused on predictors of acute colonic graft versus host disease but did not present outcomes related to the success of the transplant.[27] A separate report of the same patients found a significantly higher patient survival rate in the group that received fish oil supplementation and improvement in biochemical markers of the systemic inflammatory response.[28]

Question 2. What is the evidence that omega-3 fatty acid supplementation is renoprotective (improves glomerular filtration rate or increases kidney size) or is protective against primary kidney disease recurrence following kidney transplantation?

No study reported kidney size as a measure of renal function following transplantation or described primary disease recurrence following kidney transplantation. Two case reports suggested that fish oil supplementation improved proteinuria in patients who developed recurrent immunoglobulin A (IgA) nephropathy.[29,30] The observation is potentially important since some studies have found a benefit from fish oil supplementation in IgA nephropathy in the non-transplant setting.[31,32]

Eleven randomized-controlled trials in 14 publications and one prospective cohort study reported the effects of fish oil supplementation on GFR. No consistent benefit was observed in patients treated shortly after transplantation or those with stable renal function in whom treatment was started several months after transplantation, although there were exceptions. The magnitude of benefit suggested in trials with positive findings was modest, and, as noted above, did not translate into improved graft survival with up to 1-year of followup.[9,12,15,33]

Comparison of studies with positive and negative findings did not reveal any patient or study-related factors that could account for the heterogeneity. Two of the largest studies that reached disparate conclusions had almost identical designs.[8,9] In both, there was improvement in the GFR during the 12-month observation period in treated and control patients. In the study with positive findings,[9] GFR in the fish oil group increased from 42 at 1 month to 45, to 49, and to 53 ml/min/1.73m^2 at 3, 6, and 12 months, respectively. Corresponding values in the control group were 32, 38, 41, and 40. The differences were statistically significant at the 3, 6, and 12 month time-points.

By contrast, in the study with the negative results,[8] GFR increased from 46.1 ml/min/1.73m^2 at 1 month to 54.4 at 12 months in the fish oil group and from 43.2 to 52.5 in the control group at the same time points. Thus, in both studies there were similar degrees of improvement in both treated and control patients relative to baseline. The main difference between studies was the lower values of GFR at all time points in the control group in the study with the positive findings.[9] This may have been due to fewer episodes of rejection in the fish oil group. However, given the small size of the study, it is also possible that unmeasured factors contributed to relatively poor graft function in the control arm. On the other hand, lower baseline values of GFR or higher rates of rejection for the control group did not appear to account for the positive finding that was observed in a different trial.[15]

Question 3. What is the evidence that omega-3 fatty acid supplementation lowers cardiovascular disease risk factors or events in organ transplant recipients (adults or children)?

Several factors are well known to be associated with the risk of cardiovascular disease. These include serum lipoproteins, blood pressure, diabetes mellitus, and related metabolic disorders. Multiple studies have demonstrated that improvement or suppression of these factors can reduce the risk. The effects of omega-3 fatty acid supplementation on these risk factors have been reviewed in detail in the non-transplant setting.[34] A large, consistent benefit was found only for triglyceride levels. Little or no effect was found for a variety of other cardiovascular risk factors and markers of cardiovascular disease.

Question 4. What is the evidence that omega-3 fatty acid supplementation reduces serious infectious complications following organ transplantation?

Infections are an important cause of morbidity and mortality following all forms of organ transplantation. Animal and limited human data suggest that supplementation with omega-3 fatty acids may modulate the host's ability to respond to infections.[35,36] However, no study included in this evidence report described infectious outcomes. Thus, its benefit in the transplant setting could not be determined.

Question 5. What is the evidence that any benefits to organ transplant recipients from omega-3 fatty acid supplementation differ in different subsets of patients?

Two controlled trials in kidney transplantation (with a total of 53 patients in the fish oil group and 64 patients in the coconut oil group), both from the same center, described outcomes in patients with and without an episode of rejection.[17,18] In one of these reports, patients who had received fish oil supplementation demonstrated a significantly better recovery of renal function following an episode of histologically-confirmed rejection.[17] The authors concluded that fish oil supplementation favorably influenced renal function in the recovery phase following a rejection episode.

In an earlier report, the authors analyzed a subset of patients without an episode of rejection during the course of study.[18] Patients receiving fish oil had a significantly higher filtration fraction, a significantly lower effective renal plasma flow (164 versus 262 mL/min per 1.73 m^2) and a significantly better response of the GFR following amino acid infusion (15.3 versus 10.6 percent).

Question 6. What is the evidence that effects of omega-3 fatty acid supplementation on outcomes of interest vary depending on the time of administration relative to transplantation procedures (pre- or post-transplant)?

All studies evaluated patients who received fish oil supplementation after transplant. While there was no individual study in which patients were randomly assigned to receive supplementation at different time points relative to the transplant, variability was observed across studies allowing for indirect comparisons. The data do not support a clear relationship between the time in which the supplement was begun and the treatment effect.

Question 7. What is the evidence in patients (adults or children) who receive an organ transplant that the benefits of omega-3 fatty acid supplementation interact with the concomitant administration of various immunosuppressive agents/drugs?

No study in any of the types of transplantation provided a detailed evaluation of the interaction between omega-3 fatty acid supplementation and the various immunosuppressive drugs, except for dosing of cyclosporine (discussed below).

Question 8. What is the evidence in patients (adults or children) who receive an organ transplant that serum levels of immunosuppressive agents/drugs are altered by omega-3 fatty acid supplementation?

Included studies used differing immunosuppressive protocols which varied in the choice of agent, target (and achieved) blood levels of CsA for induction and maintenance therapy, and use of concomitant immunosuppressive agents such as corticosteroids and anti-thymocyte globulin. Furthermore, no study evaluated levels and dosages of all the immunosuppressant drugs that were used concurrently.

The effect of fish oil supplementation on immunosuppression was most fully described for CsA. Several studies in kidney and heart transplantation reported trough and total doses of CsA in patients who received or did not receive omega-3 fatty acids. Fish oil did not appear to have an effect on either of these measures. Considered together, these data provide evidence against a clinically significant interaction between CsA and fish oil. A possible exception was one study that suggested that fish oil supplementation may improve CsA absorption and metabolism in kidney transplant patients.[10]

Question 9. What is the evidence in patients (adults or children) who receive an organ transplant that omega-3 fatty acid supplementation can replace or reduce the need for other more potent anti-inflammatory or immunosuppressive drugs (such as steroids and non-steroidal anti-inflammatory drugs)?

No study reported that fish oil supplementation reduced or replaced the need for other more potent anti-inflammatory drugs. Potential effects on CsA absorption are described above.

Limitations

The main limitation relates to the quantity and quality of the available evidence and its applicability to contemporary transplantation procedures. By far the largest experience has been in kidney transplantation. Varied inclusion criteria, study designs, outcome measures, assessment of compliance, and insufficient reporting limited detailed comparisons among studies with positive and negative findings, which may have permitted a better understanding of the heterogeneous results, especially for renal function.

All but one study (and one unpublished report) used fish oil as the source of omega-3 fatty acids. Thus, this report cannot address the effects of supplementation with ALA. Furthermore, there were insufficient data to determine the relationship between the background diet and the optimal ratio of omega-3 and omega-6 fatty acids on the outcomes of interest. All studies began omega-3 fatty acid supplementation after transplantation. Because it may take up to 3 weeks for supplementation to have an effect on the production of various cytokines, it is possible that supplementation prior to transplant could have an influence on the outcomes.

Some controlled trials in humans found a benefit of fish oil supplementation on renal function. This suggests that fish oil supplementation could possibly benefit a subset of patients. However, no clear patient or transplant-related characteristics emerged from careful comparisons of the studies to identify such patients. Furthermore, whether the magnitude of the observed changes would translate into clinically important outcomes (such as improved graft survival) is uncertain, especially since the study durations were generally 1 year or less.

The applicability of the results to contemporary transplantation procedures is also unclear since most of the studies were performed several years ago, with some more than a decade old. The technology for all transplantation procedures

continues to improve with a larger choice of immunosuppressive agents, a better understanding of how to use them, and the means to address the known complications of transplantation including some of the important outcomes (such as hyperlipidemia and hypertension) where the benefits of fish oil supplementation had been anticipated. Thus, whether fish oil supplementation could have a benefit in the setting of contemporary transplantation procedures is uncertain. A draft report of a study in kidney transplantation using contemporary protocols suggested a possible benefit in achieving complete steroid withdrawal but the precise contribution of the fish oil supplements in achieving this objective could not be determined.

Future Research

Future research with omega-3 fatty acid supplementation in transplantation might focus on the following objectives:

- A more detailed understanding of factors associated with improvement in renal function with fish oil or ALA supplementation in all forms of transplantation.
- Long-term followup studies on patients enrolled in the studies included in this report to determine whether any of the observed benefits were durable or translated into other improved outcomes.
- Determination of whether fish oil supplementation could benefit treatment or prevention of IgA nephropathy following transplantation.
- Additional studies in bone marrow transplantation where a benefit on acute colonic graft versus host disease and a survival benefit have been suggested.
- Long-term followup studies in patients undergoing heart transplantation to determine whether there is a benefit on post-transplant coronary disease.

Availability of the Full Report

The full evidence report from which this summary was taken was prepared for the Agency for Healthcare Research and Quality (AHRQ) by the Tufts-New England Medical Center Evidence-based Practice Center under Contract No. 290-02-0022. It is expected to be available in February 2005. At that time, printed copies may be obtained free of charge from the AHRQ Publications Clearinghouse by calling 800-358-9295. Requesters should ask for Evidence Report/Technology Assessment No. 115, *Effects of Omega-3 Fatty Acids on Organ Transplantation*. In addition, Internet users will be able to access the report and this summary online through AHRQ's Web site at www.ahrq.gov.

Suggested Citation

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Evidence Report

Chapter 1. Introduction

This evidence report has been prepared by the Tufts-New England Medical Center (Tufts-NEMC) Evidence-based Practice Center (EPC) concerning the health benefits of omega-3 fatty acids on transplantation. These reports are among several that address topics related to omega-3 fatty acids, and that were requested and funded by the Office of Dietary Supplements, National Institutes of Health, through the EPC program at the Agency for Healthcare Research and Quality (AHRQ). Three EPCs - the Tufts-NEMC EPC, the Southern California EPC-RAND, and the University of Ottawa EPC - each produced evidence reports. To ensure consistency of approach, the 3 EPCs collaborated on selected methodological elements, including literature search strategies, rating of evidence, and data table design.

The aim of the reports is to summarize the current evidence on the health effects of omega-3 fatty acids (eicosapentaenoic acid [EPA; chemical abbreviation: 20:5 n-3], docosahexaenoic acid [DHA; 22:6 n-3], alpha-linolenic acid [ALA, 18:3 n-3], and docosapentaenoic acid [DPA, 22:5 n-3]) on the following: cardiovascular disease, cancer, child and maternal health, eye health, gastrointestinal diseases, kidney diseases, asthma, autoimmune diseases, immune-mediated diseases, organ transplantation, mental health, and neurological diseases and conditions. In addition to informing the research community and the public on the effects of omega-3 fatty acids on various health conditions, it is anticipated that the findings of the reports will also be used to help define the agenda for future research.

The focus of this report is on organ transplantation. In this chapter, the metabolism, physiological functions, and the sources of omega-3 fatty acids are discussed briefly. Subsequent chapters describe the methods used to identify and review studies related to omega-3 fatty acids and organ transplantation, findings related to the effects of omega-3 fatty acids on organ transplantation, and recommendations for future research in this area.

Background

Metabolism and Biological Effects of Essential Fatty Acids

Dietary fat is an important source of energy for biological activities in human beings. Dietary fat encompasses saturated fatty acids, which are usually solid at room temperature, and unsaturated fatty acids, which are liquid at room temperature. Unsaturated fatty acids can be divided further into monounsaturated and polyunsaturated fatty acids. Polyunsaturated fatty acids can be classified on the basis of their chemical structure into two groups: omega-3 (n-3) fatty acids and omega-6 (n-6) fatty acids. The *omega-3* or *n-3* notation indicates that the first double bond from the methyl end of the molecule is in the third position. The same principle applies to the *omega-6* or *n-6* notation. Despite their differences in structure, all fats contain the same amount of energy (9 kcal/g or 37 kJ/g).

Of all fats found in food, 2 — ALA and linoleic acid (LA, 18:2 n-6) — cannot be synthesized in the human body in adequate amount, yet are necessary for proper physiological functioning.

For this reason, these 2 fats are classified as essential fatty acids. These essential fatty acids can be converted in the liver to what are commonly termed very long-chain polyunsaturated fatty acids, which have a higher number of carbon atoms and double bonds. The metabolic product of LA is arachidonic acid (AA, 20:4 n-6) and products of ALA are EPA and DHA. These very long-chain polyunsaturated fatty acids retain the omega type (n-3 or n-6) of the parent essential fatty acids.

ALA and LA comprise the majority of the total polyunsaturated fatty acids consumed in a typical North American diet. Typically, LA comprises 89% of the total polyunsaturated fatty acids consumed, while ALA comprises 9%. Smaller amounts of other polyunsaturated fatty acids make up the remainder.[1] Both ALA and LA are present in a variety of plant-based foods. For example, LA is present in high concentrations in many commonly used vegetable oils, including safflower, sunflower, soy, and corn oil. ALA, which is consumed in smaller quantities, is present in leafy green vegetables and in some commonly used vegetable oils, primarily canola and soybean oil. Some novelty oils, such as flaxseed oil, contain relatively high concentrations of ALA, but these oils are not commonly found in the food supply. Small amounts of AA come from animal products and EPA and DHA from cold-water fish.

The Institute of Medicine has recently established adequate intake levels (AI) for ALA and LA. Sufficient data were not available to establish recommended dietary allowances (RDA). The AIs for adults 19 and older are 1.1-1.6 g/day for ALA and 11-17 g/day for LA.[2] AI's for ALA and LA differ by age and gender groups, and for special conditions such as pregnancy and lactation.

As shown in Figure 1.1, EPA and DHA can act as competitors for the same metabolic pathways as AA. In human studies, the analyses of fatty-acid compositions in both blood phospholipids and adipose tissue showed reciprocal relationship between EPA plus DHA and AA. The Institute of Medicine, due to lack of sufficient data, has not established either RDAs or AIs for AA, EPA or DHA. Dietary recommendations have been made for these very long chain fatty acids by other countries worldwide, however, these specific amounts vary widely among countries.[3] Furthermore, there remain numerous unanswered questions relating to the metabolic interrelationship between omega-3 and omega-6 fatty acid. For example, it remains unclear to what extend ALA is converted to EPA and DHA in humans and whether this conversion varies among aged groups or physiological states (i.e. pregnancy), and to what extent the intake of omega-6 fatty acids impacts on the conversion rate or alters the biological effects attributed solely to EPA and DHA. Without resolution of these 2 foundational questions, it remains difficult to fully understand the relative roles of omega-6 and omega-3 fatty acid in human health.

Metabolic Pathways of Omega-3 and Omega-6 Fatty Acids

Omega-3 and omega-6 fatty acids share a common pool of enzymes and go through the same oxidation pathways while being metabolized (Figure 1.1). Once ingested, ALA and LA can be elongated and desaturated into long-chain polyunsaturated fatty acids. LA can be converted into gamma-linolenic acid (GLA, 18:3 n-6), an omega-6 fatty acid that is a positional isomer of ALA. GLA, in turn, can be converted to the very long-chain omega-6 fatty acid, AA. ALA can be converted, to a lesser extent, to the very long-chain omega-3 fatty acids, EPA and DHA. However, the conversion from parent fatty acids into very long-chain polyunsaturated fatty acids occurs slowly in humans, and conversion rates nor the determinants thereof are not well

understood. Meat is the primary food source of AA, while cold-water fish has traditionally been the primary food source of EPA and DHA.

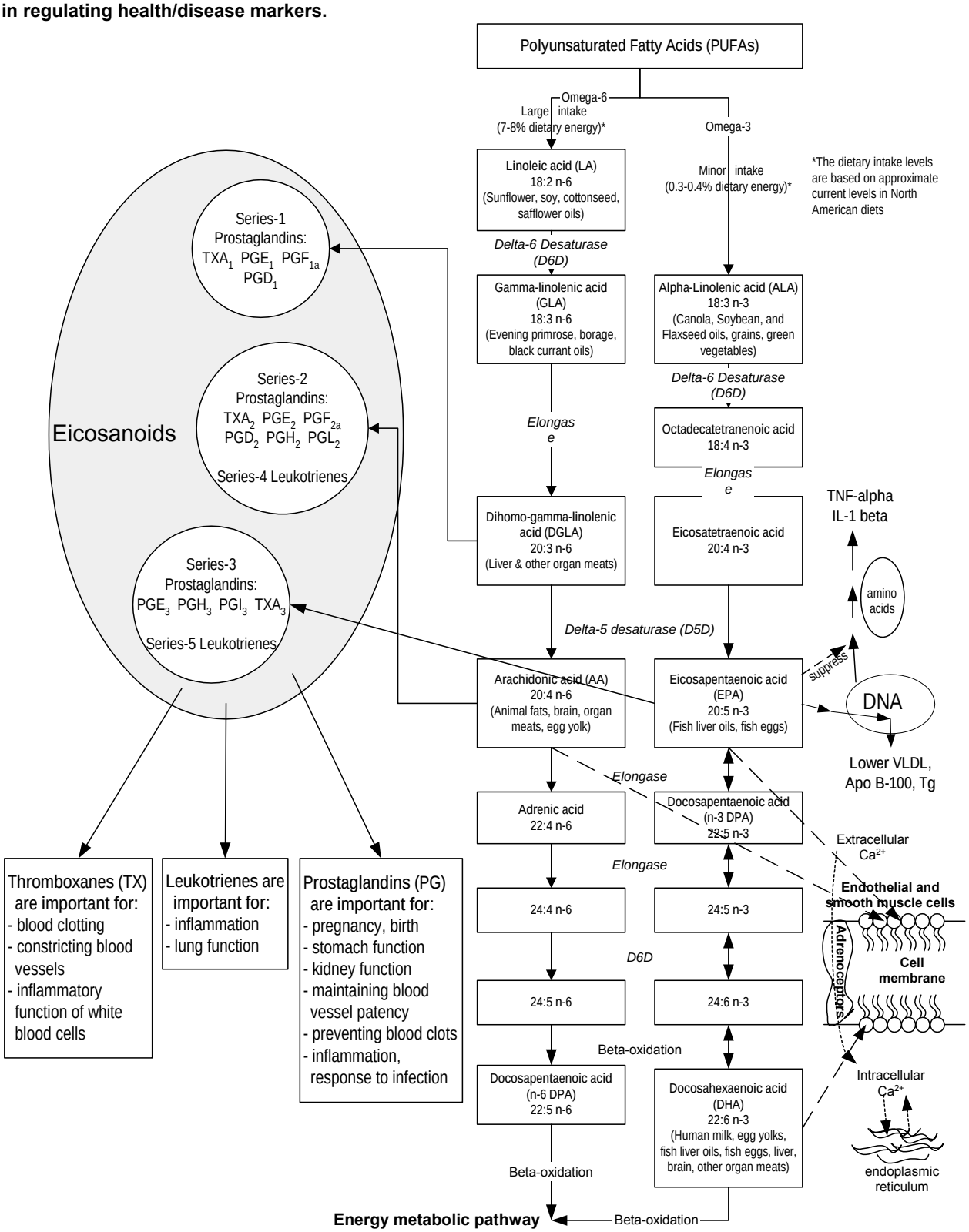
The specific biological functions of fatty acids depend on the number and position of double bonds and the length of the acyl chain. Both EPA and AA are 20-carbon fatty acids and are precursors for the formation of prostaglandins, thromboxane, and leukotrienes — hormone-like agents that are members of a larger family of substances called eicosanoids. Eicosanoids are localized tissue hormones that seem to be one of the fundamental regulatory classes of molecules in higher forms of life. They do not travel in the blood, but are synthesized in the cells and regulate a large number of processes, including the movement of calcium and other substances into and out of cells, dilation and contraction of muscles, inhibition and promotion of clotting, regulation of secretions including digestive juices and hormones, and control of fertility, cell division, and growth.[4]

As shown in Figure 1.1, AA is the precursor of a group of eicosanoids including series-2 prostaglandins and series-4 leukotrienes. EPA is the precursor to a group of eicosanoids including series-3 prostaglandins and series-5 leukotrienes. The series-2 prostaglandins and series-4 leukotrienes derived from AA are involved in accelerating platelet aggregation and enhancing vasoconstriction and the synthesis of inflammatory mediators in response to physiological stressors. The series-3 prostaglandins and series-5 leukotrienes that are derived from EPA are less physiologically potent than those derived from AA. More specifically, the series-3 prostaglandins are formed at a slower rate and work to attenuate excessive series-2 prostaglandins. Thus, adequate production of the series-3 prostaglandins, which are derived from EPA may protect against heart attack and stroke as well as certain inflammatory diseases like arthritis, lupus, and asthma.[4] In addition, animal studies, have demonstrated that EPA and DHA involved in cytoprotective activities may contribute to antiarrhythmic mechanisms.[5] Arrhythmias are a common cause of "sudden death" in heart disease.

In addition to affecting eicosanoid production as described above, EPA also affects lipoprotein metabolism and decreases the production of other compounds from AA- including cytokines, interleukin 1β (IL1β), and tumor necrosis factor α (TNFα) - that have pro-inflammatory effects. These compounds stimulate the production of collagenases and increase the expression of adhesion molecules necessary for leukocyte extravasation.[6] The mechanism responsible for the suppression of cytokine production by omega-3 fatty acids remains unknown, although suppression of eicosanoid production by omega-3 fatty acids may be involved. EPA can also be converted into the longer chain omega-3 form of docosapentaenoic acid (n-3 DPA), and then further elongated and oxygenated into DHA. EPA and DHA are frequently referred to as very long chain omega-3 fatty acids (and commonly known as "fish oil"). DHA, which is thought to be important for brain development and functioning, is present in significant amounts in a variety of food products, including fish, fish liver oils, fish eggs, and organ meats. Similarly, AA can convert into n-6 DPA.

Studies have reported that omega-3 fatty acids decrease triglycerides (Tg) and very low density lipoprotein (VLDL) in hypertriglyceridemic subjects, with a concomitant increase in high density lipoprotein (HDL). However, they appear to increase or have no effect on low density lipoprotein (LDL). Omega-3 fatty acids lowers plasma Tg by inhibiting VLDL and apolipoprotein B-100 synthesis.[7] Omega-3 fatty acids, in conjunction with transcription factors (small proteins that bind to the regulatory domains of genes), target the genes governing cellular Tg production and those activating oxidation of excess fatty acids in the liver. Inhibition of fatty acid synthesis and increased fatty acid catabolism reduce the amount of substrate available for Tg production.[8]

Figure 1.1. Classical omega-3 and omega-6 fatty acid synthesis pathways and the role of omega-3 fatty acid in regulating health/disease markers.



Population Intake of Omega-3 Fatty Acids in the United States

The major source of EPA and DHA is dietary intake of fish and fish oil, and that of ALA is dietary intake of vegetable oils (principally canola and soybean), some nuts including walnuts, and dietary supplements. Two population-based surveys, the third National Health and Nutrition Examination (NHANES III) 1988-94 and the Continuing Food Survey of Intakes by Individuals (CSFII) 1994-98, are the main source of dietary intake data for the U.S. population. NHANES III collected information on the U.S. population aged ≥2 months. Mexican Americans and non-Hispanic African-Americans, children ≤5 years old, and adults ≥ 60 years old were over-sampled to produce more precise estimates for these population groups. There were no imputations for missing 24-hour dietary recall data. A total of 29,105 participants had complete and reliable dietary recall. Complete descriptions of the methods used and fuller analyses are available in the report *Effects of Omega-3 Fatty Acids on Cardiovascular Disease*, under "Methods: Method to Assess the Dietary Intake of Omega-3 Fatty Acids in the US population" and "Results: Population Intake of Omega-3 Fatty Acids in the United States".

CSFII 1994-96, popularly known as the *What We Eat in America* survey, addressed the requirements of the National Nutrition Monitoring and Related Research Act of 1990 (Public Law 101-445) for continuous monitoring of the dietary status of the American population. In CSFII 1994-96, an improved data-collection method known as the multiple-pass approach for the 24-hour recall was used. Given the large variation in intake from day-to-day, multiple 24-hours recalls are considered to be the best suited for most nutrition monitoring and will produce stable estimates of mean nutrient intakes from groups of individuals.[9]

In 1998, the Supplemental Children's Survey, a survey of food and nutrient intake by children under age of 10, was conducted as the supplement to the CSFII 1994-96. The CSFII 1994-96, 1998 surveyed 20,607 people of all ages with over-sampling of low-income population (<130% of the poverty threshold). Dietary intake data by individuals of all ages were collected over 2 nonconsecutive days by use of two 1-day dietary recalls.

Table 1.1 reports the NHANES III survey mean intake ± the standard error of the mean (SEM), as well as, the median and range for each omega-3 fatty acid. Distributions of EPA, DPA, and DHA were skewed; therefore, the means and standard errors of the means should be used and interpreted with caution. Table 1.2 reports the CSFII survey mean and median intakes for each omega-3 fatty acid, along with SEMs, as reported in Dietary Reference Intakes by the Institute of Medicine.[2] Estimates of intake from these reports may underestimate total consumption since they do not include intake from dietary supplements and fortified foods.

Table 1.1 Estimates of the mean±standard error of the mean (SEM) intake of linoleic acid (LA), alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) in the United States population, based on analyses of a single 24-hour dietary recall of NHANES III data

	Grams/day		% Kcal/day	
	Mean±SEM	**Median (range) [a]**	**Mean±SEM**	**Median (range) [a]**
LA (18:2 n-6)	14.1±0.2	9.9 (0 - 168)	5.79±0.05	5.30 (0 - 39.4)
ALA (18:3 n-3)	1.33±0.02	0.90 (0 - 17)	0.55±0.004	0.48 (0 - 4.98)
EPA (20:5 n-3)	0.04±0.003	0.00 (0 - 4.1)	0.02±0.001	0.00 (0 - 0.61)
DHA (22:6 n-3)	0.07±0.004	0.00 (0 - 7.8)	0.03±0.002	0.00 (0 -2.86)

a The distributions are not adjusted for the over-sampling of Mexican Americans, non-Hispanic African-Americans, children ≤5 years old, and adults ≥ 60 years old in the NHANES III dataset.

Table 1.2 Mean, range, median, and standard error of the mean (SEM) of usual daily intakes of linoleic acid (LA), total omega-3 fatty acids (n-3 FA), alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA) and docosahexaenoic acid (DHA) in the US population, based on CSFII data (1994-1996, 1998)

	Grams/day	
	Mean±SEM	**Median±SEM**
LA (18:2 n-6)	13.0±0.1	12.0±0.1
Total n-3 FA	1.40±0.01	1.30±0.01
ALA (18:3 n-3)	1.30±0.01	1.21±0.01
EPA (20:5 n-3)	0.028	0.004
DPA (22:5 n-3)	0.013	0.005
DHA (22:6 n-3)	0.057±0.018	0.046±0.013

Dietary Sources of Omega-3 Fatty Acids

Omega-3 fatty acids can be found in many different sources of food, including EPA and DHA from fish and shellfish, and ALA from some nuts and various plant oils. They are summarized on the USDA website http://www.nal.usda.gov/fnic/foodcomp (accessed November 3, 2003; Finfish and Shellfish Products: sr16fg15.pdf; Fats and Oils: sr16fg04.pdf; and Nut and Seed Products: sr16fg12.pdf).[10]

Potential Benefits of Omega-3 Fatty Acids in Organ Transplantation

The multiple biological effects of omega-3 fatty acids and observations in non-transplant settings provided a rationale for clinical trials in organ transplantation.[11-13] The largest experience has been in kidney transplantation in which laboratory, animal and early human studies suggested that omega-3 fatty acid supplementation, mostly fish oil, had the potential to decrease cyclosporine (CsA) nephrotoxicity, decrease rejection, improve hyperlipidemia, and reduce hypertension. Other benefits had also been suggested such as improvement in risk factors for thrombosis, restoration of erythrocyte deformability, and blood viscosity. There is far less experience in other forms of organ transplantation, although the effects of omega-3 fatty acids have been evaluated in the setting of heart, liver and bone marrow transplantation where similar benefits had been anticipated.

Reduction in CsA nephrotoxicity

A major advance in organ transplantation was the introduction of cyclosporine (CsA), which greatly improved graft survival. However, CsA is associated with many side effects, especially nephrotoxicity. CsA causes a dose-dependent decrease in glomerular filtration rate (GFR), leading to afferent arteriolar vasoconstriction an increase in blood pressure.[14-16] These effects appear to be related to alteration in the production of vasodilatory and vasoconstrictive eicosanoids. In particular, CsA-induced kidney dysfunction is associated with increased production of thromboxane A2, leukotriene C4, and leukotriene D4.[17,18]

Kidney dysfunction occurring within the first few weeks after transplantation may be reversible. Possible causes include acute tubular necrosis, rejection, vascular thrombosis, urinary

obstruction or leak, hemolytic-uremic syndrome, and CsA nephrotoxicity. Amelioration of CsA-induced vasoconstriction by omega-3 fatty acids would be clinically relevant. Of greater concern is chronic nephropathy, which is characterized by the development of diffuse interstitial fibrosis and progressive loss of kidney function.[19]

Animal studies of cyclosporine nephrotoxicity demonstrated that supplementation with omega-3 fatty acids improved markers of nephrotoxicity while reducing tissue and urine concentrations of thromboxane A2.[20] Similar results have been observed in cell culture studies in which macrophages stimulated with CsA produced less thromboxane A2 when animal had been fed a diet enriched with fish oil.[21] Human studies also demonstrated that supplementation with fish oil reduced production of thromboxane A2.[22]

Reduction in rejection

Several lines of evidence suggested that omega-3 fatty acids had the potential to reduce organ rejection following transplantation. Enhanced immunosuppressive effects of CsA and delayed hypersensitivity were observed in rats undergoing heart transplantation.[23,24] Reduction in generation of pro-inflammatory products (such as interleukins-1, -2, and-6, and tumor necrosis factor alpha) had also been described in humans and animals.[25-28] Expression of these cytokines is increased in kidney allograft rejection.[29-34] Interleukin-1 and tumor necrosis factor alpha both stimulate the production of interleukin-6 (a primary mediator of the acute phase response) while also participating in B- and T-cell activation and maturation.[33-35] Tumor necrosis factor alpha and interleukin-1 also stimulate macrophages and increase the expression of the class II major histocompatability complex.[33,34,36]

Hyperlipidemia

Hyperlipidemia is common following organ transplantation.[37]Atherosclerosis resulting from hyperlipidemia is associated with increased long-term morbidity and mortality related to heart and cerebrovascular disease, particularly following kidney transplantation. Data from the United Network for Organ Sharing suggest that overall 10-year patient survival following kidney transplantation is 58 and 77 percent, for recipients of deceased donor and living related allografts, respectively.[38] Cardiovascular disease remains the major cause of death with a functioning graft.[39]

The most frequently observed form of hyperlipidemia is hypertriglyceridemia, although some patients have isolated hypercholesterolemia. Regardless of the type of transplant, the cause is multifactorial, but in large part related to the use of corticosteroids and other immunosuppressive agents such as CsA.

The potential effect of omega-3 fatty acid supplementation on lipid metabolism in the non-transplant setting has been reviewed in detail in a previous evidence report from the Tufts-NEMC EPC.[40] The available data suggested that there is a large, consistent benefit of omega-3 fatty acids only on triglyceride levels while small or inconsistent effects were found for a variety of other cardiovascular risk factors and markers of cardiovascular disease.

Hypertension

Hypertension is common following organ transplantation. Although its etiology is incompletely understood, it is generally agreed that CsA is a major contributor. Studies in bone marrow and heart transplantation (settings in which initial or baseline kidney dysfunction is less likely to be present and thus contribute to hypertension) demonstrated that the incidence of hypertension was below 10 percent prior to the introduction of CsA, compared with 33 to 60 percent following bone marrow transplantation and 70 to 100 percent following heart transplantation after CsA had been introduced.[41]

A potential modest benefit of omega-3 fatty acids on blood pressure may result from favorable changes in the eicosanoid profile, helping to restore the balance between vasodilatory and vasoconstrictive eicosanoids. In a systematic review in the non-transplant setting conducted by the Tufts-NEMC EPC,[40] fish oil supplementation was associated with a mean net change in systolic and diastolic blood pressure of -2.1 mm Hg (95% confidence interval -3.2, -1.0) and -1.6 mm Hg (-2.2, -1.0), respectively.[42]

Miscellaneous effects

A variety of other potential benefits from omega-3 fatty acid supplementation have been proposed in the non-transplant setting, all of which provided the basis for study in patients undergoing transplantation.

- The observation that an elevated level of leukotriene B4 was a risk factor for acute colonic graft versus host disease following bone marrow transplantation suggested that omega-3 fatty acid supplementation may help prevent this complication.[43]

- Dietary supplementation with fish oil improved endothelial function in hypercholesterolemic and atherosclerotic porcine models.[44-46] Endothelial dysfunction is known to be present in patients undergoing heart transplantation.[47,48]

- CsA may decrease erythrocyte deformability, a mechanism that may contribute to its toxicity. Supplementation with fish oil had favorable effects on erythrocyte deformability in healthy subjects and those on dialysis.[49-51]

- Fish oil decreased whole blood viscosity in healthy subjects.[52-54]

Chapter 2. Methods

Overview

This evidence report on omega-3 fatty acids and organ transplantation is based on a systematic review of the literature. The Tufts-New England Medical Center Evidence-based Practice Center (Tufts-NEMC EPC) held meetings and teleconferences with technical experts including a Technical Expert Panel (TEP) as well as individual experts in relevant areas of transplantation to identify specific issues central to this report. A comprehensive search of the medical literature was conducted to identify studies addressing the key questions. Evidence tables of study characteristics and results were compiled, and the methodological quality of the studies was appraised. Study results were summarized with qualitative reviews of the evidence, summary tables, and meta-analyses, as appropriate.

A number of individuals and groups supported the Tufts-NEMC EPC in preparing this report. The TEP served as our science partner. It included technical experts, representatives from the Agency for Healthcare Research and Quality (AHRQ), and institutes at the National Institutes of Health (NIH) to work with the EPC staff to refine key questions, identify important issues, and define parameters to the report. Additional domain expertise was obtained through local experts who joined the EPC.

The Tufts-NEMC EPC also worked in conjunction with EPCs at the University of Ottawa and the Southern California EPC-RAND. The 3 EPCs coordinated efforts to produce evidence reports on 10 topics related to omega-3 fatty acids over a 2-year period, with the goal of producing evidence reports with a uniform format. Evidence table layout, and study quality assessment were standardized. In addition, literature searches for all evidence reports were performed by the University of Ottawa EPC, using identical search terms for studies of omega-3 fatty acids. The 3 EPCs agreed on a common definition of omega-3 fatty acids; however some variation in definitions and study eligibility criteria were permitted that reflected different topics and key questions. The studies included are described below, under Full Article Inclusion Criteria.

Key Questions Addressed in this Report

Nine key questions are addressed in this report, which fall under 5 major categories.

Graft-Related Outcomes

Question 1. What is the evidence that omega-3 fatty acid supplementation reduced rejection episodes or graft failure in patients (adults or children) who received an organ transplant?

Question 2. What is the evidence that omega-3 fatty acid supplementation is renoprotective (improves glomerular filtration rate or increases kidney size) or is protective against primary kidney disease recurrence following kidney transplantation?

Cardiovascular Disease-Related Outcomes

Question 3. What is the evidence that omega-3 fatty acid supplementation lowers cardiovascular disease risk factors or events in organ transplant recipients (adults or children)?

Infectious Outcomes

Question 4. What is the evidence that omega-3 fatty acid supplementation reduces serious infectious complications following organ transplantation?

All Outcomes

Question 5. What is the evidence that any benefits to organ transplant recipients from omega-3 fatty acid supplementation differ in different subsets of patients?

Question 6. What is the evidence that effects of omega-3 fatty acid supplementation on outcomes of interest vary depending on the time of administration relative to transplantation procedures (pre- or post-transplant)?

Effects On Immunosuppressive Agents And Related Drugs

Question 7. What is the evidence in patients (adults or children) who receive an organ transplant that the benefits of omega-3 fatty acid supplementation interact with the concomitant administration of various immunosuppressive agents/drugs?

Question 8. What is the evidence in patients (adults or children) who receive an organ transplant that serum levels of immunosuppressive agents/drugs are altered by omega-3 fatty acid supplementation?

Question 9. What is the evidence in patients (adults or children) who receive an organ transplant that omega-3 fatty acid supplementation can replace or reduce the need for other more potent anti-inflammatory or immunosuppressive drugs (such as steroids and non-steroidal anti-inflammatory drugs)?

Analytic Framework

To guide our assessment of studies that examine the association between omega-3 fatty acids and transplantation outcomes, we developed an analytic framework that maps the specific linkages associating the populations of interest, the exposures, modifying factors, and outcomes

of interest (Figure 2.1). The framework, depicted graphically below, presents the key components of the study questions:

1) What type of organ transplantation did the participants receive?

2) What were the interventions?

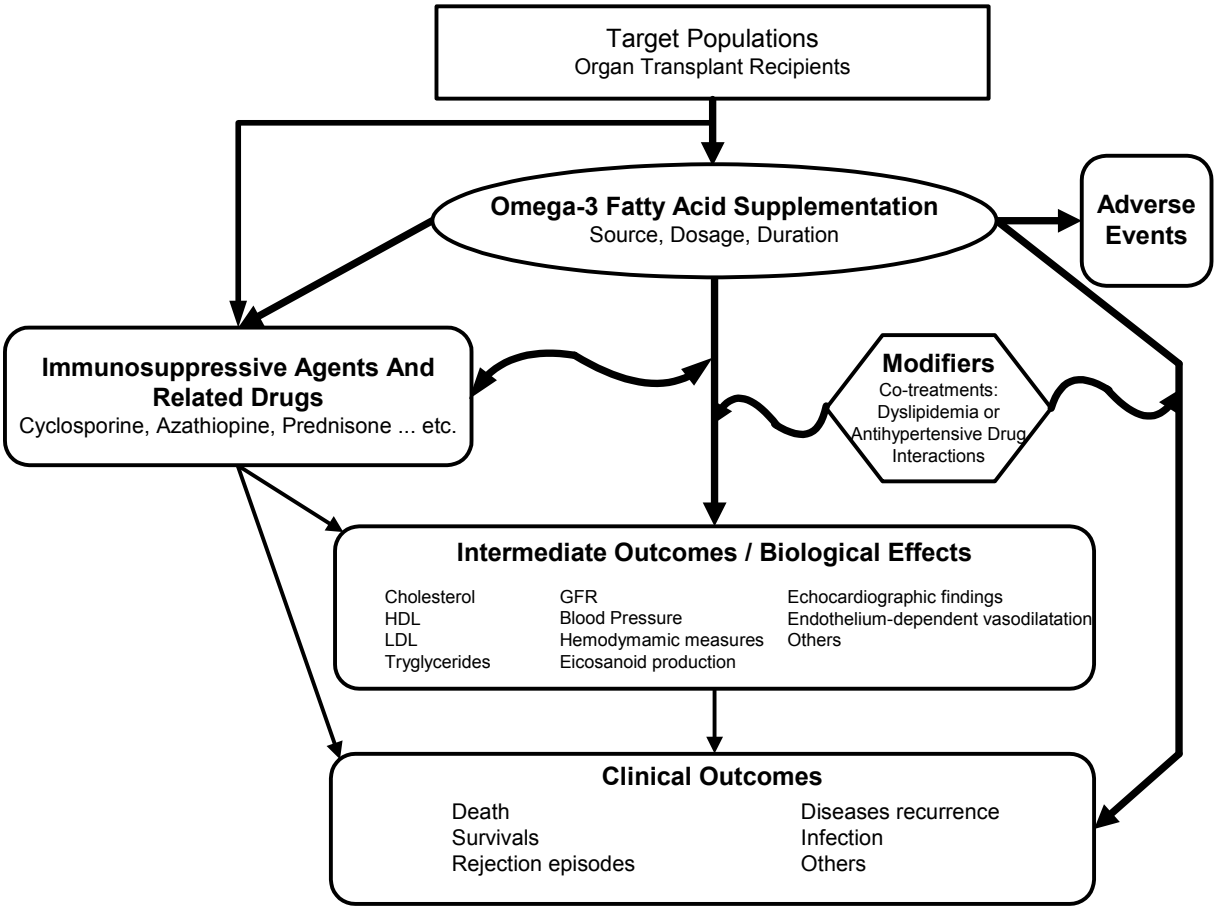
3) What were the outcomes of interest (intermediate and clinical outcomes)?

4) What were the study designs?

The analytic framework illustrates the chain of logic that evidence must support to link the intervention (exposure to omega-3 fatty acids) to improved clinical outcomes.

This report reviews the evidence addressing the associations or effects of omega-3 fatty acid supplementation in organ transplant recipients on graft-related, cardiovascular-disease related, infectious, and all other transplantation-related outcomes. Also examined are effects on immunosuppressive agents and related drugs.

Figure 2.1. Analytic framework for omega-3 fatty acid intervention and transplantation outcomes. Populations of interest are noted in the top rectangle, exposure in the oval, outcomes in the rounded rectangles, and effect modifiers in the hexagon. Thick connecting lines indicate associations and effects reviewed in this and the accompanying report. Lists noted in a smaller font indicate the specific factors reviewed. GFR indicates glomerular filtration rate; HDL, high-density-liproproten cholesterol; LDL, low-density-lipoprotein cholesterol.



The most important questions relating to omega-3 fatty acid supplementation pertain to their effects on clinical outcomes such as graft survival or cardiovascular events. However, some of these (such as cardiovascular events) are difficult to assess since they may not occur for many years after transplantation. As a result, established risk factors for such adverse outcomes (such as hyperlipidemia) are also relevant since they may provide a surrogate measure of potential treatment benefits. Thus, in addition to clinical events such as episodes of rejection and rates of graft survival, this report examines whether omega-3 fatty acid supplementation reduces the likelihood or severity of risk factors (such as hyperlipidemia, high blood pressure) for clinical events.

Some of these measures are potentially modified by various factors, including use of concomitant drugs (such as lipid lowering agents), demographic features (e.g., sex, age), baseline diet, the time in which treatment was begun relative to the transplant, and subject characteristics

(e.g., baseline renal function). This report considers the potential influences of these factors on the observed results following omega-3 fatty acid supplementation.

The analytic framework does not directly address the level of evidence that is necessary to evaluate each of the effects. Large randomized controlled trials that are adequately blinded and otherwise free of substantial bias provide the best evidence to prove a causal relationship between intervention and outcome. Thus, the current analysis relies as much as possible on high quality, randomized controlled trials.

However, randomized controlled trials are not always available (or feasible), and may not be well-conducted or reported. Thus, other types of study designs must also be considered. Crossover trials have the advantage of controlling fully for bias due to differences between study arms but may introduce bias due to incomplete washout or an order effect. In addition, they are generally small and have a narrow range of subjects. Uncontrolled trials and observational studies provide lesser degrees of evidence that are usually hypothesis-generating regarding causality.

Literature Search Strategy

We conducted a comprehensive literature search to address the key questions (Appendix A.1, available electronically at http://www.ahrq.gov/clinic/epcindex.htm). Relevant studies were identified primarily through search strategies conducted in collaboration with the University of Ottawa EPC. The Tufts-NEMC EPC used the Ovid search engine to conduct preliminary searches on the MEDLINE database. The final searches used 6 databases including MEDLINE, MEDLINE In Process and Other Non-Indexed Citations, Embase, CAB abstracts, BIOSIS abstracts, and Central Cochrane Database of Systematic Reviews from 1966 to week 4 2003. Subject headings and text words were selected so that the same set could be applied to each of the different databases. Following the initial electronic search, tables of contents of major transplant and clinical specialty journals were hand searched during the period while this report was being completed until preparation of the final manuscript.

Additional sources of published and unpublished data were sought by contacting the TEP as well as authors of controlled trials identified in our initial search. Bibliographies of all retrieved studies (including review articles) were also examined.

Study Selection

Abstract Screening

All abstracts identified through the literature search were screened manually and in triplicate by three independent investigators. Triplicate screening was performed because the modest number of abstracts allowed us to gather additional data for methodology research pertaining to the most efficient method of abstract screening. Eligibility criteria were defined broadly to include all studies (regardless of language of publication, experimental design, or size) that evaluated any potential source of omega-3 fatty acids in human subjects who underwent organ

transplantation, and reported any outcome. Any abstract identified by any independent investigator was retrieved for further review.

Full Article Inclusion Criteria

The full text of studies selected by the abstract screening process was reviewed by 3 independent investigators. Studies of any design (including controlled trials, cohort studies, case series and case reports), size, and language were included provided that they reported any outcome in adults or children undergoing organ transplantation who received omega-3 fatty acids.

Studies were excluded if they focused on nonhuman subjects, were review articles or other articles without primary sources of data, focused on subjects who did not undergo organ transplantation, did not use omega-3 fatty acids, or if the amount of omega-3 fatty acids could not be quantified. Acceptable sources of omega-3 fatty acids included fish oil, vegetable oils containing ALA (i.e., canola, rapeseed, soybean, flaxseed, linseed, walnut, mustard seed), Mediterranean diet, or other sources where the quantity was reported explicitly. Pharmaceutical companies and individuals in relevant countries were contacted when a brand name of a fish oil supplement was provided without a quantitative description of its components.

The authors, study locations, and dates of all retrieved studies were compared to identify duplicate reports of the same subjects. Where there was any ambiguity, an attempt was made to contact authors of the relevant publications. Duplicate reports were included if they provided additional data; however, subjects were included and accounted for only once.

Data Extraction Process

Electronic data extraction forms and a database were created in a multi-step process during which the key study questions were translated into a structure that was applicable to all types of transplants and outcomes of interest. Frequent and regular discussions helped to ensure use of uniform definitions. Thus, multiple versions of the data extraction forms were tested by several investigators on samples of the included studies, until a final version was achieved. All investigators were trained on how to complete the form to assure consistency among extractors.

All studies were extracted by 3 independent investigators to allow for future methodology research aimed at comparing double versus single data extraction. The extraction team included investigators skilled in foreign languages so that non-English studies could be included.

Study features extracted included the design, blinding, randomization method, allocation concealment method, country, funding source, duration, quantity and type of omega-3 fatty acids, eligibility criteria, control interventions, sample characteristics (and their comparability), reasons for withdrawals and all reported outcomes. (Appendix B, available electronically at http://www.ahrq.gov/clinic/epcindex.htm). In addition, each study was categorized based on study quality as described below.

Two investigators compared the results of the triplicate data extraction forms. Discrepancies were resolved by discussion and review of the original study until consensus was achieved for all data points.

Grading of the Evidence

Studies accepted in evidence reports have been designed, conducted, analyzed, and reported with varying degrees of methodological rigor and completeness. Deficiencies in any of these components can lead to biased reporting and interpretation of the results. While it is desirable to grade individual studies to highlight the degree of potential bias, the grading of study quality is not straightforward. Most factors commonly used in quality assessment of randomized controlled trials have not been sufficiently validated to be certain about their relationship to estimates of treatment effects.[55] Thus, there is still no uniform approach to grade studies. As a result, various EPCs have previously used different approaches to grade study quality.

Common Elements for Grading Methodological Quality of Randomized Controlled Trials in Evidence Reports

As part of the overall omega-3 fatty acid project, the 3 collaborating EPCs agreed to use the Jadad Score and adequacy of random allocation concealment as elements to grade individual randomized controlled trials.[56,57] The EPCs also agreed to permit inclusion of other quality elements that were considered to be appropriate for a generic quality score.

There was consensus among the 3 EPCs that studies should not be graded using a single, quantitative summary score, since such scores are often arbitrary and unreliable.[58] The Jadad Score assesses the quality of randomized controlled trials using 3 criteria: adequacy of randomization, double blinding, and dropouts.[56] Studies fulfilling all three criteria receive a maximum score of 5 points. In addition, adequacy of allocation concealment was assessed using the criteria by Schulz et al, as "adequate," "inadequate," or "unclear".[57]

Generic Summary Quality Grade for Studies

A limitation of the Jadad and Schulz scores is that they address only some aspects of the methodological quality. These scores do not include other elements of study quality, such as potential biases due to reporting and analytic problems. Furthermore, these scoring systems are applicable only to randomized controlled trials.

Thus, to supplement these scores, a 3-category grading system (A, B, C) was applied to each study. This grading system has been used in most of the previous evidence reports from the Tufts-NEMC EPC as well as in evidence-based clinical practice guidelines.[59] This system defines a generic grading system that is applicable to varying study designs including randomized controlled trials, cohort, and case-control studies:

A Category A studies have the least bias and results are considered valid. A study that adheres mostly to the commonly held concepts of high quality including the following: a formal randomized study; clear description of the population, setting, interventions and comparison groups; clear description of the content of the placebo used; appropriate measurement of outcomes; appropriate statistical and analytic methods and reporting; no reporting errors; less than 20% dropout; clear reporting of dropouts; and no obvious bias.

B Category B studies are susceptible to some bias, but not sufficient to invalidate the results. They do not meet all the criteria in category A because they have some deficiencies, but none likely to cause major bias. The study may be missing information, making it difficult to assess limitations and potential problems.

C Category C studies have significant bias that may invalidate the results. These studies have serious errors in design, analysis or reporting, have large amounts of missing information, or discrepancies in reporting.

In addition to applying these 3 grading systems, additional comments relating to potential sources of bias and other study limitations were recorded by each investigator during the data extraction process. Such comments are included in the evidence tables.

Applicability grades, used in other evidence reports related to omega-3 fatty acids, were not included. The grades were designed to address the relevance of a given study to a population of interest. Such a framework was not considered to be relevant in the current report since all studies focused on patients undergoing organ transplantation, which is already a narrowly defined population.

Reporting Results

Results that are included in this report were determined through discussions with members of the TEP as well as additional experts in transplantation. This process allowed us to focus on the major outcomes of interest (and methods for their measurement) that were relevant to the TEP key questions, were available in the identified literature, and relevant for specific area of transplantation. These endpoints are featured in the evidence tables, but all measured endpoints are also included.

- Major outcomes for kidney transplantation included the post-transplant glomerular filtration rate (GFR), blood pressure, lipid profile, patient and graft survival, episodes of rejection, and dose and trough levels of CsA.

- Major outcomes for heart transplantation included post-transplant hypertension, renal function, lipid levels, rejection episodes (including surrogate markers) and coronary disease (including surrogate markers).

- All outcomes for other forms of transplant (i.e, bone marrow and liver) were included in the evidence tables since, as will be noted below, only 1 study in each category was identified.

As a general rule, when more than 1 time-point was reported for a specific outcome (e.g., glomerular filtration rate), the result representing the longest time point from study inception was included in the primary analysis. However, additional analyses were performed for questions that were of clinical interest or relevant to the TEP questions (e.g., examining the effects of fish oil supplementation on early versus late rejection).

Studies describing renal function after transplantation frequently described the results of more than 1 method to assess it. All methods are described in the evidence tables. However, the most rigorous method was highlighted and used for comparison across studies whenever available. In particular, direct measurement of the GFR with a radioisotope study or inulin clearance was considered to provide the best estimate of renal function compared with indirect methods (such as the calculated GFR) or serologic markers such as the plasma concentration of blood urea nitrogen or creatinine.[60]

Important covariates and study characteristics were also featured. These included, for example, the doses and types of immunosuppressant medications, type of transplant (live donor versus cadaveric), specific time in which the omega-3 fatty acid was introduced relative to the transplant, duration of follow-up, concomitant use of antihypertensive medications and lipid lowering agents, all of which may have an influence on the major outcomes of interest.

Many of the outcomes of interest were continuous variables such as blood pressure, GFR, and lipid levels. For these outcomes, the summary tables describe 3 sets of data: the mean baseline level in the omega-3 fatty acid arm, the net change of the outcome, and the reported *P* values of the difference between the omega-3 fatty acid and the control arms. The net change of the outcome is the difference between the change in the omega-3 fatty acid arm and the change in the control arm:

$$\text{Net change} = (\text{Omega-3}_{\text{Final}} - \text{Omega-3}_{\text{Initial}}) - (\text{Control}_{\text{Final}} - \text{Control}_{\text{Initial}}).$$

While some studies reported adjusted and unadjusted within-arm and between-arm (net) differences, to maintain consistency across studies, we calculated the unadjusted net change using the above formula for all studies when the data were available. All exceptions and caveats are described in footnotes.

We included only the reported *P* values for the net differences. We did not calculate any *P* values, but, when necessary, used provided information on the 95% confidence interval or standard error of the net difference to determine whether it was less than .05. We included any reported *P* value less than .10. Those above .10 and those reported as "non-significant" were described as "NS" (non-significant) in the tables.

For measures expressed using standard or Systeme International (SI) units (e.g. lipid levels), the original units reported in the study were included in the evidence tables. However, all such measurements were converted to standard units in the summary and results tables to facilitate comparisons.

Uncontrolled trials were described (e.g. case reports), and, when within group comparisons were made, the within-group change was reported along with its associated *P* value.

Meta-analysis

For dichotomous or categorical variables, the rates in the treatment and control groups were expressed as a relative risk and 95% confidence intervals. Among these, there were sufficient, clinically comparable data to combine the results of graft or patient survival and rejection episodes in kidney transplantation. This was accomplished using a random effects model meta-analysis.[61]

For rejection episodes, calculations were performed with the patient (not the rejection episode) as the unit of analysis (since individual patients could have had more than one rejection

episode). Thus, the proportion of patients having a rejection episode at various time points (rather than the total number of rejection episodes) was compared across treatment groups.

Evidence and Summary Tables

The evidence is described in two complementary ways:

Evidence tables offer a detailed description of the studies that addressed each of the key questions. These tables provide information about the study design, patient characteristics, inclusion and exclusion criteria, interventions and comparison groups evaluated, and outcomes. Outcome data are reported in the units and metrics reported in the articles. Each study appears once regardless of how many interventions our outcomes were reported. Studies are ordered alphabetically by the first author.

Summary tables report succinctly using summary measures of the main outcomes. They include information regarding study size, intervention and control, study population, outcome measures, and methodological quality. These tables were developed by condensing information from the evidence tables. Outcome units and metrics are reported in standard units and as in common metrics, regardless of how these were reported in the articles. They are designed to facilitate comparisons and synthesis across studies. Studies reporting multiple outcomes may appear several times in summary tables.

Studies are grouped first according to the time of introduction of omega-3 fatty acids relative to the transplant and then by the dose of omega-3 fatty acids used. Controlled trials are featured separately from uncontrolled trials and case series.

Chapter 3. Results

This chapter summarizes results of our literature search and findings from the studies that passed our screening and selection process. We considered all types of transplants together in attempting to answer the key questions posed by the TEP whenever feasible. An example is the effect of omega-3 fatty acid supplementation on the pharmacokinetics of cyclosporine, an interaction that may be apparent regardless of the type of transplant. On the other hand, all key questions were also addressed with specific consideration of the different transplantation types (i.e., kidney, heart, bone marrow, and liver) since the potential effects may vary by transplant type and because there are clinical issues specific to each form of transplantation.

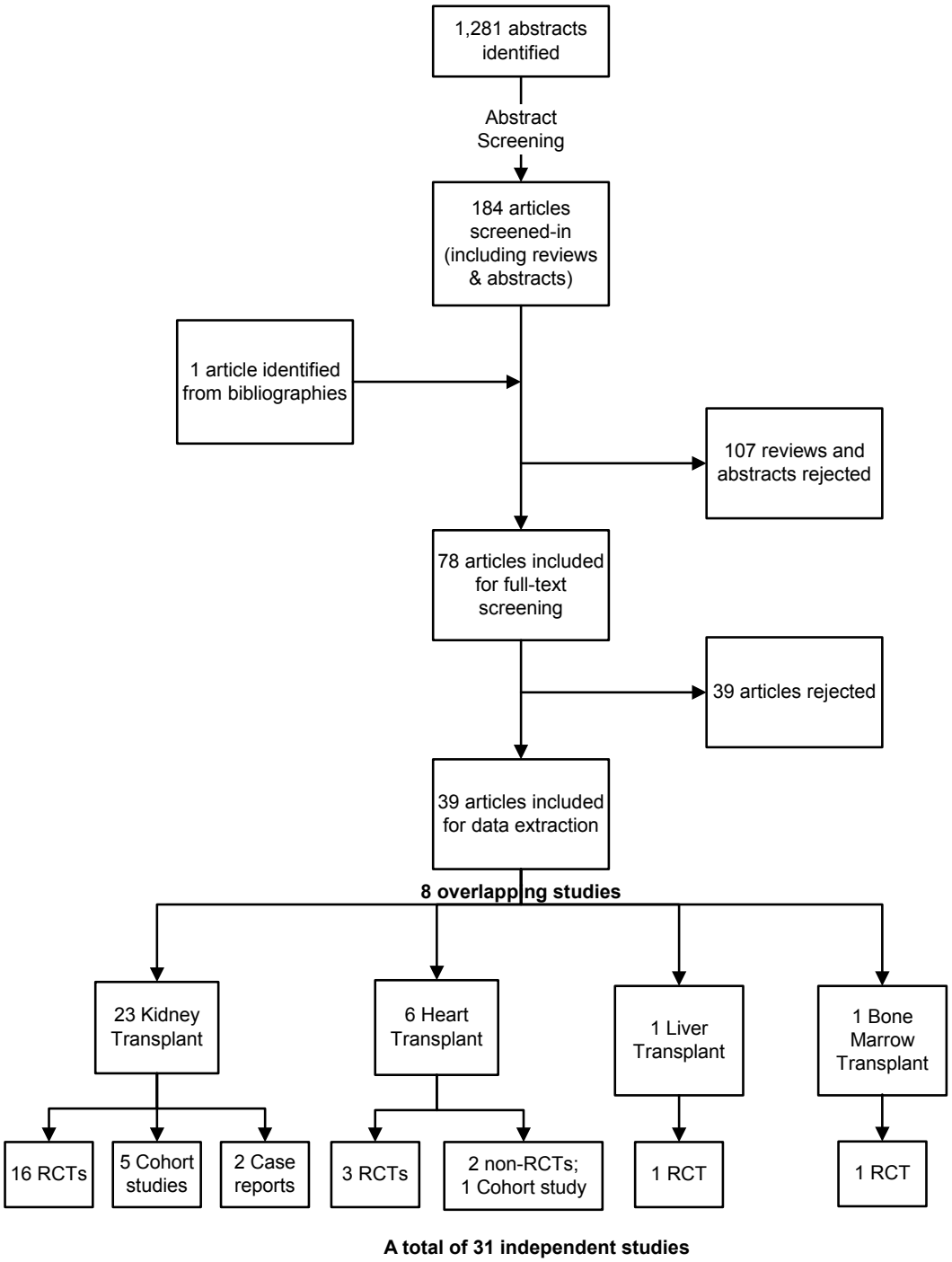
Summary of Studies Found

The literature search identified 1,281 abstracts. From these, and from the articles found in bibliographies, a total of 78 studies were ultimately selected for full-text screening (based upon the initial abstract screening and review of the bibliographies of retrieved studies including review articles). Thirty nine of these were rejected because they did not fulfill inclusion (See Reference List of Rejected Articles) criteria leaving 39 for inclusion. Careful additional review of these studies revealed 8 that were duplicate reports of the same patients leaving a total of 31 independent reports. There were 23 kidney transplant studies with a total of 846 patients, 6 heart transplant studies with 233 patients, 1 liver transplant study with 26 patients, and 1 bone marrow transplant study with 17 patients. The study designs of the qualifying studies include 21 RCTs, 2 non-RCTs, 6 prospective cohort studies and 2 case reports (Figure 3.1). Fish oil supplements were used in all but 1 heart transplant study in which a Mediterranean diet was used.[62] Since the biological effects of long-chain omega-3 fatty acids (EPA and DHA) are different from ALA, the results should be considered separately. As a result, the findings of this report apply almost exclusively to fish oil supplementation.

Twelve study authors of the largest controlled trials were contacted (by telephone or email or both) and, of them, 5 responded. None was aware of additional published or unpublished data. Similarly, the final list of included studies was considered to be complete after review by the TEP. One member of the TEP reported that he was involved in a pilot study involving omega-3 fatty acids in kidney transplantation that had not yet been completed; he provided a draft manuscript, which is described at the end of this chapter.

The studies are described in the evidence tables, which have been designed to feature key elements of the studies and allow for easy comparison across studies.

Figure 3.1. Summary of study selection processes. RCTs indicates randomized-controlled trials; non-RCT indicates non-randomized-controlled trials



Quality of the Studies

Studies were generally small, and many had important methodological limitations as indicated by the quality measures in summary tables. Masking and methods of randomization were generally not well described. Even among studies in which masking of patients and caregivers was described, it is likely that patients and caregivers became unmasked since fish oil supplementation was frequently associated with a fishy taste and dyspeptic side-effects in the active intervention arm, especially early in the course of treatment. Many controlled trials did not use isocaloric treatments or fats with comparable fatty-acid profiles in the control group, potentially biasing comparisons, especially for cardiovascular outcomes. Furthermore, there was variability in the degree to which compliance was assessed.

Similarly, there was variability in the rigor with which endpoints were defined and measured. Important covariates (such as use of antihypertensive agents or the intensity of immunosuppression) were often not well described or uniformly applied even when the study considered outcomes that may have been confounded by these factors.

Summary results were potentially underpowered since very few controlled studies analyzed the statistical significance for net differences in effects. Most studies only analyzed differences between groups at various time points during the study.

Graft Related Outcomes

Question 1: What is the evidence that omega-3 fatty acid supplementation reduced rejection episodes or graft failure in patients (adults or children) who received an organ transplant?

Kidney Transplantation

Patient survival

There were 7 deaths out of a total of 846 kidney transplant patients, all of which were reported in 3 studies.[63-65] A total of 4 patients died with a functional graft within 1 year of transplant (1 patient in the fish oil group and 3 patients in the placebo group).[63] One patient died of myocardial infarction in the placebo group.[64] In a 9-month randomized controlled trial (RCT), 2 patients in the fish oil group died due to hemorrhagic shock from removal of native polycystic kidney and intestinal infarction.[65]

Graft survival

A total of 10 RCTs, with 291 patients in the fish oil group and 312 patients in the placebo or control group, described graft survival among kidney transplant recipients.[28,63-70] However, most studies did not perform quantitative, graft survival analyses underscoring the excellent overall results in kidney transplantation regardless of fish oil supplementation. One exception was a

RCT in which one-year graft survival tended to be better in the fish oil group, although results did not achieve statistical significance.[64] Two other RCTs showed no statistically significant difference in one-year graft and patient survival rates between fish oil and placebo or control group.[28,67]

Fish oil supplementation was begun 3 days post-transplant in 7 of these 10 reports with a total of 228 and 234 subjects in the fish oil and control groups, respectively (Table 3.1). The studies were all of low or intermediate quality. The pooled relative risk of graft survival in those receiving fish oil supplementation was 1.00 (95% CI 0.96, 1.05). There was no statistical heterogeneity among studies.

Table 3.1 Effects of Fish oil on Graft Survival in Randomized-Controlled Trials in Kidney Transplant Patients

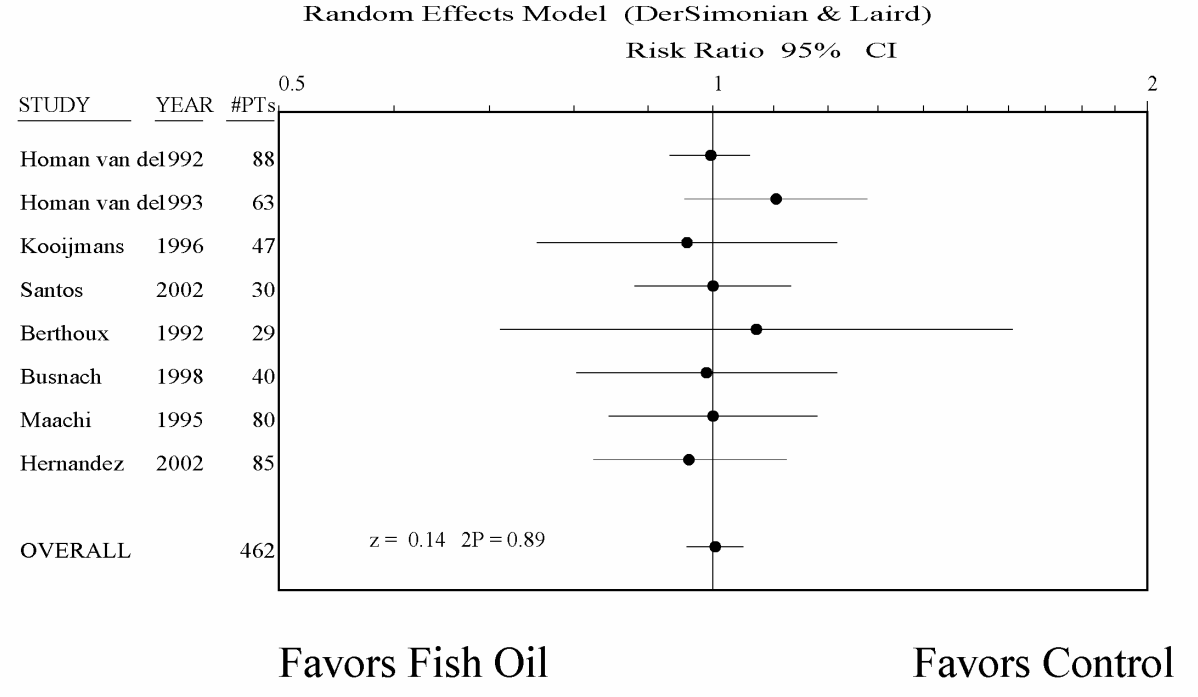
Author, Year	Fish oil EPA+DHA (g/d)	Placebo or Control Arm	Treatment Duration	Fish oil		Control		RR (95% CI)	Treatment Started (Post-transplant)	Quality [b]		
				Event	Total	Event	Total			Summary	Jadad	Allocation Conceal
Homan van der Heide, 1992	3.0	Coconut oil	1 mo	39	40	47	48	1.00 (0.93-1.06)	Day 3	B	3	Un
Homan van der Heide, 1993	3.0	Coconut oil	1 yr	30	31	28	32	1.11 (0.96-1.28)	Day 3	B	3	Un
Kooijmans-Coutinho, 1996	3.0	Coconut oil	1 yr	20	24	20	23	0.96 (0.75-1.22)	Day 3	B	5	In
Santos, 2000	3.0	Placebo	1 yr	15	15	15	15	1.00 (0.88-1.13)	Day 2	B	2	Un
Berthoux, 1992	2.7	No placebo	1 yr	11	14	11	15	1.07 (0.71-1.61)	Day 3	C	1	Un
Busnach, 1998	2.6	Olive oil	9 mo	17	19	19	21	0.99 (0.80-1.22)	Day 1	B	3	Un
Maachi, 1995	2.5	No placebo	1 yr	35	40	35	40	1.00 (0.85-1.18)	Day 3	C	1	Un
Hernandez, 2002	1.9	Soy oil	3 mo [a]	39	45	36	40	0.96 (0.83-1.12)	Day 2	B	3	Un
Random effects model meta-analysis: Total patients =				**206**	**228**	**211**	**234**	**1.00 (0.96-1.05)**				

Yr = year(s); mo = month(s); RR = Relative risk of fish oil arm to placebo/controlled arm; CI = confidence interval; Event = Number of survived grafts

[a] Treatment stopped at 3 months with follow-up results observed at 1 year

[b] Ad = adequate allocation concealment; In = inadequate allocation concealment; Un = allocation concealment unclear. See Methods.

Figure 3.2. Random Effects Model Meta-Analysis of Graft Survival in Randomized-Controlled Trials in Kidney Transplant Patients



In 2 studies,[66,68] fish oil was begun at 16 weeks and over one year post-transplant. Thus, the enrolled patients would be expected to have relatively stable renal function compared to the studies in which treatment was begun within days after transplant. No benefit from fish oil treatment was observed in either study (Table 3.2).

Table 3.2 Effects of Fish oil on Graft Survival in Randomized-Controlled Trials in Kidney Transplant Patients Who Received Delayed Treatment

Author, Year	Fish oil EPA+DHA (g/d)	Placebo or Control Arm	Treatment Duration	Fish oil Event	Fish oil Total	Control Event	Control Total	RR (95% CI)	Treatment Started (Post-transplant)	Quality [b] Summary	Quality [b] Jadad	Quality [b] Allocation Conceal
Bennet, 1995	5.4	Corn oil	26 wks	22	22	50	50 [a]	0.99 (0.92-1.06)	16 weeks	B	3	Un
	2.7	Corn oil	26 wks	18	18	50	50 [a]	0.98 (0.91-1.06)				
Castro, 1997	3.0	Simvastatin 10 mg/d	3 mo	18	18	25	25	0.99 (0.94-1.03	≥ 1 year	C	2	In

Wks = weeks; mo = month(s); RR = Relative risk of fish oil arm to placebo/controlled arm; Event = Number of survived grafts

[a] Data on high-dose and low-dose controls were combined.

[b] Ad = adequate allocation concealment; In = inadequate allocation concealment; Un = allocation concealment unclear. See Methods.

Furthermore, all grafts and patients survived in 2 prospective cohort studies with a total of 42 kidney transplant recipients who received fish oil treatments at least 6 months post-transplant.[71,72]

Rejection Episodes

Acute rejection episodes were described at varying time points in a total of 11 controlled trials, including 297 patients in the fish oil group and 282 patients in the placebo or control group.[28,63-67,69,70,73-76] The studies were all of low or intermediate quality. In all but 2 studies (published in 3 papers[66,75,76]), treatment had been initiated within 3 days following transplantation.

One study reported only total episodes of rejection according to treatment (rather than the proportion of patients having a rejection episode), noting a statistically significant reduction in the total number of rejection episodes in the group receiving fish oil.[64] However, it was not possible to tell whether these differences could have been accounted for by multiple episodes of rejection in a small number of patients (or even a single patient). The authors described six episodes of rejection in the fish oil group compared with 10 in the control group at one month. In the second and third months, there was only 1 acute rejection episode in the fish oil group compared with 9 in the control group (P=0.016). In months 4 through 6, there were no rejection episodes in either group. Between month 6 and 12, there was 1 rejection episode in each group. Thus, during the year after transplantation, the total number of acute rejection episodes was significantly lower in the fish oil group than in the controls (8 versus 20, P=0.029). These results did not translate into statistically significant improved graft survival at one year (97 versus 84 percent, P=0.097).

The other 8 randomized controlled trials (in which treatment was started within 3 days post-transplant) described the proportion of patients with at least one rejection episode. The results for "early" and "late" rejection (as defined above) were combined using a random effects model, which showed no significant benefit at any time point examined (Table 3.3). Results for 2 studies that reported rejection episodes between 2 to 9 and 3 to 12 months were not pooled since the time points reported combined "early" and "late" episodes together.[63,65] The pooled relative risk of a rejection episode in those receiving fish oil supplementation was 0.91 (95% CI 0.75, 1.11) in four studies with a total of 224 subjects that reported the longest follow-up (i.e., 1 year). There was no significant heterogeneity among the studies. To allow for clinically meaningful comparisons across studies, rejection episodes were defined as being "early" (within the first 6 months of transplant) or "late" (after 6 months), corresponding with generally accepted clinical criteria.

Table 3.3 Effects of Fish oil on the Proportion of Patients with an Acute Rejection Episode in Randomized-Controlled Trials in Kidney Transplant Patients Who Received Treatment Immediately after Transplant

Author, Year	Fish oil EPA+DHA (g/d)	Placebo or Control Arm	Treatment Duration	Fish Oil		Control		RR (95% CI)	Treatment Started (Post-transplant)	Quality [b]		
				Event	Total	Event	Total			Summary Jadad		Allocation Conceal
Homan van der Heide, 1992	3.0	Coconut oil	1 mo	15	40	12	48	1.50 (0.80-2.82)	Day 3	B	3	Un
Kooijmans-Coutinho, 1996	3.0	Coconut oil	1 mo	11	25	11	25	1.00 (0.54-1.87)	Day 3	B	5	In
Homan van der Heide 1990a	3.0	Coconut oil	1 mo	3	14	6	17	0.61 (0.18-2.00)	Day 3	B	3	Un
Busnach, 1998	2.6	Olive oil	1 mo	3	17	2	19	1.68 (0.32-8.88)	Day 1	B	3	Un
Hernandez, 2002	1.9	Soy oil	1 mo	16	45	12	40	1.19 (0.64-2.19)	Day 2	B	3	Un
Random effects meta-analysis: Total patients =				**48**	**141**	**43**	**149**	**1.16 (0.83-1.63)**				
Kooijmans-Coutinho, 1996	3.0	Coconut oil	2-3 mo	13	23	3	24	4.52 (1.48-13.8)	Day 3	B	5	In
Hernandez, 2002	1.9	Soy oil	2-3 mo	4	45	4	40	0.89 (0.23-3.3)	Day 2	B	3	Un
Random effects meta-analysis: Total patients =				**17**	**68**	**7**	**64**	**2.04 (0.43-9.62)**				
Busnach, 1998	2.6	Olive oil	2-9 mo	0	17	1	19	-	Day 1	B	3	Un
Kooijmans-Coutinho, 1996	3.0	Coconut oil	3-12 mo	3	22	3	22	1.00 (0.23-4.42)	Day 3	B	5	In
No meta-analysis performed for this group of data												
Santos, 2000	3.0	Placebo	1 yr	4	15	6	15	0.67 (0.23-1.89)	Day 2	B	2	Un
Berthoux, 1992	2.7	No placebo	1 yr	9	14	10	15	0.96 (0.57-1.64)	Day 3	C	1	Un
Maachi, 1995	2.5	No placebo	1 yr	29	40	32	40	0.80 (0.71-1.16)	Day 3	C	1	Un
Hernandez, 2002	1.9	Soy oil	3 mo [a]	20	45	19	40	0.94 (0.59-1.48)	Day 2	B	3	Un
Random effects meta-analysis: Total patients =				**62**	**114**	**67**	**110**	**0.91 (0.75-1.11)**				

Yr = year(s); mo = month(s); RR = Relative risk of fish oil arm to placebo/controlled arm; Event = number of patients with at least one rejection episodes

[a] Treatment was stopped at 3 months with follow-up results reported at 1 year

[b] Ad = adequate allocation concealment; In = inadequate allocation concealment; Un = allocation concealment unclear. See Methods.

Figure 3.3. Random Effects Model Meta-Analysis of Proportion of Patients with an Acute Rejection Episode within First Month of Kidney Transplantation in Randomized-Controlled Trials

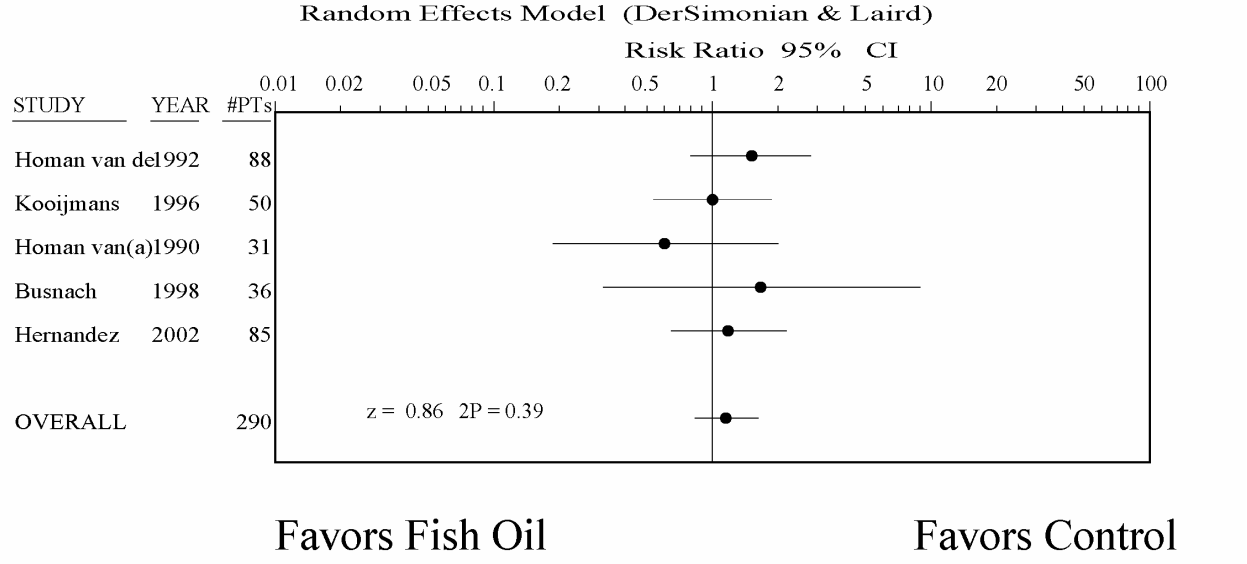
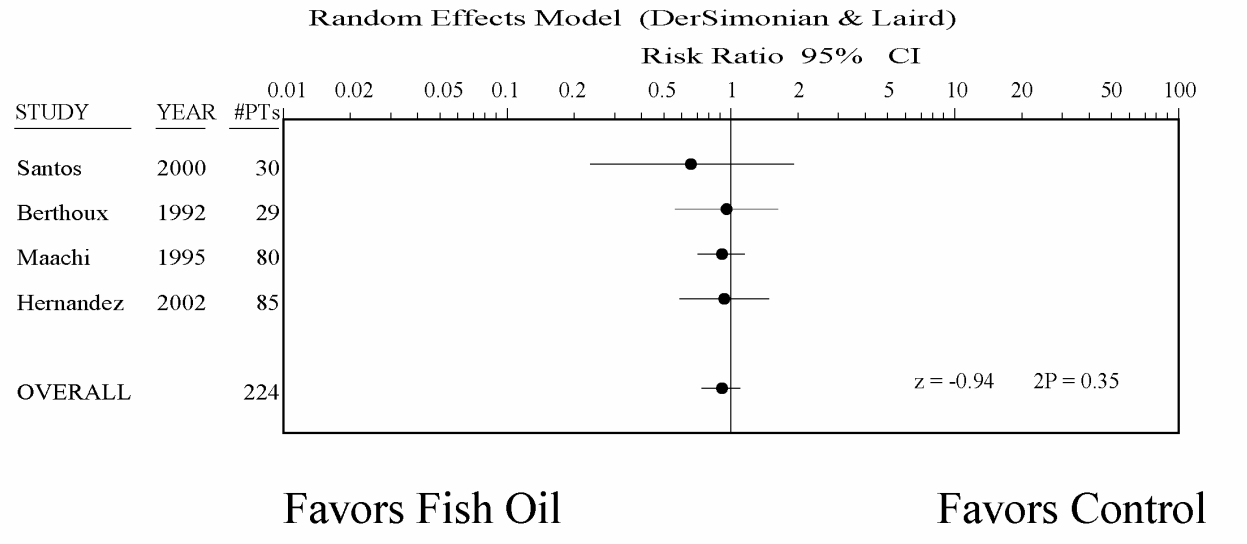


Figure 3.4. Random Effects Model Meta-Analysis of the Proportion of Patients with an Acute Rejection Episode Within One Year of Kidney Transplantation in Randomized-Controlled Trials



In 2 studies published in 3 papers[66,75,76] fish oil supplementation was begun at 16 weeks and an average of 25 months post-transplant. No significant differences in acute rejection episodes were found in either study (Table 3.4).

Table 3.4 Effects of Fish oils on the Proportion of Patients with an Acute Rejection Episode in Randomized-Controlled Trials in Kidney Transplant Patients Who Received Delayed Treatment

Author, Year	Fish oil EPA+DHA (g/d)	Placebo or Control Arm	Treatment Duration	Fish Oil		Control		RR (95% CI)	Treatment Started (Post-transplant)	Quality [c]		
				Event	Total	Event	Total			Summary	Jadad	Allocation Conceal
Bennet, 1995	5.4	Corn oil	26 wks	2 [b]	22	2	50 [a]	2.27 (0.34-15.1)	16 weeks	B	3	Un
	2.7	Corn oil	26 wks	0	18	2	50 [a]	0.54 (0.03-10.7)				
Urakaze 1989; Urakaze 1989	2.2	No treatment	6 mo	0	14	0	16	1.13 (0.02-53.7)	Mean 25 months	B	1	Un

Wks = week(s); mo = month(s); RR = Relative risk of fish oil arm to placebo/controlled arm; Event = number of patients with at least one rejection episodes

[a] Data on high-dose and low-dose controls were combined.

[b] Authors stated that plasma EPA values in these 2 patients were not different from values in placebo, indicating noncompliance.

[c] Ad = adequate allocation concealment; In = inadequate allocation concealment; Un = allocation concealment unclear. See Methods.

Overall, either immediate or delayed supplementation with fish oil showed no benefit on graft survival among patients who had kidney transplants. No reduction in either early or late acute rejections was found with fish oil supplementation.

Heart Transplantation

Although 6 studies described a variety of outcomes in a total of 233 heart transplant recipients (see Evidence Table II). [62,77-81], the studies were small, had various designs, and there was little detailed information on rejection episodes or graft survival from which to derive inferences regarding the effect of omega-3 fatty acid supplementation.

- In 1 report, 2 patients (one in the treatment group and the other a control) died of "vascular rejection" at 7 and 8 weeks and were excluded from the analysis.[77] Graft survival was similar in both treatment groups (14 of 15 in those receiving fish oil supplementation and 14 of 15 in those receiving corn oil).

- One episode of acute rejection was described in the control group in another study.[78] A 60-year-old patient with angiographic evidence of accelerated coronary disease died of congestive heart failure secondary to myocardial infarction in the fish oil group.

- Similar graft survival was described for patients receiving fish oil supplementation (21 of 23) or corn oil (20 of 22) in another RCT.[80]

- All grafts survived in 41 transplant recipients in an open-label prospective cohort study of a Mediterranean diet, which is rich in ALA.[62]

- Two patients in the placebo group dropped out of a RCT due to acute rejection.[81]

Other Transplants

A study of liver transplantation focused on the renal effects of fish oil supplementation in those with stable liver graft function (at least 6 months after transplant). [82] The study duration was only two months. No effects on rejection or graft survival were described.

A study in bone marrow transplant recipients focused on predictors of acute colonic graft versus host disease but did not present outcomes related to the success of the transplant.[43] A separate report of the same patients[83] found a significantly higher patient survival rate in the group that received fish oil supplementation and improvement in biochemical markers of the systemic inflammatory response.[83]

Question 2: What is the evidence that omega-3 fatty acid supplementation is renoprotective (improves glomerular filtration rate or increases kidney size) or is protective against primary kidney disease recurrence following kidney transplantation?

Kidney transplantation

No study reported kidney size as a measure of renal function following transplantation or described primary disease recurrence following kidney transplantation. Two case reports suggested that fish oil supplementation improved proteinuria in patients who developed recurrent IgA nephropathy.[84,85] The observation is potentially important since some studies have found a benefit from fish oil supplementation in IgA nepropathy in the non-transplant setting.[86,87]

Eleven randomized-controlled trials in 14 publications and 1 prospective cohort study reported the effects of fish oil supplementation on GFR (Table 3.5 & 3.6). No consistent benefit was observed in patients treated shortly after transplantation or those with stable renal function in whom treatment was started several months after transplantation, although there were exceptions. The magnitude of benefit suggested in trials with positive findings was modest, and, as noted above, did not translate into improved graft survival with up to 1-year of follow-up.[64,67,69,88]

Comparison of studies with positive and negative findings did not reveal any patient or study-related factors that could account for the heterogeneity. Two of the largest studies that reached disparate conclusions had almost identical designs.[63,64] In both, there was improvement in the GFR during the 12-month observation period in treated and control patients. In the study with positive findings,[64] GFR in the fish oil group increased from 42 to 45, to 49, and to 53 ml/min/1.73m^2 from at 1, 3, 6, and 12 months, respectively. Corresponding values in the control group were 32, 38, 41, and 40. The differences were statistically significant at the 3, 6, and 12 month time-points.

By contrast, in the study with the negative results,[63] GFR increased from 46.1 ml/min/1.73m^2 at 1 month to 54.4 at 12 months in the fish oil group and from 43.2 to 52.5 in the control group at the same time points. Thus, in both studies there were similar degrees of improvement in both treated and control patients relative to baseline. The main difference between studies was the lower values of GFR at all time points in the control group in the study with the positive findings.[64] This may have been due to fewer episodes of rejection in the fish oil group. However, given the small size of the study, it is also possible that unmeasured factors contributed to

relatively poor graft function in the control arm. On the other hand, lower baseline values of GFR or higher rates of rejection for the control group did not appear to account for the positive finding that was observed in a different trial.[69]

Table 3.5 Effects of Fish Oil on Glomerular Filtration Rate (GFR) or Creatinine Clearance (Cr Cl) in Randomized-Controlled Trials

Author, Year	GFR or Cr Cl method	Treatment Started (Post-transplant)	Fish oil N	Fish oil EPA+DHA (g/d)	Placebo or Control N	Placebo or Control	Results [a] Base (ml/min/ (1.73m^2))	Results [a] Net Δ	Results [a] P	Quality [b] Summary	Quality [b] Jadad	Quality [b] Allocation Conceal
			Kidney Transplant									
Hernandez, 2002	EDTA	Day 2	45	1.9	40	Soy oil	50.8	+2.8	n.d.	B	3	Un
Santos, 2000	EDTA	Day 2	15	3.0	15	Placebo	ND	+4.1 [c]	n.d.	C	2	Un
Homan van der Heide, 1992	Cr Cl	Day 3	39	3.0	47	Coconut oil	ND	+4.0 [d]	n.d.	C	3	Un
Homan van der Heide, 1993	^{125}I	Day 3	30	3.0	28	Coconut oil	42.0	+3.0	n.d.	B	3	Un
Kooijmans-Coutinho, 1996	^{125}I	Day 3	14	3.0	17	Coconut oil	46.1	-1.0	n.d.	B	5	In
Homan van der Heide, 1990a	^{125}I	Day 3	14	3.0	17	Coconut oil	ND	-4.0 [c]	n.d.	C	2	Un
Berthoux, 1992	Inulin	Day 3	14	2.7	15	No placebo	44.6 [e]	+0.2	n.d.	C	1	Un
Maachi, 1995	Inulin	Day 3	40	2.5	40	No placebo	47.5	+2.1	n.d.	C	1	Un
Bennett, 1995	DTPA	16 wks	22	5.4	50	Corn oil	68.0	-19.0	n.d.	B	3	Un
			18	2.7			73.0	-19.0	n.d.			
Homan van der Heide, 1990b	^{125}I	9 mo	11	3.0	10	Corn oil	56.0	+16.5	<.01	B	3	Un
Schut ,1993; Schut,1993 ; Schut ,1992; Levi, 1992	^{125}I	1 yr	5	Fish oil: 3.0 + CsA	5	Corn oil + CsA	57.0	-10.0	n.d.	B	2	Un
			5	Fish oil: 3.0 +CsA & Pred	5	Corn oil + CsA + Pred	50.0	+3.0	n.d.			
			5	Fish oil: 3.0 +Aza & Pred	4	Corn oil + Aza + Pred	62.0	+5.0	n.d.			
			Heart Transplant									
Andreassen, 1997	Cr Cl	Day 4	14	3.4	14	Corn oil	57.0	+7.0	n.d.	B	2	Un
Holm, 2001; Holm, 2001	Cockroft & Gaults	Mean 6 yrs (range 1-12 yrs)	21	3.4	20	Corn oil	ND	+5.0 [f]	n.d.	B	3	Un
			Liver Transplant									
Badalamenti, 1995	Inulin	ND	13	3.6	13	Corn oil	71.0	+20.4	.05	B	3	Un

ND = no data; n.d. = not done; NS = not significant; DTPA = ^{99m}Tc-diethylenetriaminepentaacetate; ^{125}I = ^{125}I-iothalamate; EDTA = [^{51}Cr] EDTA; Inulin = Inulin clearance; wks = weeks ; mo = months ; yrs = years

[a] Base = Baseline level in treatment arm; Net Δ = Net difference in effect of omega-3 fatty acids and effect of control, see Methods; P = p-value of the net difference between treatment and control arms.

[b] Ad = adequate allocation concealment; In = inadequate allocation concealment; Un = allocation concealment unclear. See Methods.

[c] Only the difference after intervention between the 2 groups could be calculated due to lack of baseline data.

[d] Only the difference after intervention between the 2 groups could be calculated due to lack of baseline data. Median values were used because mean values were not reported.

[e] No baseline data were available; the 3-month measures served as baseline values.

[f] Estimated from figure.

Table 3.6 Effects of Fish Oil on Glomerular Filtration Rate (GFR) in a Prospective Cohort Study in Kidney Transplant Recipients

Author, Year	GFR	Treatment Started (Post-transplant)	N	Fish oil EPA+DHA (g/d)	Results [a]			Quality
					Base (ml/min/ (1.73m^2))	Δ	P W/in	
Hansen 1995a	DTPA	Mean 16 (range 6-71) months	10	3.5	61.9	+2.2	NS	B

ND = no data; n.d. = not done; NS = not significant; DTPA = ^{99m}Tc-diethylenetriaminepentaacetate

[a] Base = Baseline level in treatment arm; Δ = difference of the effect at the end of the study to the baseline. P W/in = p-value for the change within group.

Heart Transplantation

Renal function was also examined in studies of heart transplant recipients. Although the effect of fish oil supplementation on renal function in transplants other than kidney was not specifically requested in the key question above, it is useful to compare renal outcomes with fish oil supplementation in other forms of transplant.

Three controlled trials in 4 reports in heart transplantation, with a total of 79 patients in the fish oil group and 77 patients in the control group, described the effect of fish oil supplementation on renal function.[77,78,80,89] Two of these reported both serum creatinine levels and GFR or creatinine clearance (Table 3.5).

In 1 report, measured creatinine clearance 6 months after transplant improved in both treated and control patients with an insignificantly higher value in the group randomized to fish oil supplementation.[77]

No significant difference was observed in the calculated GFR in a second trial.[89] However, serum creatinine increased significantly in the control group but did not increase in the group receiving fish oil supplementation. The calculated GFR decreased in the placebo group while remaining unchanged in the fish oil group.

In a third trial, serum creatinine levels remained stable in a group receiving fish oil supplementation while they increased in a group receiving bezafibrate.[78] While the differences were statistically significant, serum creatinine alone is considered to be a poor measure of renal function.

Other Transplants

Renal function was evaluated in 1 controlled trial[90] in liver transplantation (Table 3.5). GFR increased by 33 percent in patients randomized to receive fish oil supplementation compared with no change in the corn oil group. The mean percent change was statistically significant (P=0.05).

Cardiovascular Disease-Related Outcomes

Question 3: What is the evidence that omega-3 fatty acid supplementation lowers cardiovascular disease risk factors or events in organ transplant recipients (adults or children)?

Several factors are well known to be associated with the risk of cardiovascular disease. These include serum lipoproteins, blood pressure, diabetes mellitus, and related metabolic disorders. Multiple studies have demonstrated that improvement or suppression of these factors can reduce the risk. The effects of omega-3 fatty acid supplementation on these risk factors have been reviewed in detail in the non-transplant setting.[40] A large, consistent benefit was found only for triglyceride levels. Little or no effect was found for a variety of other cardiovascular risk factors and markers of cardiovascular disease.

Kidney Transplantation

Cardiovascular risk factors evaluated in studies of kidney transplantation focused on the effects of fish oils on lipid profiles and on blood pressure.

Total Cholesterol

Changes in total cholesterol were described in 8 randomized controlled trials (a total of 186 and 147 patients in the fish oil and control groups, respectively) and 2 uncontrolled studies (a total of 44 patients in the fish oil group) (Table 3.7, 3.8; 3.9). The studies were all of low or intermediate quality. A lesser degree of increase in total cholesterol in the fish oil group compared with control was described in 1 controlled trial.[28] Total cholesterol increased from 187 to 234 mg/dL by month 3 in the fish oil group compared with 176 to 251 mg/dL in controls. Fish oil supplementation was less effective than simvastatin or lovastatin in 2 controlled trials.[68,91]

Table 3.7 Randomized-Controlled Trials of the Effects of Fish Oil on Total Cholesterol (Duration: 12 weeks to 1 year)

Author, Year	Lipid lowering drugs	Treatment Started (Post-transplant)	Fish oil N	Fish oil EPA+DHA (g/d)	Placebo or Control N	Placebo or Control	Results [a] Base (mg/dl)	Results [a] Net Δ	Results [a] P	Quality [b] Summary	Quality [b] Jadad	Quality [b] Allocation Conceal
			Kidney Transplant									
Busnach, 1998	ND	Day 1	21	2.6	21	Olive oil	202	-9	n.d.	B	3	Un
Santos, 2000	ND	Day 2	15	3.0	15	Placebo	155	-13	n.d.	B	2	Un
Hernandez, 2002	ND	Day 2	45	1.9	40	Soy oil	187	-28	n.d.	B	3	Un
Berthoux, 1992	ND	Day 3	14	2.7	15	No placebo	242 [c]	-22	n.d.	C	1	Un
Maachi, 1995	ND	Day 3	40	2.5	40	No placebo	233 [c]	-19	n.d.	C	1	Un
Yoa, 1994	ND	Mean 36 months	12	1.2	11	Olive oil	208	+8	n.d.	B	2	Un

Table 3.7 Randomized-Controlled Trials of the Effects of Fish Oil on Total Cholesterol (Duration: 12 weeks to 1 year) (continued)

Author, Year	Lipid lowering drugs	Treatment Started (Post-transplant)	Fish oil N	Fish oil EPA+DHA (g/d)	Placebo or Control N	Placebo or Control	Results [a] Base (mg/dl)	Results [a] Net Δ	Results [a] P	Quality [b] Summary	Quality [b] Jadad	Quality [b] Allocation Conceal
			Heart Transplant									
Andreassen, 1997	Methyl-prednisolone	Day 4	14	3.4	14	Corn oil	193	-28	NS	B	2	Un
Ventura, 1993	ND	Mean 3.5 months	10	3.0	6	Corn oil	275	-32	n.d.	B	3	Un
Holm, 2001	Statins	Mean 6 (range 1-12) years	21	3.4	20	Corn oil	267	0	NS	B	3	Un

ND = no data; n.d. = not done; NS = not significant

[a] Base = Baseline level in treatment arm; Net Δ = Net difference in effect of omega-3 fatty acids and effect of control, see Methods; P = p-value of the net difference between treatment and control arms.

[b] Ad = adequate allocation concealment; In = inadequate allocation concealment; Un = allocation concealment unclear. See Methods.

[c] No baseline data were available; the 3-month measures served as baseline values.

Table 3.8 Randomized- and non-Randomized-Controlled Trials of the Effects of Fish Oil vs. Other Lipid-Lowering Drugs on Total Cholesterol (Duration: 3 to 6 months)

Author, Year	Lipid lowering drugs	Treatment Started (Post-transplant)	Cohorts N	Cohorts Source	Cohorts Dose	Results [a] Base (mg/dl)	Results [a] Δ	Results [a] P W/in	Results [a] P Btw	Quality [b] Summary	Quality [b] Jadad	Quality [b] Allocation Conceal
			Kidney Transplant									
Castro, 1997	None	≥ 1 year	18	Fish oil	EPA+DHA = 3.0 g/d	266	-26	<.001	n.d.	C	2	In
			25	Simvastatin	10 mg/d	271	-43	<.001				
Rodriguez, 1997	None	40.3 mo	18	Fish oil	EPA+DHA = 3.0 g/d	272	-34	<.001	<0.01	B	2	Un
		50.9 mo	16	Lovastatin	20 mg/d	278	-57	<.001				
			Heart Transplant									
Barbir, 1992	ND	ND	44	Fish oil	EPA+DHA = 3.0 g/d	286	0	n.d.	.0003	C	1	Un
			43	Bezafibrate	400 mg/day	278	-33	n.d.				

ND = no data; n.d. = not done; NS = not significant; mo = months

[a] Base = Baseline level in treatment arm; Δ = difference of the effect at the end of the study to the baseline. P W/in = p-value for the difference within the group. P Btw = p-value for the net difference between the study arms.

[b] Ad = adequate allocation concealment; In = inadequate allocation concealment; Un = allocation concealment unclear. See Methods.

Table 3.9 Prospective Cohort Studies of the Effects of Omega-3 Fatty Acids on Total Cholesterol (Duration: 8 weeks to 6 months)

Author, Year	Lipid lowering drugs	Treatment Started (Post-transplant)	Cohorts				Results [a]			Quality
			N	Source	g/d		Base (mg/dl)	Δ	P W/in	
			Kidney Transplant							
Sweny, 1993 ; Sweny, 1989	ND	Mean 58 (range 13-132) months	14	Fish oil	EPA+DHA	0.06 g/kg BW/d	291	+18	NS	C
Grekas, 2001	Pravastatin 20 mg/d	Mean 8.7 years	30	Fish oil	EPA+DHA	0.30	229	-42	<.02	C
			Heart Transplant							
Salen, 1994	ND	n.d.	41	French Mediterranean diet	ALA	0.39	317	-39	.005	C

ND = no data; n.d. = not done; NS = not significant; ALA = alpha-linolenic acid dosage

[a] Base = Baseline level in treatment arm; Δ = difference of the effect at the end of the study to the baseline. P W/in = p-value for the change within the group.

High-Density Lipoprotein (HDL)

Six controlled trials (with a total of 124 and 138 patients in the fish oil and control groups, respectively) and 1 uncontrolled trial included levels of HDL cholesterol as an endpoint. No significant benefit from fish oil supplementation was observed (Table 3.10, 3.11; 3.12)

Table 3.10 Randomized-Controlled Trials of the Effects of Fish Oil on High-Density Lipoprotein (HDL) (Duration: 12 weeks to 1 year)

Author, Year	Lipid lowering drugs	Treatment Started (Post-transplant)	N	Fish oil EPA+DHA (g/d)	N	Placebo or Control	Results [a]			Quality [b]		
							Base (mg/dl)	Net Δ	P	Summary	Jadad	Allocation Conceal
			Kidney Transplant									
Santos, 2000	ND	Day 2	15	3.00	15	Placebo	36.0	+7.0	n.d.	B	2	Un
Busnach, 1998	ND	Day 1	21	2.55	21	Olive oil	45.7	+14.0	n.d.	B	3	Un
Bennett, 1995	ND	16 weeks	22	5.40	50	Corn oil	58.0	+1.0	n.d.	B	3	Un
			18	2.70			59.0	+4.0	n.d.			
Yoa, 1994	ND	Mean 36 months	12	1.20	11	Olive oil	62.0	-1.0	n.d.	B	2	Un
			Heart Transplant									
Andreassen, 1997	ND	Day 4	14	3.4	14	Corn oil	30.0	+2.0	NS	B	2	Un
Ventura, 1993	ND	Mean 3.5 months	10	3.0	6	Corn oil	47.0	-2.0	n.d.	B	3	Un
Holm, 2001; Holm, 2001	ND	Mean 6 (range 1-12) years	21	3.4	20	Corn oil	50.3	+7.7	NS	B	3	Un

ND = no data; n.d. = not done; NS = not significant;

[a] Base = Baseline level in treatment arm; Net Δ = Net difference in effect of omega-3 fatty acids and effect of control, see Methods; P = p-value of the net difference between treatment and control arms.

[b] Ad = adequate allocation concealment; In = inadequate allocation concealment; Un = allocation concealment unclear. See Methods.

Table 3.11 Randomized-Controlled Trials of the Effects of Fish Oil vs. Other Lipid-Lowering Drugs on High-Density Lipoprotein (HDL) (Duration: 3 to 6 months)

Author, Year	Lipid lowering drugs	Treatment Started (Post-transplant)	Cohorts			Results [a]				Quality [b]		
			N	Source	Dose	Base (mg/dl)	Δ	P W/in	P Btw	Summary	Jadad	Allocation Conceal
			Kidney Transplant									
Castro, 1997	None	≥ 1 year	18	Fish oil	EPA+DHA = 3.0 g/d	63.0	-10.0	<.01	n.d.	C	2	In
			25	Simvastatin	10 mg/d	58.0	-2.0	NS				
Rodriguez, 1997	None	40.3 mo	18	Fish oil	EPA+DHA = 3.0 g/d	48.1	+1.1	NS	NS	B	2	Un
		50.9 mo	16	Lovastatin	20 mg/d	60.2	+0.1	NS				
			Heart Transplant									
Barbir, 1992	ND	n.d.	44	Fish oil	EPA+DHA = 3.0 g/d	41.4	0	n.d.	.0023	C	1	Un
			43	Bezafibrate	400 mg/day	40.6	+12.2	n.d.				

ND = no data; n.d. = not done; NS = not significant; mo = months

[a] Base = Baseline level in treatment arm; Δ = difference of the effect at the end of the study to the baseline. P W/in = p-value for the difference within the group. P Btw = p-value for the net difference between the study arms.

[b] Ad = adequate allocation concealment; In = inadequate allocation concealment; Un = allocation concealment unclear. See Methods.

Table 3.12 Prospective Cohort Studies of the Effects of Omega-3 Fatty Acids on High-Density Lipoprotein (HDL)

Author, Year	Lipid lowering drugs	Treatment Started (Post-transplant)	Cohorts				Results [a]			Quality
			N	Source	g/d		Base (mg/dl)	Δ	P W/in	
			Kidney Transplant							
Grekas, 2001	Pravastatin 20 mg/d	Mean 8.7 yrs	30	Fish oil	EPA+ DHA	0.3	46.0	+3.0	NS	C
			Heart Transplant							
Salen, 1994	ND	n.d.	41	French Mediterranean diet	ALA	0.39	54.1	+0.8	NS	C

ND = no data; n.d. = not done; NS = not significant

[a] Base = Baseline level in treatment arm; Δ = difference of the effect at the end of the study to the baseline. P W/in = p-value for the change within the group.

Low-Density Lipoprotein (LDL)

Four controlled trials (with a total of 91 and 106 patients in the fish oil and control groups, respectively) and 1 uncontrolled study included levels of LDL cholesterol as an endpoint (Table 3.13, 3.14; 3.15). No significant benefit was observed in the controlled trials. Lovastatin was significantly more effective than fish oil in 1 study.[91]

Table 3.13 Randomized-Controlled Trials of the Effects of Fish Oil on Low-Density Lipoprotein (LDL) (12 weeks to 1 year)

Author, Year	Lipid lowering drugs	Treatment Started (Post-transplant)	Fish oil N	Fish oil EPA+DHA (g/d)	Placebo or Control N	Placebo or Control	Results [a] Base (mg/dl)	Results [a] Net Δ	Results [a] P	Quality [b] Summary	Quality [b] Jadad	Quality [b] Allocation Conceal
			Kidney Transplant									
Santos, 2000	ND	Day 2	15	3.00	15	Placebo	100	+13	n.d.	B	2	Un
Bennett, 1995	ND	16 weeks	22	5.40	50	Corn oil	133	0	n.d.	B	3	Un
			18	2.70			176	-3	n.d.			
			Heart Transplant									
Ventura, 1993	ND	Mean 3.5 months	10	3.0	6	Corn oil	185	-22	n.d.	B	3	Un
Holm, 2001 ; Holm, 2001	ND	Mean 6 (range 1-12) years	21	3.4	20	Corn oil	170	0	NS	B	3	Un

ND = no data; n.d. = not done; NS = not significant

[a] Base = Baseline level in treatment arm; Net Δ = Net difference in effect of omega-3 fatty acids and effect of control, see Methods; P = p-value of the net difference between treatment and control arms..

[b] Ad = adequate allocation concealment; In = inadequate allocation concealment; Un = allocation concealment unclear. See Methods.

Table 3.14 Randomized- and non-Randomized-Controlled Trials of the Effects of Fish Oil vs. Other Lipid-Lowering Drugs on Low-Density Lipoprotein (LDL) (Duration: 3 to 6 months)

Author, Year	Lipid lowering drugs	Treatment Started (Post-transplant)	Cohorts N	Cohorts Source	Cohorts Dose	Results [a] Base (mg/dl)	Results [a] Δ	Results [a] P W/in	Results [a] P Btw	Quality [b] Summary	Quality [b] Jadad	Quality [b] Allocation Conceal
			Kidney Transplant									
Castro, 1997	None	≥ 1 year	18	Fish oil	EPA+DHA = 3.0 g/d	162	-4	NS	n.d.	C	2	In
			25	Simvastatin	10 mg/d	177	-33	<.01				
Rodriguez, 1997	None	40.3 mo	18	Fish oil	EPA+DHA = 3.0 g/d	105	-7	NS	<.01	B	2	Un
		50.9 mo	16	Lovastatin	20 mg/d	121	-42	<.01				
			Heart Transplant									
Barbir, 1992	ND	n.d.	44	Fish oil	EPA+DHA = 3.0 g/d	201	0	n.d.	.0002	C	1	Un
			43	Bezafibrate	400 mg/day	193	-35	n.d.				

ND = no data; n.d. = not done; NS = not significant; mo = months

[a] Base = Baseline level in treatment arm; Δ = difference of the effect at the end of the study to the baseline. P W/in = p-value for the difference within the group. P Btw = p-value for the net difference between the study arms.

[b] Ad = adequate allocation concealment; In = inadequate allocation concealment; Un = allocation concealment unclear. See Methods.

Table 3.15 Prospective Cohort Studies of the Effects of Omega-3 Fatty Acids on Low-Density Lipoprotein (LDL) (Duration: 8 weeks to x months)

Author, Year	Lipid lowering drugs	Treatment Started (Post-transplant)	Cohorts				Results [a]			Quality
			N	Source		g/d	Base (mg/dl)	Δ	P W/in	
			Kidney Transplant							
Grekas, 2001	Pravastatin 20 mg/d	Mean 8.7 yrs	30	Fish oil	EPA+ DHA	0.3	151	-27	<.03	C
			Heart Transplant							
Salen, 1994	ND	n.d.	41	French Meditteranean diet	ALA	0.39	240	-35	.004	C

ND = no data; n.d. = not done; NS = not significant

[a] Base = Baseline level in treatment arm; Δ = difference of the effect at the end of the study to the baseline. P W/in = p-value for the change within the group.

Triglycerides

Nine controlled trials (with a total of 200 and 199 patients in the fish oil and control groups, respectively) and 3 uncontrolled studies (with a total of 52 patients in the fish oil group) included triglycerides as an outcome (Table 3.16, 3.17; 3.18). While there were exceptions, in aggregate, the data support a benefit of fish oil in lowering serum triglyceride concentrations, which is consistent with observations made in the non-transplant setting.[40] One study comparing fish oil supplementation to lovastatin found the former to be more effective in reducing triglycerides.[91]

Table 3.16 Randomized-Controlled Trials of the Effects of Fish Oil on Triglycerides (Duration: 12 weeks to 1 year)

Author, Year	Lipid lowering drugs	Treatment Started (Post-transplant)	Fish oil		Placebo or Control		Results [a]			Quality [b]		
			N	EPA+DHA (g/d)	N		Base (mg/dl)	Net Δ	P	Summary	Jadad	Allocation Conceal
			Kidney Transplant									
Busnach, 1998	ND.	Day 1	21	2.6	21	Olive oil	208	-107	n.d.	B	3	Un
Santos, 2000	ND	Day 2	15	3.0	15	Placebo	150	+46	n.d.	B	2	Un
Hernandez, 2002	ND	Day 2	45	1.9	40	Soy oil	203	-46	n.d.	B	3	Un
Berthoux, 1992	ND	Day 3	14	2.7	15	No placebo	138 [c]	-0.8	n.d.	C	1	Un
Maachi, 1995	ND	Day 3	40	2.5	40	No placebo	137	-25	n.d.	C	1	Un
Urakaze, 1989; Urakaze, 1989	ND	Mean 25 months	14	2.2	16	No placebo	148	-42	NS	B	1	Un
Yoa, 1994	ND	Mean 36months	12	1.2	11	Olive oil	133	+9	n.d.	B	2	Un

Table 3.16 Randomized-Controlled Trials of the Effects of Fish Oil on Triglycerides (Duration: 12 weeks to 1 year) (continued)

Author, Year	Lipid lowering drugs	Treatment Started (Post-transplant)	Fish oil N	Fish oil EPA+DHA (g/d)	Placebo or Control N	Placebo or Control	Results [a] Base (mg/dl)	Net Δ	P	Quality [b] Summary	Jadad	Allocation Conceal
			Heart Transplant									
Andreassen, 1997	ND	Day 4	14	3.4	14	Corn oil	181	-71	<.05	B	2	Un
Ventura, 1993	ND	Mean 3.5 months	10	3.0	6	Corn oil	157	-6	n.d.	B	3	Un
Holm, 2001; Holm, 2001	ND	Mean 6 (range 1-12) years	21	3.4	20	Corn oil	195	-62	.07	B	3	Un

ND = no data; n.d. = not done; NS = not significant

[a] Base = Baseline level in treatment arm; Net Δ = Net difference in effect of omega-3 fatty acids and effect of control, see Methods; P = p-value of the net difference between treatment and control arms.

[b] Ad = adequate allocation concealment; In = inadequate allocation concealment; Un = allocation concealment unclear. See Methods.

[c] No baseline data were available; the 3-month measures served as baseline values.

Table 3.17 Randomized- and non-Randomized-Controlled Trials of the Effects of Fish Oil vs. Other Lipid-Lowering Drugs on Triglycerides (Duration: 3 to 6 months)

Author, Year	Lipid lowering drugs	Treatment Started (Post-transplant)	Cohorts N	Source	Dose	Results [a] Base (mg/dl)	Δ	P W/in	P Btw	Quality [b] Summary	Jadad	Allocation Conceal
			Kidney Transplant									
Castro, 1997	None	≥ 1 year	18	Fish oil	EPA+DHA = 3.0 g/d	203	-47	.02	n.d.	C	2	In
			25	Simvastatin	10 mg/d	180	-46	<.01				
Rodriguez, 1997	None	Mean 40.3 mo	18	Fish oil	EPA+DHA = 3.0 g/d	261	-64	<.01	<.05	B	2	Un
		Mean 50.9 mo	16	Lovastatin	20 mg/d	235	-36	NS				
			Heart Transplant									
Barbir, 1992	ND	n.d.	44	Fish oil	EPA+DHA = 3.0 g/d	292	-96	n.d.	NS	C	1	Un
			43	Bezafibrate	400 mg/day	257	-85	n.d.				

ND = no data; n.d. = not done; NS = not significant; mo = months

[a] Base = Baseline level in treatment arm; Δ = difference of the effect at the end of the study to the baseline. P W/in = p-value for the difference within the group. P Btw = p-value for the net difference between the study arms.

[b] Ad = adequate allocation concealment; In = inadequate allocation concealment; Un = allocation concealment unclear. See Methods.

Table 3.18 Prospective Cohort Studies of the Effects of Omega-3 Fatty Acids on Triglycerides (Duration: 5 days to 6 months)

Author, Year	Lipid lowering drugs	Treatment Started (Post-transplant)	Cohorts				Results [a]			Quality
			N	Source		g/d	Base (mg/dl)	Δ	P W/in	
			Kidney Transplant							
Zolotarski, 2003	ND	Day 1	8	Fish oil	EPA+ DHA	0.1 g/kg BW/d	159	+11	NS	C
Sweny, 1993; Sweny, 1989	ND	Mean 58 (range 13-132) months	14	Fish oil	EPA+ DHA	0.06 g/kg BW/d	278	-103	<.003	C
Grekas, 2001	Pravastatin 20 mg/d	Mean 8.7 yrs	30	Fish oil	EPA+ DHA	0.3	169	-45	<.03	C
			Heart Transplant							
Salen, 1994	ND	n.d.	41	French Mediterranean diet	ALA	0.39	317	-39	.005	C

ND = no data; n.d. = not done; NS = not significant; BW = body weight

[a] Base = Baseline level in treatment arm; Δ = difference of the effect at the end of the study to the baseline. P W/in = p-value for the change within the group.

Mean Arterial Blood Pressure

Nine controlled trials (with a total of 228 and 241 patients in the fish oil and control groups, respectively) and 2 uncontrolled studies (with a total of 28 patients in the fish oil group) evaluated changes in blood pressure following kidney transplantation (Table 3.19 & 3.20). There were potentially clinically important differences among reports in use of specific antihypertensive agents and criteria for introducing them, limiting direct comparisons. Nevertheless, no consistent benefit of fish oil supplementation on mean arterial blood pressure was observed.

Table 3.19 Randomized-Controlled Trials of the Effects of Fish Oil on Mean Arterial Blood Pressure (MAP)

Author, Year	Anti-hypertensive agents	Treatment Started (Post-transplant)	N	Fish oil EPA+DHA (g/d)	N	Placebo or Control	Results [a]			Quality [b]		
							Base (mmHg)	Net Δ	P	Summary	Jadad	Allocation Conceal
			Kidney Transplant									
Santos, 2000	β-blockers plus diuretics (if needed) or centrally acting vasodilators ; calcium channel blockers, or ACE inhibitors (2nd line)	Day 2	15	3.0	15	Placebo	101	+4.0	n.d.	B	2	Un
Hernandez, 2002	β-blockers, α-adrenergic antagonists, calcium channel blockers, diuretics as needed	Day 2	45	1.9	40	Soy oil	106	-1.7	n.d.	B	3	Un
Homan van der Heide, 1993	Diuretics, β-blockers, vasodilatory agent. calcium channel blockers as needed	Day 3	30	3.0	28	Coconut oil	100	-7.0	n.d.	B	3	Un
Homan van der Heide, 1992	ND	Day 3	39	3.0	47	Coconut oil	ND	-3.0 [c]	n.d.	C	3	Un
Kooijmans-Coutinho, 1996	β-blockers plus diuretics (if needed) or centrally acting vasodilators ; calcium channel blockers (rescue Rx)	Day 3	20	3.0	18	Coconut oil	108	-3.5	n.d.	B	5	In
Homan van der Heide, 1990a	ND	Day 3	14	3.0	17	Coconut oil	ND	-1.0 [c]	n.d.	C	2	Un
Bennett, 1995	Calcium antagonists, ACE inhibitors	16 weeks	22 18	5.4 2.7	50	Corn oil	109 104	-9.7 -5.0	n.d. n.d.	B	3	Un
Homan van der Heide, 1990b	Diuretics, β-blockers	9 months	11	3.0	10	Corn oil	106	-10.5	<.01	B	3	Un
Urakaze, 1989; Urakaze, 1989	ND.	Mean 25 months	14	2.2	16	No placebo	104	-3.0	NS	B	1	Un
			Heart Transplant									
Andreassen, 1997	Enalapril as needed	Day 4	14	3.4	14	Corn oil	93	-8.9	<.01	B	2	Un
Ventura, 1993	Calcium-channel blocker, ACE inhibitor, or both	Mean 3.5±1.5 months	10	3.0	6	Corn oil	120	-18.0	n.d.	B	3	Un
Holm, 2001; Holm, 2001	ACE, calcium antagonist, β-blockers, diuretics	Mean 6 (1-12) years	21	3.4	20	Corn oil	105	-6.7	.02	B	3	Un

Table 3.19 Randomized-Controlled Trials of the Effects of Fish Oil on Mean Arterial Blood Pressure (MAP) (continued)

Author, Year	Anti-hypertensive agents	Treatment Started (Post-transplant)	N	Fish oil EPA+DHA (g/d)	N	Placebo or Control	Results [a] Base (mmHg)	Net Δ	P	Quality [b] Summary	Jadad	Allocation Conceal
			Liver Transplant									
Badalamenti, 1995	ND	n.d.	13	3.6	13	Corn oil	101	-3.0	n.d.	B	3	Un

ND = no data; n.d. = not done; NS = not significant;
[a] Base = Baseline level in treatment arm; Net Δ = Net difference in effect of omega-3 fatty acids and effect of control, see Methods; P = p-value of the net difference between treatment and control arms.
[b] Ad = adequate allocation concealment; In = inadequate allocation concealment; Un = allocation concealment unclear. See Methods.
[c] Only the difference after intervention between the 2 groups could be calculated due to lack of baseline data.

Table 3.20 Prospective Cohort Studies and a non-Randomized-Controlled Trial of the Effects of Fish Oil on Mean Arterial Blood Pressure (MAP)

Author, Year	GFR or Cr Cl method	Treatment Started (Post-transplant)	N	Fish oil EPA+DHA (g/d)	Results [a] Base (mmHg)	Δ	P W/in	Quality
			Kidney Transplant					
Hansen 1995a	ACE inhibitors, calcium antagonist, β-blockers, diuretics, hydralazine	Mean 16 (range 6-71) months	10	3.5	106	0	NS	B
Hansen 1995b	Diuretics, Diltiazem, β-blockers, ACE inhibitors	Mean 42±17 months	9	Fish oil: 3.5 + CsA	121	-2.0	n.d.	B
		Mean 149±44 months	9	Fish oil:3.5 + AzA	110	-7.0	<.05	
			Heart Transplant					
Fleischhauer, 1993	Diltiazem, Hydralazine, Enalapril, Captopril, Clonidine	1 to 6 years	7	5.7	116	-9.0	NS	C
			7	No fish oil	114	-5.0	NS	

ND = no data; n.d. = not done; NS = not significant
[a] Base = Baseline level in treatment arm; Δ = difference of the effect at the end of the study to the baseline. P W/in = p-value for the change within group.

Heart Transplantation

Several studies in heart transplant recipients evaluated cardiovascular risk factors post transplant (Table 3.7 – 3.20). The following summarizes the main findings in each study.

- A statistically significant reduction in systolic and diastolic blood pressure and serum triglycerides levels was reported in 1 RCT.[77] A statistically significant correlation was

found between the changes in systolic blood pressure and the dose of EPA and DHA. However, use of enalapril was also permitted in both groups. Data were insufficiently reported to determine whether the total dose of enalapril and proportion of patients receiving enalapril were similar across groups, raising the possibility of confounding.

- Bezafibrate was significantly more effective than fish oil supplementation in lowering total cholesterol, HDL and LDL levels in a non-RCT.[78] No significant differences were observed in triglyceride levels.

- No significant differences were observed in mean arterial pressure or heart rate in a controlled trial.[79] Patients receiving fish oil supplements showed a normal vasodilator response to acetylcholine infusion compared with control patients, who demonstrated a vasoconstrictor response. The authors concluded that fish oil supplementation significantly altered endothelium-dependent coronary vasodilation in heart transplant recipients, a group known to have endothelial dysfunction. Whether this change altered the natural history of atherosclerosis following transplant could not be determined.

- No change in systolic or diastolic blood pressure compared with a significant increase in these parameters in the corn oil group was observed in a RCT.[89] A significant reduction in triglyceride levels was observed while no significant differences were found for total cholesterol, HDL, or LDL. The percentage of subjects who were considered to be normotensive at 12 months was significantly higher in the fish oil group (9 of 21 compared with 0 of 20). A significant correlation was observed between changed in systolic blood pressure and serum concentrations of EPA and DHA.

Patients received several additional antihypertensive drugs during the course of the study raising the possibility of confounding. However, the authors stated that all medications remained unchanged during the three months prior to the investigation and during the study.

- A prospective cohort study of the French Mediterranean diet found a significant reduction in total cholesterol and LDL levels compared with pretreatment values.[62] However since total calories and percentage of saturated fats in the French Mediterranean diet were significantly decreased at the same time, the observed effects could not be solely attributed to ALA. No significant changes were observed in serum triglycerides or HDL, or weight. A significant reduction in platelet aggregation was also described.

- In a RCT, a significant reduction in mean arterial pressure and systemic vascular resistance was described in a group receiving fish oil supplementation when results were compared with baseline.[81] Whether these changes were significant compared with the placebo group was not described, although no changes in those receiving corn oil were reported. The authors also reported a reduction in left ventricular mass compared with baseline values in the fish oil group.

Other Transplants

Lipid profiles were not reported in the studies of bone marrow and liver transplantation.[83,90]. In the RCT of liver transplant, fish oil supplementation had no significant effect on mean arterial pressure compared to the placebo (Table 3.19).

Infectious Outcomes

Question 4. What is the evidence that omega-3 fatty acid supplementation reduces serious infectious complications following organ transplantation?

Infections are an important cause of morbidity and mortality following all forms of organ transplantation. Animal and limited human data suggest that supplementation with omega-3 fatty acids may modulate the host's ability to respond to infections.[13,92]However, no study included in this evidence report described infectious outcomes. Thus, its benefit in the transplant setting could not be determined.

All Outcomes

Question 5. What is the evidence that any benefits to organ transplant recipients from omega-3 fatty acid supplementation differ in different subsets of patients*?*

Kidney Transplantation

Two controlled trials in kidney transplantation (with a total of 53 patients in the fish oil group and 64 patients in the coconut oil group), both from the same center, described outcomes in patients with and without an episode of rejection.[73,74] In 1 of these reports, patients randomized to the fish oil group demonstrated a significantly better recovery of renal function following an episode of histologically-confirmed rejection. [73] The authors concluded that fish oil supplementation favorably influenced renal function in the recovery phase following a rejection episode.

In an earlier report the authors analyzed a subset of patients without an episode of rejection during the course of study.[74] Patients receiving fish oil had a significantly higher filtration fraction, a significantly lower effective renal plasma flow (164 versus 262 mL/min per 1.73 m^2) and a significantly better response of the GFR following amino acid infusion (15.3 versus 10.6 percent).

Other Transplants

Effects of omega-3 fatty acid supplementation on subsets of patients were not reported for heart, liver, or bone marrow transplantation.

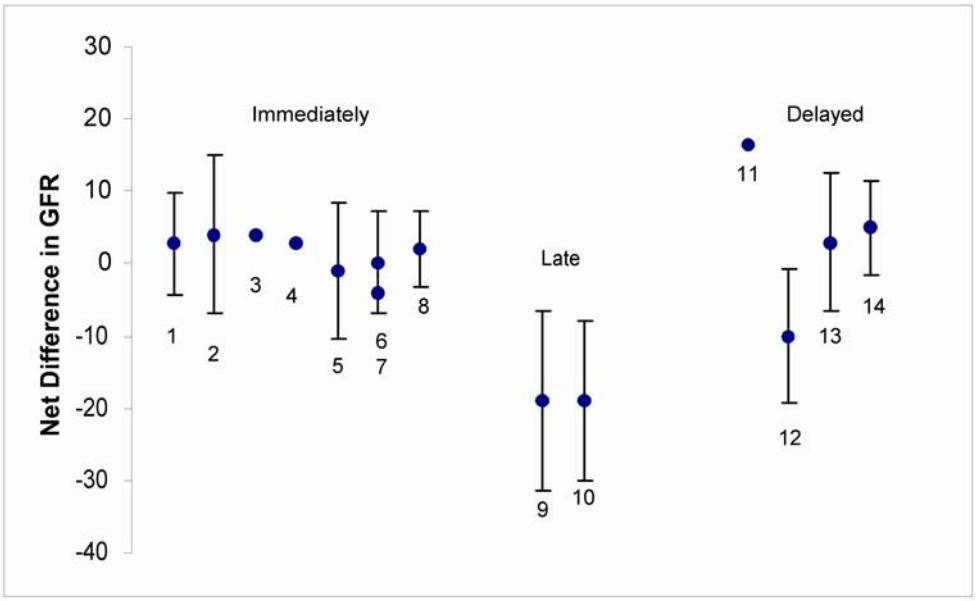
Question 6. What is the evidence that effects of omega-3 fatty acid supplementation on outcomes of interest vary depending on the time of administration relative to transplantation procedures (pre- or post-transplant)?

Kidney Transplantation

All studies evaluated patients who received fish oil supplementation after transplant. While there was no individual study in which patients were randomly assigned to receive supplementation at different time points relative to the transplant, variability was observed across studies allowing for indirect comparisons.

Figure 3.5 depicts the net difference in GFR and 95% confidence intervals across studies in kidney transplant recipients who received supplementation at various intervals following the transplant. Higher values suggest better renal function in those who received fish oil supplementation. Confidence intervals could not be calculated for four studies in which the standard deviation was not reported.[64,73,74,88] Nevertheless, the data do not support a clear relationship between the time in which the supplement was begun and the treatment effect.

Figure 3.5 Net differences in GFR and 95% Confidence Intervals Across Randomized-Controlled Trials in Kidney Transplant Recipients who Received Fish Oil Supplementation at Various Intervals Post-Operatively



1. Hernandez, 2002
2. Santos, 2000
3. Homan van der Heide, 1992
4. Homan van der Heide, 1990a
5. Homan van der Heide, 1993
6. Kooijmans-Coutinho, 1996
7. Berthoux, 1992
8. Maachi, 1995
9. Bennett, 1995 (high dose)
10. Bennett, 1995 (low dose)
11. Homan van der Heide, 1990b
12. Schut ,1993 (CsA)
13. Schut ,1993 (CsA + Pred)
14. Schut ,1993 (AzA + Pred)

The plotted data points represent the longest follow-up values considered in each report. Thus, it is possible that there may be differences in benefit related to the timing of supplementation at earlier time intervals following transplantation. However, even if such a relationship existed, the clinical significance is unclear since the benefit did not appear to be durable or (as noted above) translate into improved graft survival.

Other Transplants

Omega-3 fatty acid supplementation was started after transplant in all heart transplant recipients ranging from as early as four days post transplant[77] to as late as six years after transplant.[89] In two studies, the specific time was not described.[62,78] No study described a relationship between time of transplant and treatment effects. Similarly, no relevant data were described in the studies of liver and bone marrow transplantation.

Effects on Immunosuppressive Agents and Related Drugs

Question 7. What is the evidence in patients (adults or children) who receive an organ transplant that the benefits of omega-3 fatty acid supplementation interact with the concomitant administration of various immunosuppressive agents/drugs?

No study in any of the types of transplantation provided a detailed evaluation of the interaction between omega-3 fatty acid supplementation and the various immunosuppressive drugs, except for dosing of cyclosporine (discussed below).

One series of reports on kidney transplantation of the same patients in three separate publications[93-95] compared outcomes in patients treated with CsA versus those treated with azathioprine. The following observations were made:

- Administration of fish oil was associated with significant improvement in fibrinolysis in patients receiving CsA but not azathioprine.[93]
- Erythrocyte deformability improved with fish oil in patients treated with CsA but not azathioprine. [94]
- No change in blood viscosity was apparent in CsA or azathioprine treated patients receiving fish oil despite the improvement in erythrocyte deformability noted in the CsA group.[95]

Question 8. What is the evidence in patients (adults or children) who receive an organ transplant that serum levels of immunosuppressive agents/drugs are altered by omega-3 fatty acid supplementation?

Included studies used differing immunosuppressive protocols which varied in the choice of agent, target (and achieved) blood levels of CsA for induction and maintenance therapy, and use of concomitant immunosuppressive agents such as corticosteroids and anti-thymocyte globulin (see Evidence Table Ib, Evidence Table II & III). Furthermore, no study evaluated levels and dosages of all the immunosuppressant drugs that were used concurrently.

The effect of fish oil supplementation on immunosuppression was most fully described for CsA. Several studies in kidney and heart transplantation reported trough and total doses of CsA in patients who received or did not receive omega-3 fatty acids (Table 3.21). Fish oil did not appear to have an effect on either of these measures. Considered together, these data provide evidence against a clinically significant interaction between CsA and fish oil.

However, the trough and total doses of CsA do not provide a complete picture of its pharmacokinetics. Another measure of the intensity to exposure to CsA is the area time-concentration curve, generally referred to as the "area under the curve" (AUC). The AUC is generally considered to be the most useful indicator to exposure to CsA, since it reflects the intra-and inter-patient variability among concentrations after dosing.[96]

The AUC (as well as maximal concentration, minimal concentration) at 8 five-hour time points was evaluated in a RCT in kidney transplantation. [65] Study patients received quadruple immunosuppressive therapy, which included CsA, antilymphocyte globulin, azathioprine, and 6-methylprednisolone. After one year, patients who received fish oil had a significantly lower plasma creatinine concentration (1.26 versus 1.88 mg/dL) and higher peak CsA levels. CsA dosages were comparable. The AUC was higher in patients who received fish oil and they had less variance in the time to peak levels, although differences in these measures did not achieve statistical significance. The authors concluded that this pattern provided evidence for better CsA absorption and metabolism in kidney transplant patients receiving fish oil.

Table 3.21 Changes in Serum Levels of Cyclosporine (CsA) in Randomized-Controlled Trials of Fish Oil Supplementation

Author, Year	Anti-Rejection Treatments	Treatment Started (Post-transplant)	Fish oil		Placebo or Control		Results [a]			Quality [b]		
			N	EPA +DHA (g/d)	N		Base (ng/mL)	Net Δ	P	Summary	Jadad	Allocation Conceal
			Kidney Transplant									
Kooijmans-Coutinho, 1996	Methylprednisolone	Day 3	14	3.0	17	Coconut oil	288	-49	n.d.	B	5	In
Homan van der Heide, 1993	Methylprednisolone	Day 3	30	3.0	28	Coconut oil	245	-37	n.d.	B	3	Un
Homan van der Heide, 1992	Methylprednisolone	Day 3	39	3.0	47	Coconut oil	ND	+22[d]	n.d.	C	3	Un
Santos, 2000	ND	Day 2	15	3.0	15	Placebo	ND	+20[d]	n.d.	C	2	Un
Homan van der Heide, 1990a	Methylprednisolone	Day 3	14	3.0	17	Coconut oil	ND	-4.0[d]	n.d.	C	2	Un
Berthoux, 1992	ND	Day 3	14	2.7	15	No placebo	433 [c]	-29	n.d.	C	1	Un
Maachi, 1995	ND	Day 3	40	2.5	15	No placebo	438	+2.1	n.d.	C	1	Un
Hernandez, 2002	Methylprednisolone	Day 2	45	1.9	40	Soy oil	244	+0.5	n.d.	B	3	Un
Homan van der Heide, 1990b	ND	9 mo	11	3.0	10	Corn oil	90	-3.0	NS	B	3	Un
			Heart Transplant									
Andreassen, 1997	Methylprednisolone	Day 4	14	3.4	14	Corn oil	342	+6.0	n.d.	B	2	Un
Barbir, 1992[e]	ND	ND	44	3.0	43	Bezafibrate 400 mg/d	199	+38	NS	C	1	Un

ND = no data; n.d. = not done; NS = not significant

[a] Base = Baseline level in treatment arm; Net Δ = Net difference in effect of omega-3 fatty acids and effect of control, see Methods; P = p-value of the net difference between treatment and control arms.

[b] Ad = adequate allocation concealment; In = inadequate allocation concealment; Un = allocation concealment unclear. See Methods.

[c] No baseline data were available; the 3-month measures served as baseline values.

[d] Only the difference after intervention between the 2 groups could be calculated due to lack of baseline data.

[e] Non-randomized controlled trial

Question 9. What is the evidence in patients (adults or children) who receive an organ transplant that omega-3 fatty acid supplementation can replace or reduce the need for other more potent anti-inflammatory or immunosuppressive drugs (such as steroids and nonsteroidal anti-inflammatory agents)?

No study reported that fish oil supplementation reduced or replaced the need for other more potent anti-inflammatory drugs. Potential effects on CsA absorption are described above.

Unpublished Data

The frequency with which clinical trials of omega-3 fatty acid supplementation in transplantation have appeared in the literature has decreased in recent years. The last relevant publication described in this evidence report was in 2002.

No additional publications were encountered while preparing this report, and no members of the TEP were aware of unpublished data that had been presented in preliminary form. Only 1 unpublished manuscript was uncovered after contact with the TEP.[97] The manuscript has been submitted for publication but a preliminary version was provided by Dr. Wesley Alexander.

The report included 64 patients who were enrolled in 3 sequential pilot open-label studies designed to evaluate the effects of CsA dose and length of administration in a steroid-free protocol in kidney transplant recipients (cadaveric and live donor). All patients had been treated with thymoglobulin induction, sirolimus (rapamycin), mycophenolate mofetil (MMF), CsA, and immunonutrients (arginine and canola oil). The amount of ALA consumed was approximately 1.93 grams per day.

Corticosteroids were avoided in most patients while MMF was discontinued in 70 percent of patients by two years. Despite the reduction in these immunosuppressive drugs, only 15 rejection episodes were observed in the first two years, and none past 24 months. Combining all patients, 84 percent were rejection-free at one year while 70 percent of patients during the past three years were receiving monotherapy with sirolimus (rapamycin) and the dietary supplements. There were no late cardiac events or patients who developed diabetes mellitus.

These preliminary data suggest that the immunosuppressive protocols used combined with the immunonutrients may have long-term benefits in patients undergoing kidney transplant. However, the degree to which omega-3 fatty acid supplementation as canola oil contributed to these benefits is unclear.

Chapter 4. Discussion

This chapter summarizes the findings in this report and provides recommendations for future research.

Overview

Studies included in this report were based on a systematic review of 1,281 abstracts and 78 full-text articles. Additional data were sought by reviewing the bibliographies of retrieved citations (including review articles), through discussions with the TEP and other experts in the respective areas of transplantation, and contact with authors of major controlled trials. Inclusion criteria were defined broadly to be as comprehensive as possible. Primary sources of data published in any language reflecting any study design and reporting any outcomes were included provided that they focused on human subjects who underwent transplantation and who received a quantifiable amount of omega-3 fatty acids.

A total of 31 independent studies were included. Duplicate reports were also included if they provided additional data but subjects were counted only once.

The majority of studies (23) focused on kidney transplantation while six were in heart transplantation and one each was in liver and bone marrow transplantation. All but 1 study (in heart transplantation) used fish oil supplements. Publication dates spanned from 1989 to 2002. Members of the TEP, authors of the included studies, and experts in transplantation were unaware of any ongoing studies, with the exception of a report that summarized three pilot open-label studies; a draft was provided by a member of the TEP.

The relatively advanced age of the included studies (most having been conducted in the 1990s) weighs against their relevance since there continue to be major advances in all the respective areas of transplantation. In particular, most of the included trials did not use newer immunosuppressant agents (such as tacrolimus, mycophenolate mofetil and rapamycin (sirolimus)) that are commonly used in contemporary transplantation procedures. The anticipated benefits of fish oil supplementation on two of the major outcomes considered in this report (renal function and hypertension) had, at least in part, been based on the use of CsA as a primary means of immunosuppression. Benefits of fish oil supplementation in the setting of other potentially nephrotoxic immunosuppressant agents have not been as well characterized in either laboratory or human studies.

Furthermore, there was variable use of concomitant therapies that can also be effective for treatment of complications following transplantation (such as statins for treatment of hyperlipidemia and calcium channel blockers for treatment of hypertension in kidney transplant recipients). Thus, whether fish oil supplementation leads to an additive benefit or can replace the use of these medications could not be determined. However, it is likely that some of these drugs would be more effective than fish oil supplementation for some of these endpoints. Two controlled trials (both in kidney transplantation) compared the efficacy of statins with fish oil supplementation.[68,91] Both found statins to be more effective for reducing total and LDL

cholesterol while one [91] found fish oil supplementation to be slightly more effective for reducing triglycerides.

A major consideration for all evaluated studies was their small size, and methodological deficiencies. Masking and methods of randomization were generally not well reported, and there was variability in the rigor with which endpoints were defined and measured. Important covariates (such as use of antihypertensive agents or the intensity of immunosuppression) were often not sufficiently described or uniformly applied even when the study considered outcomes that may have been confounded by these factors.

Main Findings

Evidence was inconclusive regarding the benefits of omega-3 fatty acid supplementation (mostly fish oil) on any outcome evaluated in any form of transplantation. A possible exception was a reduction in triglyceride levels in patients who underwent kidney transplantation, an observation that is consistent with the effects of omega-3 fatty acid supplementation in the non-transplant setting.[40] There were no other consistent benefits on other major cardiovascular risk factors such as blood pressure or the development of diabetes mellitus.

A reduction in acute colonic graft versus host disease and a survival benefit was suggested in a small RCT in bone marrow transplantation.[83,98] However, there have been no additional studies to confirm these observations raising concern as to whether the authors or other groups may not have been able to reproduce these results.

The benefit on renal function, suggested in several of the individual studies in kidney, heart, and liver transplantation, was inconsistent, and not clearly related to features of the specific study design or patient characteristics. At best, the improvement in GFR was modest, and did not translate into better graft survival or any other clinically important outcome with up to one-year of follow-up. Nevertheless, it is possible that a modest degree of benefit might translate into improved kidney outcomes with longer duration of follow-up. However, the available data do not provide guidance as to which, if any, patients, might benefit from such treatment.

No benefit on early or late rejection episodes or graft survival was detected in meta-analyses in kidney transplantation. However, 1 study suggested that the total number of rejection episodes was reduced[64] while in 2 others (also from the same group), recovery from rejection episodes appeared to be faster in those receiving fish oil supplementation.[73,74]

The available data suggest that fish oil supplementation does not cause a clinically important interaction with CsA. No significant changes in total doses of CsA or trough levels were observed in studies of kidney and heart transplant recipients. However, the most detailed single study evaluated CsA pharmacokinetics in the presence of fish oil concluded that the AUC was higher in patients who received fish oil and they had less variance in the time to peak levels. These differences did not achieve statistical significance. The authors concluded that this pattern provided evidence for better CsA absorption and metabolism in kidney transplant patients receiving fish oil. The clinical significance of these observations is unclear. Whether fish oil supplementation caused an interaction with any other immunosuppressive drug such as azathioprine could not be determined since no study attempted to describe such associations.

Limitations

The main limitation relates to the quantity and quality of the available evidence and its applicability to contemporary transplantation procedures. By far the largest experience has been in kidney transplantation. Varied inclusion criteria, study designs, outcome measures, assessment of compliance, and insufficient reporting limited detailed comparisons among studies with positive and negative findings, which may have permitted a better understanding of the heterogeneous results, especially for renal function.

All but 1 study (and 1 unpublished report) used fish oil as the source of omega-3 fatty acids. Thus, this report cannot address the effects of supplementation with ALA. Furthermore, there were insufficient data to determine the relationship between the background diet and the optimal ratio of omega-3 and omega-6 fatty acids on the outcomes of interest. All studies began omega-3 fatty acid supplementation after transplantation. Because it may take up to 3 weeks for supplementation to have an effect on the production of various cytokines, it is possible that supplementation prior to transplant could have an influence on the outcomes.

Some controlled trials in humans found a benefit of fish oil supplementation on renal function. This suggests that fish oil supplementation could possibly benefit a subset of patients. However, no clear patient or transplant-related characteristics emerged from careful comparisons of the studies to identify such patients. Furthermore, whether the magnitude of the observed changes would translate into clinically important outcomes (such as improved graft survival) is uncertain, especially since the study durations were generally 1year or less.

The applicability of the results to contemporary transplantation procedures is also unclear since most of the studies were performed several years ago, with some more than a decade old. The technology for all transplantation procedures continues to improve with a larger choice of immunosuppressive agents, a better understanding of how to use them, and the means to address the known complications of transplantation including some of the important outcomes (such as hyperlipidemia and hypertension) where the benefits of fish oil supplementation had been anticipated. Thus, whether fish oil supplementation could have a benefit in the setting of contemporary transplantation procedures is uncertain. A draft report of a study in kidney transplantation using contemporary protocols suggested a possible benefit in achieving complete steroid withdrawal but the precise contribution of the fish oil supplements in achieving this objective could not be determined.

Future Research

Future research with omega-3 fatty acid supplementation in transplantation might focus on the following objectives:

- A more detailed understanding of factors associated with improvement in renal function with fish oil or ALA supplementation in all forms of transplantation.

- Long-term follow-up studies on patients enrolled in the studies included in this report to determine whether any of the observed benefits were durable or translated into other improved outcomes.

- Determination of whether fish oil supplementation could benefit treatment or prevention of IgA nephropathy following transplantation.

- Additional studies in bone marrow transplantation where a benefit on acute colonic graft versus host disease and a survival benefit have been suggested.

- Long-term follow-up studies in patients undergoing heart transplantation to determine whether there is a benefit on post-transplant coronary disease.

- Long-term follow-up studies in patients undergoing kidney transplantation to determine whether there is a benefit on post-transplant cardiovascular events.

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Other Reasons for Rejection

Reason: Only one patient with transplant got fish oil and the impact on lipid levels was not extractable

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List of Acronyms/Abbreviations

Acronyms	Abbreviation
AA (20:4 n-6)	Arachidonic acid
ACE	Angiotensin-converting enzyme
AHRQ	Agency for Healthcare Research and Quality
AI	Adequate intake
ALA (18:3 n-3)	Alpha linolenic acid
Apo	Apoprotein
Aza	Azathioprine
BMI	Body mass index
BP	Blood pressure
CAB	Commonwealth Agricultural Bureau
cAMP	Cyclic adenosine monophosphate
CCTR	Cochrane Central Register of Controlled Trials
CPK	Creatinine phosphokinase
CsA	Cyclosporine
CSF II	Continuing Food Survey of Intakes by Individuals 1994-1998
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
DHA (22:6 n-3)	Decosahexaenoic acid
DM	Diabetes mellitus
DPA (22:5 n-3 or n-6)	Docosapentaenoic acid
DRI	Dietary reference intakes
DTPA	Diethylenetriamine pentoacetic acid
EFA	Essential fatty acid
EPA (20:5 n-3)	Eicosapentaenoic acid
EPC	Evidence-based Practice Center
FDA	Food and Drug Administration
GLA (18:3 n-6)	Gamma linolenic acid
GFR	Glomerular filtration rate
HRZMS	Hawksley random zero mercury sphygmomanometer
HDL	High density lipoprotein
HTN	Hypertension
IL	Interleukin
IOM	Institute of Medicine
LA (18:2 n-6)	Linoleic acid
LC PUFA	Long-chain polyunsaturated fatty acid
LDL	Low density lipoprotein
LP	Lipoprotein
LT	Leukotriene
MAP	Mean arterial pressure
NCHS	National Center for Health Statistics
NHANES III	National Health and Nutrition Examination 1988-1994
NEMC	New England Medical Center
NIH	National Institutes of Health
ODS	Office of Dietary Supplements
PAH	Para-aminohippurate
PG	Prostaglandin

Acronyms	Abbreviation
PIR	Poverty Income Ratio
PUFA	Polyunsaturated fatty acid
RBC	Red blood cell
RDA	Recommended dietary allowances
SBP	Systolic blood pressure
SD	Standard deviation
SEM	Standard error of the mean
TEP	Technical Expert Panel
Tg	Triglycerides
TNF	Tumor necrosis factor
TPA	Tissue plasminogen activator
Tx	Thromboxane
UO	University of Ottawa
USDA	United States Department of Agriculture
VCAM	Vascular cell adhesion molecule
VEB	Ventricular ectopic beats
VF	Ventricular fibrillation
VFT	Ventricular fibrillation threshold
VLDL	Very low density lipoprotein
VPB	Ventricular premature beat

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Appendixes

MEDLINE AND EMBASE: Omega 3 and drugs with controlled trial filter

1. exp fatty acids, omega-3/
2. fatty acids, essential/
3. Dietary Fats, Unsaturated/
4. linolenic acids/
5. exp fish oils/
6. (n 3 fatty acid$ or omega 3).tw.
7. docosahexa?noic.tw,hw,rw.
8. eicosapenta?noic.tw,hw,rw.
9. alpha linolenic.tw,hw,rw.
10. (linolenate or cervonic or timnodonic).tw,hw,rw.
11. menhaden oil$.tw,hw,rw.
12. (mediterranean adj diet$).tw.
13. ((flax or flaxseed or flax seed or linseed or rape seed or rapeseed or canola or soy or soybean or walnut or mustard seed) adj2 oil$).tw.
14. (walnut$ or butternut$ or soybean$ or pumpkin seed$).tw.
15. (fish adj2 oil$).tw.
16. (cod liver oil$ or marine oil$ or marine fat$).tw.
17. (salmon or mackerel or herring or tuna or halibut or seal or seaweed or anchov$).tw.
18. (fish consumption or fish intake or (fish adj2 diet$)).tw.
19. diet$ fatty acid$.tw.
20. or/1-19
21. dietary fats/
22. (randomized controlled trial or clinical trial or controlled clinical trial or evaluation studies or multicenter study).pt.
23. random$.tw.
24. exp clinical trials/ or evaluation studies/
25. follow-up studies/ or prospective studies/
26. or/22-25
27. 21 and 26
28. (Ropufa or MaxEPA or Omacor or Efamed or ResQ or Epagis or Almarin or Coromega).tw.
29. (omega 3 or n 3).mp.
30. (polyunsaturated fat$ or pufa or dha or epa or long chain or longchain or lc$).mp.
31. 29 and 30
32. 20 or 27 or 28 or 31
33. follow up studies/
34. (follow up or followup).tw.
35. exp case-control studies/ or case control study/
36. (case adj20 control).tw.
37. exp longitudinal studies/ or longitudinal study/
38. longitudinal.tw.
39. exp cohort studies/ or cohort analysis/

40. cohort.tw.
41. (random$ or rct).tw.
42. exp randomized controlled trials/ or randomized controlled trial/
43. exp random allocation/
44. exp double-blind method/ or double blind procedure/
45. exp single-blind method/ or single blind procedure/
46. randomized controlled trial.pt.
47. clinical trial.pt. or exp clinical trial/
48. (clin$ adj trial$).tw.
49. ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).ti,ab.
50. exp placebos/ or placebo/
51. placebo$.tw.
52. exp research design/ or exp methodology/
53. exp evaluation studies/ or exp postmarketing surveillance/
54. exp prospective studies/ or prospective study/
55. exp comparative study/
56. or/33-55
57. exp glucocorticoids/ or exp glucocorticoids, synthetic/ or exp glucocorticoid/
58. (glucocorticoids or hydroxycorticosteroids or 11-hydroxycorticosteroids or corticosterone or hydrocortisone or 18-hydroxycorticosterone or tetrahydrocortisol or 17-hydroxycorticosteroids or cortisone or cortodoxone or hydroxypregnenolone or tetrahydrocortisone).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
59. (glucocorticoids, synthetic or beclomethasone or betamethasone or betamethasone 17-valerate or clobetasol or desoximetasone or dexamethasone or dexamethasone isonicotinate or diflucortolone or flumethasone or fluocinolone acetonide or fluocinonide or fluocortolone or fluorometholone or fluprednisolone or flurandrenolone or melengestrol acetate or methylprednisolone or methylprednisolone hemisuccinate or paramethasone or prednisolone or prednisone or triamcinolone or triamcinolone acetonide).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
60. exp immunosuppressive agents/ or exp immunosuppressive agent/
61. (immunosuppressive agents or 6-mercaptopurine or antilymphocyte serum or azaserine or azathioprine or busulfan or cladribine or coformycin or cyclophosphamide or cyclosporine or cyclosporins or cytarabine or ellipticines or fluorouracil or gliotoxin or ifosfamide or methotrexate or muromonab-cd3 or pentostatin or razoxane or sirolimus or tacrolimus or thalidomide or thiamphenicol or thioinosine or triamcinolone acetonide).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
62. okt3.mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
63. fk506.mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
64. rs-61443.mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
65. mycophenolic acid.mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
66. rapamycin.mp. [mp=title, abstract, subject headings, drug trade name, original title, device

manufacturer, drug manufacturer name]
67. acyclovir.mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
68. or/57-67
69. 32 and 56 and 68
70. 69
71. limit 70 to human
72. 71
73. limit 72 to english language
74. 71 not 73

MEDLINE AND EMBASE: Omega3 and Transplant

1. exp fatty acids, omega-3/
2. fatty acids, essential/
3. Dietary Fats, Unsaturated/
4. linolenic acids/
5. exp fish oils/
6. (n 3 fatty acid$ or omega 3).tw.
7. docosahexa?noic.tw,hw,rw.
8. eicosapenta?noic.tw,hw,rw.
9. alpha linolenic.tw,hw,rw.
10. (linolenate or cervonic or timnodonic).tw,hw,rw.
11. menhaden oil$.tw,hw,rw.
12. (mediterranean adj diet$).tw.
13. ((flax or flaxseed or flax seed or linseed or rape seed or rapeseed or canola or soy or soybean or walnut or mustard seed) adj2 oil$).tw.
14. (walnut$ or butternut$ or soybean$ or pumpkin seed$).tw.
15. (fish adj2 oil$).tw.
16. (cod liver oil$ or marine oil$ or marine fat$).tw.
17. (salmon or mackerel or herring or tuna or halibut or seal or seaweed or anchov$).tw.
18. (fish consumption or fish intake or (fish adj2 diet$)).tw.
19. diet$ fatty acid$.tw.
20. or/1-19
21. dietary fats/
22. (randomized controlled trial or clinical trial or controlled clinical trial or evaluation studies or multicenter study).pt.
23. random$.tw.
24. exp clinical trials/ or evaluation studies/
25. follow-up studies/ or prospective studies/
26. or/22-25
27. 21 and 26
28. (Ropufa or MaxEPA or Omacor or Efamed or ResQ or Epagis or Almarin or Coromega).tw.
29. (omega 3 or n 3).mp.
30. (polyunsaturated fat$ or pufa or dha or epa or long chain or longchain or lc$).mp.

31. 29 and 30
32. 20 or 27 or 28 or 31
33. exp transplants/
34. exp transplantation immunology/
35. exp transplantation/
36. (posttransplant$ or pretransplant$ or pre transplant$ or post transplant$).tw.
37. transplant$.mp.
38. transplant$.hw.
39. tr.fs.
40. graft$.mp,hw.
41. exp graft rejection/
42. (allotransplant$ or xenotransplant$ or heterotransplant$ or autotransplant$ or isotransplant$).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
43. (allograft$ or xenograft$ or homograft$ or heterograft$ or autograft$ or isograft$).mp.
44. exp postoperative complications/ or exp postoperative complication/
45. or/33-44
46. 32 and 45
47. limit 46 to human
48. 47
49. limit 48 to english language
50. 48 not 49

Study Inclusion or Exclusion

Submit This Section

Reasons for rejection:

- ○ **Review article or other without primary data (look at references type potential additional references here)** [ ]
- ○ **Not human study**
- ○ **Omega 3 fatty acids not use (see below for a list of the potential sources of omega 3) or the amount of omega 3 fatty acids used not quantified**
- ○ **Subjects did not undergo organ transplantation**
- ○ **Other reasons:** [ ]

Is this article REJECTED?

- ○ **Yes**
- ○ **No**

Include study with intervention/exposure: fish (Liver) oils, vegetable oils containing omega-3 FAs (Canola/rapeseed oil, soybean oil, flaxseed/linseed oil), walnut oil, mustard seed oil), or other sources of omega-3 FAs where the quantity of omega-3 FAs is EXPLICITLY reported

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Submit This Section

Instructions

After carefully reading the Article, Please Review the List of Questions.

Check off all questions that are potentially addressed by this paper.

Use a LOW THRESHOLD for checking a question.

Ie, If you think this paper might answer a question, check off the question.

It's better to incorrectly connect a paper to a question than to incorrectly not mark a paper as addressing a question.

However, a study should DIRECTLY address a problem.

----- -----

Submit This Section

Type of transplantation ☐ ND

☐ Kidney Transplant

☐ Heart Transplant

☐ Bone Marrow Transplant

☐ Liver Tansplant

☐ Other Tansplant:

Graft-related outcomes ☐ ND

☐ Q1. What is the evidence that omega-3 fatty acid supplementation reduced rejection episodes or graft failure in patients (adults or children) who received an organ transplant.

☐ Q2. What is the evidence that omega-3 fatty acid supplementation is renoprotective (improves glomerular filtration rate or increases kidney size) or is protective against primary kidney disease recurrence following kidney transplantation?

Cardiovascular disease-related outcomes ☐ ND

☐ Q3. What is the evidence that omega- 3 fatty acid supplementation lowers cardiovascular disease risk factors or events in organ transplant recipients (adults or children)?

Infectious outcomes ☐ ND

☐ Q4. What is the evidence that omega-3 fatty acid supplementation reduces serious infectious complications following organ transplantation?

All outcomes ☐ ND

☐ Q5. What is the evidence that any benefits to organ transplant recipients from omega-3 fatty acid supplementation differ in different subsets of patients?

☐ Q6. What is the evidence that effects of omega-3 fatty acid supplementation on outcomes of interest vary depending on the time of administration relative to transplantation procedures (pre- or post-transplant)?

Effects on immunosuppressive agents and related drugs ☐ ND

☐ Q7. What is the evidence in patients (adults or children) who receive an organ transplant that the benefits of omega-3 fatty acid supplementation interact with the concomitant administration of various immunosuppressive agents/drugs?

☐ **Q8. What is the evidence in patients (adults or children) who receive an organ transplant that serum levels of immunosuppressive agents/drugs are altered by omega-3 fatty acid supplementation?**

☐ **Q9. What is the evidence in patients (adults or children) who receive an organ transplant that omega-3 fatty acid supplementation can replace or reduce the need for other more potent anti-inflammatory or immunosuppressive drugs (such as steroids and NSAIDs)?**

Submit This Section

Study Design and Characteristics

Submit This Section

Prospective vs Retrospective?

○ **Prospective**

○ **Retrospective**

Longitudinal vs Cross-sectional? ☐ ND

○ **Longitudinal (start and end of trial separated in time, multiple measurements made)**

○ **Cross-sectional (single time point, single set of measurements made)**

○ **Unclear (Explain:)**

What is the specific study design? ☐ ND

○ **Clinical Trial: Randomized Parallel**

○ **Clinical Trial: Randomized Cross-over**

○ **Clinical Trial: Factorial Design (2x2 table design often used to examine the interactions between 2 interventions)**

○ **Clinical Trial: Non-Randomized Controlled trial**

○ **Clinical Trial: Non-Randomized Non-Controlled trial (single cohort given Tx)**

○ **Observational: Single Cohort (all subjects analyzed as single group)**

○ **Observational: Multiple Cohorts (distinct groups)**

○ **Observational: Case-Control (not as sub-analysis of other trial)**

○ **Observational (quasi): Nested Case Control (as sub-analysis of other study)**

○ **Case report or series**

○ **Miscellaneous: Other or Mixed (Describe:)**

Comments about Study Design:

Was any aspect of this trial reported elsewhere? ☐ **ND**

○ **Yes**

○ **No**

Submit This Section

Check all responses that apply. Complete all sections fully. Check ND if data not reported

Country in which study conducted (where subjects live) ☐ **ND**

☐ **US**

☐ **Canada**

☐ **Denmark**

☐ **Finland**

☐ **Germany**

☐ **Greece**

☐ **Italy**

☐ **Japan**

☐ **Netherlands**

☐ **Norway**

☐ **Sweden**

☐ **UK (England, Scotland, Wales, Northern Ireland; NOT Ireland)**

☐ **Other(s) [Separate countries with commas]:**

Number of Sites (enter # or "multiple"): ☐ **ND**

Funding source: ☐ **ND**

☐ **Government**

☐ **Industry (specify which):**

☐ **Private -- non-industry (specify which):**

☐ **Hospital**

☐ **Unclear (specify which):**

Submit This Section

Eligibility

Submit This Section

Patient Eligibility

Inclusion Criteria:

Exclusion Criteria (withdraws before randomization):

Dropouts (withdraws after randomization):

Comment about Eligibility Criteria:

Submit This Section

Quality

Submit This Section

Instructions

Questions in quality section are designed for controlled trials only. Skip the whole section if NOT a controlled trial.

Submit This Section

Blinding

Check ND box if the data not reported

Were subjects explicitly reported to be blinded to intervention? ☐ **ND**

- ○ **Yes blinded**
- ○ **Not blinded**
- ○ **Unclear (Explain:)**

Were caregivers (or researchers) explicitly reported to be blinded to intervention? ☐ **ND**

- ○ **Yes blinded**
- ○ **Not blinded**
- ○ **Unclear (Explain:)**

Were outcome assessors explicity reported to be blinded to intervention? ☐ **ND**

- ○ **Yes blinded**
- ○ **Not blinded**
- ○ **Unclear (Explain:)**

If blinding was reported but it was not clearly reported who was blinded, was blinding reported as: ☐ **ND**

- ○ **"Single Blind"**
- ○ **"Double Blind"**
- ○ **Other:**

Comments about Blinding

Submit This Section

Jadad Score

If "Randomized" Trial:

Did authors explicitly state that study was "randomized"? ☐ ND

- ○ Yes
- ○ No

Was the method of randomization described AND appropriate? ☐ ND

- ○ Yes (What was method?) [ ]
- ○ No

Did authors explicitly state that study was "double blind"? ☐ ND

- ○ Yes
- ○ No

Was the method of double blinding described AND appropriate? ☐ ND

- ○ Yes (What was method?) [ ]
- ○ No

Do authors describe withdraw and dropouts? ☐ ND

- ○ Yes
- ○ No

Compute Jadad Score (0 to 5 points) [ ] ☐ ND

Submit This Section

Allocation Concealment

If Randomized trial:

Allocation Concealment = Method by which allocation (which cohort a subject was assigned to) is concealed from subject, caretaker, and all others involved in study. The purpose is to prevent subjects being allocated to one or another cohort based on any subject or researcher characteristics or biases (such as peaking into envelope to give sicker patients active treatment because "they need it more.")

Examples (of both good and bad allocation concealment) = Central randomization site, Pharmacy-randomization, Opaque envelope, Alternating, List

What was method of Allocation Concealment? ☐ ND

- ○ None reported
- ○ Reported (What was method?) [ ]

Schulz score: rate the allocation concealment schedule in the trial

- ○ **Adequately concealed trial (eg. the referent group, that were deemed to have taken adequate measures to conceal allocation (ie, central randomization; numbered or coded bottles or containers; drugs prepared by the pharmacy; serially numbered, opaque, sealed envelopes; or other description that contained elements convincing of concealment)**
- ○ **Inadequately concealed trial (eg. alternation or reference to case record numbers or to dates of birth)**
- ○ **Unclearly concealed trial (Authors either did not report an allocation concealment approach at all or reported an approach that did not fall into one of the categories just named. This group undoubtedly contained a mixture of inadequately and adequately concealed trials, but with the latter probably in the minority)**

Submit This Section

Demographics Quality

Please discard the ND check box for each quetion in this section.

Are statistical analyses (eg, p-values) reported comparing groups?

- ○ **Yes**
- ○ **No**

Is there a Difference in Age among groups? ☐ ND

- ○ **Yes (describe below)**
- ○ **No**
- ○ **ND / NA / Unclear**

Is there a Difference in Sex Ratio among groups? ☐ ND

- ○ **Yes (describe below)**
- ○ **No**
- ○ **ND / NA / Unclear**

Is there a Difference in Race among groups? ☐ ND

- ○ **Yes (describe below)**
- ○ **No**
- ○ **ND / NA / Unclear**

Is there a Difference in blood pressures among groups? ☐ ND

- ○ **Yes (describe below)**
- ○ **No**
- ○ **ND / NA / Unclear**

Is there a Difference in Lipids among groups? ☐ ND

- ○ **Yes (describe below)**
- ○ **No**
- ○ **ND / NA / Unclear**

Submit This Section

UI#
First Author, year:
Data Extractor:
Date Completed:

Study characteristics:
# of recruited subjects:
# of evaluated subjects:
# of transplant subjects who received omega-3 FA treatment(s):

Brief description of study design:

Omega-3 treatment(s):
Unit (gram/day, %kcal/day, %kcal per kg body weight):
ALA:
EPA:
DHA:
Or
Name of fish oil supplement:

Duration of omega-3 treatment(s):

Duration of follow-up (after omega-3 treatment stopped):

Control/Placebo group(s):

Were background diets different between groups (Yes/No/ND/NA):
If Yes, what is the
total energy intake:
total fat intake:
total protein intake:
total carbohydrate intake:

Subjects' demographic characteristics:
Mean age or age range:
Males (%):

Treatments received other than omega-3 FAs:

	Immune suppressors	Anti-hypertension	Anti-hyperlipidemia	Others
Omega-3 Tx group				
Control Group				

Outcomes definitions (See Addendum for the outcome categories)

	Outcome	Definitions or measures
A. Events:		
B. Renal functions:		
C. New onset diseases or conditions:		
D. Biochemical markers:		
E. Infections:		
F. Drug pharmacokinetics:		
G. Other outcomes:		

Effects of omega-3 FA treatments

Outcomes	Treatment group(s) n=	Control group(s) n=

Other result summary, including adverse events related to both drugs and omega-3 FA treatment:

Internal Validity (Quality of Methods)

A. Randomized control trial. Complete methods and results (incl. Inclusion/exclusion criteria) Proper randomization and/or blinding, correct analyses performed.
B. Non-randomized control trial or other prospective design (prospective cohort or case-control study). Proper selection of control group. Not all criteria of A. Some deficiencies; however, unlikely to cause major bias.
C. Retrospective or no control group. Significant design or reporting errors, large amount of missing information or bias.

***Overall study quality (A/B/C):**

Bias/Limitation:

Note or comments:

Omega-3 fatty acids and transplantation – Outcome Categories

Events

1. Patient survival
2. Graft survival
3. Number of patients with acute rejection episode(s)
4. Number of acute rejection episodes
5. Organ dysfunction events

Renal function

1. Creatinine: serum creatinine (mmol/lt), Creatinine clearance (ml/min/1.73m^2) or GFR [(a) Creatinine clearance (ml/min/1.73m^2) measured by 24h urine collection, (b) Creatinine clearance calculated by Cockroft formula, (c) Inulin clearance] with or without Glucagon stimulation]
2. RPF (PAH clearance) with or without Glucagon stimulation
3. Filtration fraction (GFR/RPF)
4.

<u>New onset</u> diseases or conditions

1. Hypertension
2. Diabetes
3. Hyperlipidemia
4. Osteoporosis
5.

Biochemical markers

1. Blood pressures: SBP, DBP, MBP
2. Lipids: triglycerides, total cholesterol, LDL, VLDL, HDL
3. Nitrogen balance: blood urea nitrogen (BUN), uric acid, glutamic oxaloacetic transaminase (SGOT)
4. Diabetes: insulin, glucose intolerance
5. Omega-3 FA metabolites: prostaglandins, thrombaxines
6. Thrombotic measures: degree of platelet aggregation, red blood cell filterability (V_{RBC}/min)
7. Misc.: interleukins

Infections

Drug pharmacokinetics

1. Cyclosporine levels
2. Adverse events related both drugs and omega-3 FA treatment

* fatty acids composition in total lipids of RBC membranes is a measure to show the “biological change in the body” for the consumed fatty acids. For the purpose of this review, we do not need to extract data for this.

Appendix C. Evidence Table Ia. Study Characteristics for Omega-3 Fatty Acids and Kidney Transplantation

Author, year UI# Design	Study Characteristics	Graft	Eligibility Criteria	Omega-3 FA Intervention	Compliance	Control
Bennett, 1995 7871564 RCT: Parallel	N3 enrolled: 40 Control enrolled: 50 Age (yr), N3: ND Age (yr), control: ND %Male, N3: ND %Male, control: ND Duration: 26 weeks Country: USA sites: 3	C or L	Inclusion criteria: patients between 18 and 70 years of age could be of either sex with either cadaveric or living related renal transplants. Patients could have had a previous unsuccessful renal transplantation. Exclusion criteria: (i) myocardial infarction or cardiac arrhythmia within the previous 6 months, (ii) acute or chronic liver disease, or a history of malignancy within the past 2 years, (iii) any investigational drug use within the past 3 months, (iv) severe gastrointestinal malabsorptive diseases or severe chronic obstructive lung diseases, pregnancy or lactation, (v) experienced a rejection episode within the 2-week interval prior to period 2; (vi) active infection	High dose MaxEPA® EPA: 3.24 g/d DHA : 2.16 g/d Low dose MaxEPA® EPA: 1.62 g/d DHA : 1.08 g/d Start: 16 weeks post-operatively	Total plasma EPA levels	Corn oil
Berthoux, 1992 1465872 RCT: Parallel	N3 enrolled: 17 Control enrolled: 15 Age (yr), N3: 46.0±13.9 SD (14 patients) Age (yr), control: 42.9±10.7 SD % Male, N3: 43 (14 patients) % Male, control: 73 Duration: 1 yr Country: France Site: 1	C: all	Inclusion criteria: recipients of cadaveric donor transplant Exclusion criteria: none reported	MaxEPA® EPA: 1.62 g/d DHA: 1.08 g/d Start: day 3 post-operatively	ND	No placebo
Busnach, 1998 9589380 RCT: Parallel	N3 enrolled: 21 Control enrolled: 21 Age (yr), N3: 44±2.6 SE Age (yr), control: 39±2.1 SE % Male, N3: 48 % Male, control: 67 Duration: 1 yr Country: Italy Site: 1	C or L	Inclusion criteria: all kinds of kidney grafts without clinically significant lipid disorders Exclusion criteria: patients who had been treated with hypolipemic drugs in the three months preceding transplantation	Esapent® EPA + DHA: 5.1 g/d then changed to 2.55 g/d from day 30 Start: day 1 post-operatively	ND	Olive oil

Appendix C. Evidence Table Ia. Study Characteristics for Omega-3 Fatty Acids and Kidney Transplantation

Author, year UI# Design	Study Characteristics	Graft	Eligibility Criteria	Omega-3 FA Intervention	Compliance	Control
Butani, 2000 10910466 Case report	One 12 yr-old boy Duration: 1 yr Country: USA	ND	Kidney transplant	MaxEPA® EPA: 2.16 g DHA: 1.44 g Start: not clear	ND	ND
Castro, 1997 9351079 RCT: Parallel	N3 enrolled: 18 Control enrolled: 25 Age (yr), N3: 43.4±11.7SD Age (yr), control: 45.6±9.4 SD % Male, N3: 33 %Male, control: 44 Duration: 3 months Country: Portugal Sites: 1	ND	Inclusion criteria: >=1 year post-renal transplant stable renal function and with persistent hypercholesterolemia (total cholesterol > 200 mg/dL, mean 292±48 mg/dL) after cholesterol reduction diet for 12 weeks Exclusion criteria: none reported	EPA: 1.8 g/d DHA: 1.2 g/d Start: >=1 year	ND	Simvastatin 10mg/d
Grekas, 2001 11474227 Single-arm cohort	N3 enrolled: 24 Age: 45.0±10.4 SD % Male: 63 Duration: 8 weeks Country: Greece Site: 1	L: all	Inclusion criteria: renal transplant patients with stable renal function (serum creatinine<2mg/dl) and persistent hypercholesterolemia (total cholesterol>200mg/dl) after 4-week lipid lowering diet Exclusion criteria: diabetic or receiving beta-blocker therapy patients	Prolipid EPA: 0.18 g/d DHA: 0.12 g/d Start: 8.7±2.9 SD years	ND	No control
Hansen, 1995a 8559499 Single-arm cohort	N3 enrolled: 12 Age (yr), CsA: 42 (rang 22-56) %Male, CsA: 58 Duration: 12 weeks Country: Denmark Sites: 1	ND	Inclusion criteria: non-diabetic renal transplant recipients. Serum creatinine below 180 umol/l. No acute or chronic rejection. Exclusion criteria: received dihydropyridine calcium antagonists	Pikasol® EPA: 2.1 g/d DHA: 1.38 g/d Start: 16 months (range 6-71 months)	Pill counting and measurements of the plasma composition of fatty acids.	ND

Appendix C. Evidence Table Ia. Study Characteristics for Omega-3 Fatty Acids and Kidney Transplantation

Author, year UI# Design	Study Characteristics	Graft	Eligibility Criteria	Omega-3 FA Intervention	Compliance	Control
Hansen, 1995b 7703381 Multiple-arm cohorts	CsA enrolled: 9 Aza enrolled: 9 Age (yr), CsA: 49±9 SD Age (yr), Aza: 50 ±11 SD % Male, CsA: 78 %Male, Aza: 44 Duration: 10 weeks Country: Denmark Site: 1	ND	Inclusion criteria: non-diabetic renal transplant; serum creatinine below 160 umol/L for more than 22 months before study Exclusion criteria: received dihydropyridine calcium antagonists	Pikasol® EPA: 2.1 g/d DHA: 1.38 g/d Start: 42±17 (SD) months CsA group 149±44 (SD) months Aza group	Pill counting and measurements of the plasma composition of fatty acids.	ND
Hernandez, 2002 11981081 RCT: Parallel	N3 enrolled: 49 Control enrolled: 42 Age (yr), N3: 46.8±12.1SD Age (yr), control: 45.3±14.5 SD % Male, N3: 58 % Male, control: 70 Duration: 12 months Treatment duration: 3 months Country: Spain Site: 1	C: all	Inclusion criteria: consecutive patients and (i) 18-70 yr, (ii) no fish oil or immunosuppressive treatment in the 6 months prior to the study, (iii) no hemorrhagic disorders. Exclusion criteria: (i) any investigational drug used within the past 3 months, (ii) acute liver disease, (iii) Hx malignancy the past 2 yr, (iv) fish or iodine allergy, (v) pregnancy or lactation (vi) patients who experienced severe side-effects during follow-up	Epaleo® EPA: 1.26 g/d DHA: 0.66 g/d Start: 2 days post-operatively	Pill counting at each clinic visit	Soy oil: 6 g/d
Homan van der Heide, 1990a 2271089 RCT: Parallel	N3 enrolled: 14 Control enrolled: 17 Age (yr), N3: 49 (range 28-63) Age (yr), control: 47(range 22-64) % Male, N3: ND % Male, control: ND Duration: 1 month Country: Netherlands Sites: 3	ND	Inclusion criteria: patients who received kidney allografts Exclusion criteria: none reported	EPA: 1.8 g/d DHA: 1.2 g/d Start: 3 days post-operatively	ND	Coconut oil: 6 g/d fish flavoring

Appendix C. Evidence Table Ia. Study Characteristics for Omega-3 Fatty Acids and Kidney Transplantation

Author, year UI# Design	Study Characteristics	Graft	Eligibility Criteria	Omega-3 FA Intervention	Compliance	Control
Homan van der Heide, 1990b 2316014 RCT: Parallel	N3 enrolled: 12 Control enrolled: 12 Age (yr), N3: 40 (range 27-66) Age (yr), control: 37(range 17-62) % Male, N3: 60 % Male, control: 45 Duration: 3 months Country: Netherlands Sites: 2	ND	Inclusion criteria: patients who received kidney allografts, were treated with CsA and had stable renal function Exclusion criteria: none reported	Super-EPA® EPA: 1.8 g/d DHA: 1.2 g/d Start: at least 9 months post-transplant	Plasma phospholipid fatty acids measured	Corn oil: 6 g/d
Homan van der Heide, 1992 1496538 RCT: Parallel	N3 enrolled: 40 Control enrolled: 48 Age (yr), N3: 48 (range 17-68) Age (yr), control: 44(range 19-68) % Male, N3: 64 % Male, control: 59 Duration: 1 month Country: Netherlands Sites: 3	C: all	Inclusion criteria: consecutive patients who received kidney allografts Exclusion criteria: none reported	EPA: 1.8 g/d DHA: 1.2 g/d Start: 3 days post-operatively	ND	Coconut oil: 6 g/d fish flavoring
Homan van der Heide, 1993 8350886 RCT: Parallel	N3 enrolled:33 Control enrolled: 33 Age (yr), N3: 41 (range 17-69) Age (yr), control: 47(range 19-67) % Male, N3: 64 % Male, control: 59 Duration: 12 months Country: Netherlands Sites: 4	C: all	Inclusion criteria: patients who received kidney allografts, were treated with CsA and had stable renal function Exclusion criteria: patients receiving NSAIDS	EPA: 1.8 g/d DHA: 1.2 g/d Start: 3 days post-operatively	plasma cholesterol esters measured	Coconut oil: 6 g/d fish flavoring

Appendix C. Evidence Table Ia. Study Characteristics for Omega-3 Fatty Acids and Kidney Transplantation

Author, year UI# Design	Study Characteristics	Graft	Eligibility Criteria	Omega-3 FA Intervention	Compliance	Control
Kooijmans-Coutinho, 1996 8704119 RCT: Parallel	N3 enrolled: 25 Control enrolled: 25 Age (yr), N3: 43.5 (range 22-71) Age (yr), control: 47(range 27-68) % Male, N3: 52 % Male, control: 68 Duration: 12 months Treatment duration: 3 months Country: Netherlands Sites: 1	C: all	Inclusion criteria: patients who received kidney allografts and were treated with CsA Exclusion criteria: fish oil or iodine allergy; NSAIDS taken; previous non-compliance; DM	EPA: 1.8 g/d DHA: 1.2 g/d Start: 3 days post-operatively	ND	coconut oil: 6 g/d fish flavoring
Maachi, 1995 7879202 RCT: Parallel	N3 enrolled: 40 Control enrolled: 40 Age (yr), N3: 44.7±12.7 SD Age (yr), control: 42.8±11.2 SD % Male, N3: 75 % Male, control: 75 Duration: 1 yr Country: France Site: 1	C: all	Inclusion criteria: patients who received kidney allografts Exclusion criteria: none reported	MaxEPA® EPA: 1.44 g/d DHA: 0.96 g/d Start: day 3 post-operatively	ND	No placebo
Ng, 2003 12809474 Case report	One 34 yr old man Duration: 5 years Country: USA	C	Kidney transplant	EPA: 2.16 g DHA: 1.44 g Start: not clear	ND	ND
Rodriguez, 1997 Cochrane 00197406 RCT: Parallel	N3 enrolled: 18 Control enrolled: 16 Age (yr), N3: 43.83±9.38 SD Age (yr), control: 42.78±12.45 SD % Male, N3: 72 %Male, control: 69 Duration: 6 months Country: Spain Sites: 1	C	Inclusion criteria:>=6 month post-RT stable function, total cholesterol >240 mg/dl after hypolipemic diet lasting 3 mo Exclusion criteria: diabetes, nephrotic syndrome, change in hepatic function, creatinine >3 mg/dl	Beromegan® 2 g/d EPA: 1.8 g/d DHA: 1.2 g/d Start: >= 6 months post-operatively	ND	Lovastatin 20 mg/d

Appendix C. Evidence Table Ia. Study Characteristics for Omega-3 Fatty Acids and Kidney Transplantation

Author, year UI# Design	Study Characteristics	Graft	Eligibility Criteria	Omega-3 FA Intervention	Compliance	Control
Santos, 2000 11134724 RCT: Parallel	N3 enrolled: 15 Control enrolled: 15 Age (yr), N3: 37.4±10.9 SD Age (yr), control: 37.8±11.8 SD % Male, N3: 47 % Male, control: 60 Duration: 12 months Country: Portugal Sites: 1	C: all	Inclusion criteria: patients treated with CsA who had delayed graft function Exclusion criteria: primary renal nonfunction; DM	EPA: 1.8 g/d DHA: 1.2 g/d Start: 2 days post-operatively	ND	Placebo
Schut, 1993 8210973 Schut,1993 EMBASE 1993223288 Schut, 1992 14621869 Levi, 1992 1465791 RCT: Cross-over	N3 enrolled: 29 Control enrolled: 29 (cross-over) Age (yr), N3: 52.3 Age (yr), control: 52.3 % Male, N3: 62 % Male, control: 62 Duration: 8 months Treatment duration: 4 months Country: Netherlands Sites: 2	C: all	Inclusion criteria: patients with good and stable renal function who had no signs of transplant rejection Exclusion criteria: none reported	Super-EPA® EPA: 1.8 g/d DHA: 1.2 g/d Start: at least 1 yr post-transplant	Plasma phospholipid fatty acids measured	Corn oil: 6 g/d Super-EPA Pharmacaps®
Sweny, 1993 8470281 Sweny, 1989 2517328 Single-arm cohort	N3 enrolled: 14 Control enrolled: 0 Age (yr), N3: 40.8 (19-59) % Male, N3: 57 Duration: 6 months Country: UK Sites: 1	C: 13 L: 1	Inclusion criteria: patients who received kidney allografts and had chronic vascular rejection Exclusion criteria: none reported	MaxEPA® EPA: 0.036 g/k g/d DHA: 0.024 g/k g/d Mean start: 57.9 (range 13-132) months post-transplant	ND	No control arm

Appendix C. Evidence Table Ia. Study Characteristics for Omega-3 Fatty Acids and Kidney Transplantation

Author, year UI# Design	Study Characteristics	Graft	Eligibility Criteria	Omega-3 FA Intervention	Compliance	Control
Urakaze, 1989 2812166 Urakaze, 1989 2652688 RCT: Parallel	N3 enrolled: 14 Control enrolled: 16 Age (yr), N3: 30± 6 SD Age (yr), control: 33± 7 SD % Male, N3: 79 % Male, control: 56 Duration: 6 months Country: Japan Sites: 3	C: 15 L: 15	Inclusion criteria: patients who received first kidney allografts and had stable graft function Exclusion criteria: Diabetes	EPA: 1.5 g/d DHA: 0.7 g/d N3 mean start: 28±19 SD months post-transplant Controls mean start: 22±20 SD months post-transplant	EPA content in RBC	No placebo
Yoa, 1994 EMBASE 1994288697 RCT: Parallel	N3 enrolled: 12 Control enrolled: 11 Age (yr), N3: 38.5±11.01 SD Age (yr), control: 37± 14.15 SD % Male, N3: 50 % Male, control: 64 Duration: 6 months Country: France Sites: 1	ND	Inclusion criteria: patients who had stable graft function for at least 3 months before the trial Exclusion criteria: none reported	MaxEPA® EPA: 0.72g DHA: 0.48g Start: at least 5 months post-transplant Mean start: 36.13±20.72 months post-transplant	Plasma phospholipid fatty acids measured	Olive oil: 6 caps
Zolotarski, 2003 12644071 Single-arm cohort	N3 enrolled: 8 Control enrolled: 0 Age (yr), N3: 46±17 SD % Male, N3: 50 Duration: 6 months Treatment duration: 5 days Country: Israel Sites: 1	ND	ND	1g/kg MLF 541 20% emulsion (MCT:LCT:fish oil: 5:4:1) ~ 0.1 g/kg BW/d Fish oil Only during the first 5 days post-transplant	ND	No control arm

RCT = randomized controlled trial; nRCT = non-randomized-placebo-controlled trial; C = cadaver donor; L = living donor; Aza = azathiopine; CsA = cyclosporine; DM = diabetes mellitus; N3 = omegas-3 fatty acids

Appendix C. Evidence Table Ib. Concomitant Treatments for Omega-3 Fatty Acids and Kidney Transplantation

Author, year UI# Design	Immunosuppressive therapy				Co-Treatments	
	Induction therapy	Maintenance	Trough CsA levels	Anti-rejection therapy	Anti-hypertensive: Dose	Lipid-lowering: Dose
Bennett, 1995 7871564 RCT: Parallel	ND	CsA, prednisone, Aza given the optimal maintenance dosages.	ND	ND	Calcium antagonists, ACE inhibitors Dose: ND	ND
Berthoux, 1992 1465872 RCT: Parallel	CsA mean initial dose of 11 mg/kg/d steroids 30 mg/24hours 16 patients received Aza of 1 to 1.5 mg/kg/24hours	CsA was daily adjusted during first month to maintain a whole-blood trough level	268 to 640 ng/mL	ND	ND	ND
Busnach, 1998 9589380 RCT: Parallel	Antilymphocyte globulin, 100 mg/d iv from day 0 to 7 Aza 1-1.5mg/kg/d from day 1, oral CsA 10 mg/kg before graft, and 8 mg/kg in two doses from day1: 6-methylprednisolone 500mg i.v. from day 0 tapered to 60 mg on day 6, then 16mg orally from day 7, with 2 mg-tapering every two weeks down to 8 mg/kg from day 75 onwards.	Aza dose depending on blood cell counts CsA doses in order to achieve blood concentrations of 150-350ng/ml	N3: mean 322 ng/ml (range 252±98 to 1831±940) Control: mean 311ng/ml (range 226±90 to 1524±670)	ND	ND	ND

Appendix C. Evidence Table Ib. Concomitant Treatments for Omega-3 Fatty Acids and Kidney Transplantation

Author, year UI# Design	Immunosuppressive therapy				Co-Treatments	
	Induction therapy	Maintenance	Trough CsA levels	Anti-rejection therapy	Anti-hypertensive: Dose	Lipid-lowering: Dose
Butani, 2000 10910466 Case report	ND	Aza, Csa, or Prednisolone, after biopsy, was increased from 10mg daily to 80mg every other day for 3 months. Then it was gradually tapered to 40mg once every other day by 1 year post-biopsy.	ND	ND	ND	ND
Castro, 1997 9351079 RCT: Parallel	ND	N3, 18/18 patients: CsA (3.8+-1.1 mg/kg/d (SD)) plus prednisolone(394+-179mg/kg SD) 24/25 patients: CsA (3.8+-1.2 mg/kg/d) plus prednisolonedose 388+-145mg/kg (SD)	189+-30ng/ml baseline 186+-38ng/ml baseline	ND	Enalapril 11/13 in FO group, 14/17 in statin group 2 drugs: 6/13 in FO group, 5/17 in statin group 3 drugs: 2/13 in FO group, 2/13 in statin group Other drugs incl: nifedipine, diltiazem, minoxidil, amlodipine etc beta blockers as 2nd line drug	No other lipid lowering Rx
Grekas, 2001 11474227 Single-arm cohort	ND	CsA 4mg/kg BW daily Aza 2 mg/kg BW daily methylprednisolone 8 mg daily	ND	ND	ND	Pravastatin daily
Hansen, 1995a 8559499 Single-arm cohort	ND	CsA (mean 2.6 mg/kg; range 1.7-4.0 mg/kg) Aza Prednisone	Cmin before: 261±20 ng/ml after 251±20 Cmax before 1635±120 after 1540±132	ND	ACE inhibitors, calcium antagonist, beta blockers, diuretics, hydralazine: dose: ND	ND
Hansen, 1995b 7703381 Multiple-arm cohorts	ND	CsA 9/9 patients: 3.0±0.6mg/kg	Before 285±46 ng/mL After 302± ng/mL	ND	Diuretics, Diltiazem, beta blockers, ACE inhibitor	ND

Appendix C. Evidence Table Ib. Concomitant Treatments for Omega-3 Fatty Acids and Kidney Transplantation

Author, year UI# Design	Immunosuppressive therapy				Co-Treatments	
	Induction therapy	Maintenance	Trough CsA levels	Anti-rejection therapy	Anti-hypertensive: Dose	Lipid-lowering: Dose
Hernandez, 2002 11981081 RCT: Parallel	ATg (for 7 days)	CsA 8mg/kg/d started when creatinine<3mg/dl to achieve initial trough levels then tapered and adjusted according to total blood levels) Prednisone 0.3mg/kg/d (for 3 mo) then gradually reduced to 10m g/d for 1y) Aza (1.25-1.50mg/kg/d)	initial: 250 to 350ng/ml	methylprednisolone 500mg iv for 3 consecutive days if resistant OKT3 5mg/d for 10-day course	Beta blocker, α-adrenergic antagonists, calcium channel blockers plus diuretics (if necessary)	ND
Homan van der Heide, 1990a 2271089 RCT: Parallel	CsA 3mg/kg/d iv (for 72h) prednisolone20 mg/d (for 2 weeks) and then tapered by 2.5 mg every two weeks to reach maintenance dose	CsA 10mg/kg for 2 weeks then adjusted to reach trough levels prednisolone10mg/d	ND	methylprednisolone 1g iv for 3-6 days if resistant ATg 4mg/kg every other day for 5 doses	ND	ND
Homan van der Heide, 1990b 2316014 RCT: Parallel	ND	CsA N3: 5 mg/kg (4.0-8.5) CsA control: 5 mg/kg (4.5-8.0) prednisolone 10mg/d	initial and in 3 mo: N3: 90 (65-125) initial: control:133 (45-26)	ND	Diuretics 6 patients, Beta blocker 8 patients: ND	ND

Appendix C. Evidence Table Ib. Concomitant Treatments for Omega-3 Fatty Acids and Kidney Transplantation

Author, year UI# Design	Immunosuppressive therapy				Co-Treatments	
	Induction therapy	Maintenance	Trough CsA levels	Anti-rejection therapy	Anti-hypertensive: Dose	Lipid-lowering: Dose
Homan van der Heide, 1992 1496538 RCT: Parallel	CsA 3mg/kg/d iv (for 72h) prednisolone 20 mg/d (for 2 weeks) and then tapered by 2.5 mg every two weeks to reach maintenance dose	CsA 10mg/kg per os for 2 weeks then adjusted to reach trough levels prednisolone10mg/d	ND	methylprednisolone 1g iv for 3-6 days if resistant ATg 4mg/kg every other day for 5 doses	ND	ND
Homan van der Heide, 1993 8350886 RCT: Parallel	CsA 3mg/kg/d iv (for 72h) prednisolone 20 mg/d (for 2 weeks) and then tapered by 2.5 mg every two weeks to reach maintenance dose	CsA 10mg/kg for 2 weeks then adjusted to reach trough levels prednisolone10mg/d	initial: 200ng/ml	methylprednisolone 1g iv for 3-6 days if resistant ATg 4mg/kg every other day for 5 doses	persistent HT (DBP>95mmHg): diuretics, beta blocker, centrally acting vasodilatory agent (e.g. clonidine) rescue therapy: calcium channel blockers	ND
Kooijmans-Coutinho, 1996 8704119 RCT: Parallel	CsA 3mg/kg iv (for 48h)	CsA 10mg/kg/d per os plus prednisolone 20mg/d tapered to 10mg/d	250 to 500 ng/ml	methylprednisolone 1 g/d iv for 3 consecutive days if resistant ATg 5mg/d for 10-day course	first choice: beta blockers, plus diuretics (if necessary) or centrally acting vasodilators rescue therapy: calcium channel blockers	ND
Maachi, 1995 7879202 RCT: Parallel	ND	CsA 7.5 mg/kg/d prednisolone 0.5 mg/kg/d (max: 30 mg/d) azathioprine 1.5 mg/kg/d	268 to 640 ng/mL	ND	ND	ND

Appendix C. Evidence Table Ib. Concomitant Treatments for Omega-3 Fatty Acids and Kidney Transplantation

Author, year UI# Design	Immunosuppressive therapy				Co-Treatments	
	Induction therapy	Maintenance	Trough CsA levels	Anti-rejection therapy	Anti-hypertensive: Dose	Lipid-lowering: Dose
Ng, 2003 12809474 Case report	prednisone and CsA from March 1986 till IgA nephropathy in 1991. After 1 yr 5 mos PD and 2nd transplant in May 1997, same regimen of immunosuppresion continued	ND	ND	ND	ND	ND
Rodriguez, 1997 Cochrane 00197406 RCT: Parallel	ND	N3: CsA (3.07+-0.77 mg/kg/d (SD) plus prednisolone(9.09+-1.7 mg/kg) Controls: CsA (3.8+-1.52mg/kg/d) plus prednisolone (8.75+-1.29 mg/d)	ND	ND	beta blockers diuretics	No other lipid lowering Rx but lovastatin 20 mg/d as control
Santos, 2000 11134724 RCT: Parallel	CsA 6mg/Kg subsequently tapered to maintenance levels Methylprednisolone gradually reduced from 1 to 0.25g/d (for 5 days) <u>5 N3 patients, 4 controls:</u> ATg 4mg/kg (for 7-10d)	CsA prednisolone10 mg/d	100 to 300 ng/ml	ND	21/30 patients <u>first choice:</u> beta blockers, plus diuretics (if necessary) or centrally acting vasodilators <u>second line:</u> calcium channel blockers, ACE inhibitors	ND

Appendix C. Evidence Table Ib. Concomitant Treatments for Omega-3 Fatty Acids and Kidney Transplantation

Author, year UI# Design	Immunosuppressive therapy				Co-Treatments	
	Induction therapy	Maintenance	Trough CsA levels	Anti-rejection therapy	Anti-hypertensive: Dose	Lipid-lowering: Dose
Schut, 1993 8210973 Schut,1993 EMBASE 1993223288 Schut, 1992 14621869 Levi, 1992 1465791 RCT: Cross-over	ND	10/29 patients: CsA mean dose 2.8±0.9mg/kg SD 10/29 patients: CsA mean dose 3.3mg/Kg ±0.7 SD plus prednisolone(10 mg) 9/29 patients: Aza 100-150 mg/d plus prednisolone 5-10 mg/d	75-150 µg/l	ND	not specified	ND
Sweny, 1993 8470281 Sweny, 1989 2517328 Single-arm cohort	ND	9 patients: CsA plus prednisolone(0.15 mg/kg) 5 patients: Aza (2mg/kg) plus prednisolone (0.15 mg/kg)	75-150 ng/ml	ND	not specified	ND
Urakaze, 1989 2812166 Urakaze, 1989 2652688 RCT: Parallel	ND	18 patients: CsA 5mg/Kg/d 11 patients: Aza 53.1+/-31.1 mg/d all patients: prednisolone 10.4+/-3.9 mg/d	ND	ND	19 patients: Metoprolol 120mg/d 16 patients: Nifedipine 30mg/d 8 patients: Captopril 37.5mg/d	ND
Yoa, 1994 EMBASE 1994288697 RCT: Parallel	ND	CsA 283 +/-80 mg/d Corticosteroids 11.5 +/-2.5 mg/d Aza 101 +/-29 mg/d	ND	ND	ND	ND

Appendix C. Evidence Table Ib. Concomitant Treatments for Omega-3 Fatty Acids and Kidney Transplantation

Author, year UI# Design	Immunosuppressive therapy				Co-Treatments	
	Induction therapy	Maintenance	Trough CsA levels	Anti-rejection therapy	Anti-hypertensive: Dose	Lipid-lowering: Dose
Zolotarski, 2003 12644071 Single-arm cohort	ND	Steroids plus Tacrolimus Steroids plus CsA	ND	ND	ND	ND

ACE = angiotensin-converting enzyme; Aza = azathiopine; CsA = cyclosporine

Appendix C. Evidence Table Ic. Major Outcomes for Omega-3 Fatty Acids and Kidney Transplantation

Author, year UI# Design	Major Outcomes												
	GFR (method)	Other Renal Function: method	BP	Hyper-tension: definition	Rejection episodes: definition	Patient survival	Graft survival	Total Chol	Tg	LDL and/or VLDL	HDL	CsA dose	CsA levels
Bennett, 1995 7871564 RCT: Parallel	GFR (DTPA clearance) Creatinine clearance	PAH clearance	SBP DBP	ND	yes	yes	yes	ND	ND	yes	yes	yes	yes
Berthoux, 1992 1465872 RCT: Parallel	GFR (inulin clearance) Serum creatinine Calculated creatinine clearance	ERPF by PAH clearance	ND	ND	yes	yes	yes	yes	yes	ND	ND	yes	yes
Busnach, 1998 9589380 RCT: Parallel	Plasma creatinine	ND	ND	ND	yes	yes	yes	yes	yes	ND	yes	yes	yes
Butani, 2000 10910466 Case report	Serum creatinine	Microhematuria Urinary protein to creatinine ratio Proteinuria	ND	ND	ND	ND	yes	ND	ND	ND	ND	ND	ND
Castro, 1997 9351079 RCT: Parallel	Serum creatinine	ND	SBP DBP	ND	yes	ND	yes	yes	yes	yes	yes	ND	ND
Grekas, 2001 11474227 Single-arm cohort	Serum creatinine	Urine sodium	MAP	ND	ND	ND	yes	yes	yes	yes	yes	ND	yes

Appendix C. Evidence Table Ic. Major Outcomes for Omega-3 Fatty Acids and Kidney Transplantation

Author, year UI# Design	Major Outcomes												
	GFR (method)	Other Renal Function: method	BP	Hyper-tension: definition	Rejection episodes: definition	Patient survival	Graft survival	Total Chol	Tg	LDL and/or VLDL	HDL	CsA dose	CsA levels
Hansen, 1995a 8559499 Single-arm cohort	GFR (99mTc-DTPA in a total dose of 54MBq) Serum creatinine	ERPF measured by a constant infusion technique with 131I hippuran in a total dose of 7.2MBq Clearance of sodium Clearance of lithium Fractional clearance of lithium	MAP	ND	Yes Dx method: ND	ND	yes	ND	ND	ND	ND	ND	yes
Hansen, 1995b 7703381 Multiple-arm cohorts	GFR (99mTc-DTPA in a total dose of 7.2MBq and 54MBq) Serum creatinine Creatinine (24-hour urinary excretion rates)	ERPF measured by a constant infusion technique with 131I hippuran. Sodium (24-hour urinary excretion rates) Potassium (24-hour urinary excretion rates) Albumin (24-hour urinary excretion rates) Urinary excretion rate of β2-microglobulin Fractional excretion of β2-microglobulin Renal clearance of Cu Renal clearance of sodium Renal clearance of lithium	MAP	ND	Yes Dx method: ND	ND	yes	ND	ND	ND	ND	ND	yes

Appendix C. Evidence Table Ic. Major Outcomes for Omega-3 Fatty Acids and Kidney Transplantation

Author, year UI# Design	Major Outcomes												
	GFR (method)	Other Renal Function: method	BP	Hyper-tension: definition	Rejection episodes: definition	Patient survival	Graft survival	Total Chol	Tg	LDL and/or VLDL	HDL	CsA dose	CsA levels
Hernandez, 2002 11981081 RCT: Parallel	GFR (Cr-EDTA) Cr-clearance Serum creatinine	Proteinuria	MAP	ND	yes clinical Dx confirmed by percutaneous renal biopsy or FNA	ND	yes	yes	yes	ND	ND	yes	yes
Homan van der Heide, 1990a 2271089 RCT: Parallel	GFR (125I iothalamate clearance) Stimulated GFR (by dopamine, amino acids and both) Cr-clearance Serum creatinine	ERPF 131I hippuran Stimulated ERPF by dopamine, amino acids and both Filtration fraction	MAP	ND	yes Dx method: ND	ND	ND	ND	ND	ND	ND	yes	yes
Homan van der Heide, 1990b 2316014 RCT: Parallel	GFR (125I iothalamate clearance) Cr-clearance Serum creatinine	ERPF: 131I hippuran Filtration fraction	MAP	ND	ND	ND	ND	ND	ND	ND	ND	ND	yes
Homan van der Heide, 1992 1496538 RCT: Parallel	Cr-clearance Serum creatinine	ND	MAP	ND	yes histologically confirmed as cellular (interstitial) rejection	ND	ND	ND	ND	ND	ND	yes	yes

Appendix C. Evidence Table Ic. Major Outcomes for Omega-3 Fatty Acids and Kidney Transplantation

Author, year UI# Design	Major Outcomes												
	GFR (method)	Other Renal Function: method	BP	Hyper-tension: definition	Rejection episodes: definition	Patient survival	Graft survival	Total Chol	Tg	LDL and/or VLDL	HDL	CsA dose	CsA levels
Homan van der Heide, 1993 8350886 RCT: Parallel	GFR (125I iothalamate clearance)	ERPF 125I iothalamate Proteinuria Filtration fraction	MAP	DBP repeatedly >95mmHg	yes creatinine rise or no improvement for 3 consecutive days in the absence of excessive CsA levels; graft swelling and tenderness, blood eosinophilia, Na retention and fever; results of U/S; confirmed by percutaneous renal biopsy or FNA	ND	ND	ND	ND	ND	ND	yes	yes
Kooijmans-Coutinho, 1996 8704119 RCT: Parallel	GFR (125I iothalamate clearance) Cr-clearance	ERPF: 131I hippuran ERBF ERPFx(1-Ht) Filtration fraction	MAP: HRZMS	ND	yes abnormalities detected by graft palpation, increased serum Cr, Na retention and fever; confirmed by percutaneous renal biopsy or FNA	yes	yes	ND	ND	ND	ND	yes	yes

Appendix C. Evidence Table Ic. Major Outcomes for Omega-3 Fatty Acids and Kidney Transplantation

Author, year UI# Design	Major Outcomes												
	GFR (method)	Other Renal Function: method	BP	Hyper-tension: definition	Rejection episodes: definition	Patient survival	Graft survival	Total Chol	Tg	LDL and/or VLDL	HDL	CsA dose	CsA levels
Maachi, 1995 7879202 RCT: Parallel	GFR (inulin clearance) Measured creatinine clearance Calculated creatinine clearance Serum Creatinine	RPF PAH clearance Filtration fraction	ND	number of patients taking anti-hypertensive drugs	yes Dx method: ND	yes	yes	yes	yes	ND	ND	yes	ND
Ng, 2003 12809474 Case report	Serum Creatinine	Proteinuria	ND	ND	ND	yes	yes	ND	ND	ND	ND	ND	ND
Rodriguez, 1997 Cochrane 00197406 RCT: Parallel	ND	ND	ND	ND	ND	ND	ND	yes	yes	yes	yes	ND	ND
Santos, 2000 11134724 RCT: Parallel	GFR (Cr-EDTA) Cr-clearance Serum creatinine concentration	ND	SBP: ND DBP: ND	ND	Yes increased serum Cr; confirmed by percutaneous renal biopsy	ND	yes	ND	ND	yes	yes	yes	yes

Appendix C. Evidence Table Ic. Major Outcomes for Omega-3 Fatty Acids and Kidney Transplantation

Author, year UI# Design	Major Outcomes												
	GFR (method)	Other Renal Function: method	BP	Hyper-tension: definition	Rejection episodes: definition	Patient survival	Graft survival	Total Chol	Tg	LDL and/or VLDL	HDL	CsA dose	CsA levels
Schut, 1993 8210973 Schut,1993 EMBASE 1993223288 Schut, 1992 14621869 Levi, 1992 1465791 RCT: Cross-over	GFR (125I iothalamate clearance)	ERPF: 131I hippuran Filtration fraction	MAP: HRZMS	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Sweny, 1993 8470281 Sweny, 1989 2517328 Single-arm cohort	ND	RF decline: Reciprocal plasma creatinine was plotted against time (mmol/lt per month) Proteinuria	ND	ND	ND	ND	ND	yes	yes	ND	ND	ND	ND
Urakaze, 1989 2812166 Urakaze, 1989 2652688 RCT: Parallel	Serum creatinine	ND	SBP: ND DBP: ND	ND	yes Dx method: ND	ND	ND	yes	yes	ND	ND	ND	ND
Yoa, 1994 EMBASE 1994288697 RCT: Parallel	ND	ND	ND	ND	ND	ND	ND	yes	yes	yes	yes	ND	ND

Appendix C. Evidence Table Ic. Major Outcomes for Omega-3 Fatty Acids and Kidney Transplantation

Author, year UI# Design	Major Outcomes												
	GFR (method)	Other Renal Function: method	BP	Hyper-tension: definition	Rejection episodes: definition	Patient survival	Graft survival	Total Chol	Tg	LDL and/or VLDL	HDL	CsA dose	CsA levels
Zolotarski, 2003 12644071 Single-arm cohort	Serum creatinine: ND	BUN: ND	ND	ND	ND	ND	ND	ND	yes	ND	ND	ND	ND

MAP = mean arterial pressure; SBP = systolic blood pressure; DBP = diastolic blood pressure; HRZMS = Hawksley random zero mercury sphygmomanometer; Dx = diagnostic; GFR = glomerulus's filtration rate

Appendix C. Evidence Table Id. Other Outcomes for Omega-3 Fatty Acids and Kidney Transplantation

Author, year UI# Design	Other Outcomes	Definitions or measures
Bennett, 1995 7871564 RCT: Parallel	• Thromboxane B2 (pg/mg) • Platelet function	Thromboxane B2 measurement from urine by negative ion gas chromatograph mass spectroscopy, twice in each period. Platelet function was estimated by ADP, epinephrine, and collagen-induced platelet aggregation, twice in each period. Bleeding time.
Berthoux, 1992 1465872 RCT: Parallel	None	None
Busnach, 1998 9589380 RCT: Parallel	• CD4+ lymphocytes	Defined by flow cytometic analysis
Butani, 2000 10910466 Case report	None	None
Castro, 1997 9351079 RCT: Parallel	• Serum transaminase • CPK • Lipoprotein (a) mg% • ApoA1 mg% • ApoB mg% • Mean body weight	
Grekas, 2001 11474227 Single-arm cohort	• Serum potassium • Serum sodium • Lipoprotein (a) • ApoA1 • ApoB • CPK	mg/dL mEq/L mEq/L mg/dL mg/dL mg/dL
Hansen, 1995a 8559499 Single-arm cohort	• Sodium excretion • Heart rate	 beats/min

Appendix C. Evidence Table Id. Other Outcomes for Omega-3 Fatty Acids and Kidney Transplantation

Author, year UI# Design	Other Outcomes	Definitions or measures
Hansen, 1995b 7703381 Multiple-arm cohorts	• Urine (24-hour urinary excretion rates) • 6-Keto-prostaglandin F1α (24-hour urinary excretion rates) • Thromboxane B2 (24-hour urinary excretion rates) • Body weight • Heart rate	L ng ng kg beats/min
Hernandez, 2002 11981081 RCT: Parallel	• Delayed graft function • Episodes of AR per patient • OKT3 rescue therapy • TNF-α • IL-1 β • IL-2 m-RNA	Urine volume <1000cc in the absence of a fall in serum Cr concentration and with optimal hydration (described as %proportion) number of episodes administered or not % optical density between cytokines and β-actin % optical density between cytokines and β-actin % optical density between cytokines and β-actin
Homan van der Heide, 1990a 2271089 RCT: Parallel	None	None
Homan van der Heide, 1990b 2316014 RCT: Parallel	• TRVR (= total renal vascular resistance) • Platelets	[MAP/RBF]*80 (dyn*sec/cm5), RBF=RPF/(1-ht) platelet / lt
Homan van der Heide, 1992 1496538 RCT: Parallel	• Median day of rejection onset • Additional methylprednisolone needed • ATg treatment	 Dose (g) /rejection % /rejection
Homan van der Heide, 1993 8350886 RCT: Parallel	• Use of antihypertensive drugs • Additional methylprednisolone per patient • Methylprednisolone per rejection episode • Length of hospitalization during 1 year • Number of second admissions	 dose (g) dose (g) (median) days Mean number

Appendix C. Evidence Table Id. Other Outcomes for Omega-3 Fatty Acids and Kidney Transplantation

Author, year UI# Design	Other Outcomes	Definitions or measures
Kooijmans-Coutinho, 1996 8704119 RCT: Parallel	None	None
Maachi, 1995 7879202 RCT: Parallel	None	None
Ng, 2003 12809474 Case report	None	None
Rodriguez, 1997 Cochrane 00197406 RCT: Parallel	• Apo A • Apo B	mg% mg%
Santos, 2000 11134724 RCT: Parallel	• Number of anti-hypertensive drugs	absolute number

Appendix C. Evidence Table Id. Other Outcomes for Omega-3 Fatty Acids and Kidney Transplantation

Author, year UI# Design	Other Outcomes	Definitions or measures
Schut, 1993 8210973 Schut,1993 EMBASE 1993223288 Schut, 1992 14621869 Levi, 1992 1465791 RCT: Cross-over	• Elongation index • Endothelin level • Plasma arachidonic acid • Plasminogen activator activity • Plasmin-α2-antiplasmin ratio • Defects for impaired increase in plasminogen activator activity	Indicate deformable RBC When increased indicate stimulation of endothelial cell production to synthesize endothelin during CsA treatment (pg/ml) Analysis of plasma fatty acid composition (mol%) Ratio of activity before/after DDAVP Ratio of complexes before/after DDAVP- indication of plasmin generation t-PA Ag – u-PA Ag – PAI-1 Ag measurements
Sweny, 1993 8470281 Sweny, 1989 2517328 Single-arm cohort	• Total platelet count • platelet aggregation • Thromboxane A2 release	% fall in optical density resulted from the addition of the aggregating agents ADP, adrenaline and collagen release by platelets incubated with aggregating agents at 37oC
Urakaze, 1989 2812166 Urakaze, 1989 2652688 RCT: Parallel	• Blood cell count • SGOT • Uric acid • platelet aggregation • RBC filterability • Urinary metabolites of eicosanoids	mg/dl mg/dl Max OD% ml/min [PGI 2/3-M / TXB 2/3-M] ratio
Yoa, 1994 EMBASE 1994288697 RCT: Parallel	• Deformability index of RBC • Apo A1 • Apo B	Ability of RBC to cross the capillary system (hemorheological modification that explain CsA nephrotoxicity) g/lt g/lt

Appendix C. Evidence Table Id. Other Outcomes for Omega-3 Fatty Acids and Kidney Transplantation

Author, year UI# Design	Other Outcomes	Definitions or measures
Zolotarski, 2003 12644071 Single-arm cohort	• Sodium • Potassium • Ionized Calcium • Liver function	

DTPA, diethylenetriamine pentoacetic acid; PAH, para-aminohippurate; CPK, creatinine phosphokinase

Appendix C. Evidence Table Ie. Results for Omega-3 Fatty Acids and Kidney Transplantation

Author, year UI# Design	Results								Bias / Limitations / Comments
Bennett, 1995 7871564 RCT: Parallel	Outcome	Cohort	N	Baseline	Unit	SD /SE /range	Follow-up	P W/in	P Btw	Results for high and low dose placebo groups were combined. Authors conclude that delayed administration appears to have only minor clinical benefits. Poor compliance may have contributed to negative results. Paper had poor reporting but study appeared to be conducted carefully.
	SBP	Fish oil 9 g/d	22	140±19	mmHg	SD	148±21	NS	ND	
		Fish oil 18 g/d	18	145±23			137±10	NS	ND	
		Placebo	50	138±22			134±18	NS		
	DBP	Fish oil 9 g/d	22	86±13	mmHg	SD	76±13	<0.05	ND	
		Fish oil 18 g/d	18	91±11			82±8	<0.05	ND	
		Placebo	50	83±13			85±9	NS		
	GFR (DTPA)	Fish oil 9 g/d	22	73±26	ml/min	SD	59±28	NS	ND	
		Fish oil 18 g/d	18	68±38			54±24	NS	ND	
		Placebo	50	62±20			58±13	NS		
	LDL	Fish oil 9 g/d	22	176±26	mg/dl	SD	187±18	<0.05	ND	
		Fish oil 18 g/d	18	133±18			141±19	NS	ND	
		Placebo	50	146±27			144±24	NS		
	VLDL	Fish oil 9 g/d	22	46±10	mg/dl	SD	38±9	NS	ND	
		Fish oil 18 g/d	18	39±8			36±10	NS	ND	
		Placebo	50	39±10			43±8	NS		
	HDL	Fish oil 9 g/d	22	59±11	mg/dl	SD	56±9	NS	ND	
		Fish oil 18 g/d	18	58±7			52±8	NS	ND	
		Placebo	50	59±8			52±9	NS		
	Rejection episodes	Fish oil 9 g/d	22	0 episodes					ND	
		Fish oil 18 g/d	18	8 episodes in 2 patients. However, plasma EPA values in these patients were not different from values in placebo, indicating noncompliance.					ND	
		Placebo	50	5 episodes in 2 patients (5 physician-diagnosed episodes of acute CsA nephrotoxicity.)						
	Graft survival	All grafts functioned for the entire 6-month period.								
	There was a weak negative correlation (r=-0.36, p<0.01) b/w percentage of plasma EPA levels and urinary thromboxane B2. After intervention, plasma EPA levels were different from placebo (p<0.01), but not different b/w the two fish-oil treatment groups. Bleeding time at baseline in the patients randomized to high dose EPA was significantly higher than that in low dose EPA patients and in placebo patients. After intervention, this group had a further increased bleeding time, while the changes in other groups did not differ.									

Appendix C. Evidence Table Ie. Results for Omega-3 Fatty Acids and Kidney Transplantation

Author, year UI# Design	Results									Bias / Limitations / Comments
Berthoux, 1992 1465872 RCT: Parallel	Outcome	Cohort	N	3 months	Unit	SD /SE /range	Follow-up	P W/in	P Btw	No baseline measures. All outcomes compared 12-month to 3-month measures. ANOVA 2 factors (time and fish oil) analysis is equal to multiple t-test adjusting for time. A significant p-value means that fish oil and control arms are significantly different at any time point. It's not a test for the significance of net change. Compliance not specifically checked. No blinding. No placebo used. 1-year graft survival lower than would be expected. Two CsA protocols used, initially high-dose and then a low dose.
	GFR	Fish oil	14	44.6±16.2	ml/min/1.73m^2	SD	42±15.1	ND	ND	
		Control	15	31.8±10.7			29.0±11.9	ND		
	CsA level	Fish oil	14	433±210	ng/mL	SD	462±193	NS	ND	
		Control	15	472±212			530±217	NS		
	CsA dose	Fish oil	14	449±89	mg/24h	SD	385±72	NS	ND	
		Control	15	453±127			378±104	NS		
	Tg	Fish oil	14	1.56±0.88	mmol/L	SD	1.87±1.08	ND	ND	
		Control	15	2.27±0.87			2.59±1.66	ND		
	Total cholesterol	Fish oil	14	6.26±0.58	mmol/L	SD	6.76±1.20	ND	ND	
		Control	15	6.05±1.28			7.12±1.85	ND		
	Graft survival	Fish oil	11/14						NS	
		Control	11/15							
	Rejection episodes	Fish oil	15 rejections in 9 patients (out of 14 total)						NS	
		Control	13 rejections in 10 patients (out of 15 total)							
	HNT*	Fish oil	7/11						ND	
		Control	8/11							
	* Hypertension was not defined other than by use of antihypertension drugs. Patient acceptance excellent except one patient developed vomiting and nausea and dropped out.									

Appendix C. Evidence Table Ie. Results for Omega-3 Fatty Acids and Kidney Transplantation

<table>
<tr><th>Author, year
UI#
Design</th><th>Results</th><th>Bias / Limitations / Comments</th></tr>
<tr><td>Busnach, 1998
9589380

RCT: Parallel</td><td>
<table>
<tr><th>Outcome</th><th>Cohort</th><th>N</th><th>Baseline</th><th>Unit</th><th>SD /SE /range</th><th>Follow-up</th><th>P W/in</th><th>P Btw</th></tr>
<tr><td>Total cholesterol</td><td>Fish oil</td><td>16</td><td>202±13.1</td><td>mg/dl</td><td>SE</td><td>228±11</td><td>ND</td><td>ND</td></tr>
<tr><td></td><td>Olive oil</td><td>19</td><td>188±8.9</td><td></td><td></td><td>223±11</td><td>ND</td><td></td></tr>
<tr><td>Tg</td><td>Fish oil</td><td>16</td><td>208±41.9</td><td>mg/dl</td><td>SE</td><td>120±12</td><td><0.05</td><td>ND</td></tr>
<tr><td></td><td>Olive oil</td><td>19</td><td>147±15.1</td><td></td><td></td><td>166±21</td><td>NS</td><td></td></tr>
<tr><td>HDL</td><td>Fish oil</td><td>16</td><td>45.7±3.7</td><td>mg/dl</td><td>SE</td><td>59±4</td><td>NS</td><td>ND</td></tr>
<tr><td></td><td>Olive oil</td><td>19</td><td>52.7±4.8</td><td></td><td></td><td>52±2</td><td>NS</td><td></td></tr>
<tr><td>CsA dose</td><td>Fish oil</td><td>16</td><td>6.76±0.28</td><td>mg/kg</td><td>SE</td><td>4.30±0.16</td><td>ND</td><td>ND</td></tr>
<tr><td></td><td>Olive oil</td><td>19</td><td>7.28±0.27</td><td></td><td></td><td>4.38±0.15</td><td>ND</td><td></td></tr>
<tr><td>CsA level (max)</td><td>Fish oil</td><td>16</td><td>1329±647</td><td>ng/ml</td><td>SE</td><td>976±367</td><td>ND</td><td>ND</td></tr>
<tr><td></td><td>Olive oil</td><td>19</td><td>1049±468</td><td></td><td></td><td>934±345</td><td>ND</td><td></td></tr>
<tr><td>CsA level (min)</td><td>Fish oil</td><td>16</td><td>252±98</td><td>ng/ml</td><td>SE</td><td>252±59</td><td>ND</td><td>ND</td></tr>
<tr><td></td><td>Olive oil</td><td>19</td><td>260±131</td><td></td><td></td><td>226±90</td><td>ND</td><td></td></tr>
<tr><td>Graft survival</td><td>Fish oil</td><td>17/19</td><td colspan="6"></td><td>ND</td></tr>
<tr><td></td><td>Control</td><td>19/21</td><td colspan="6"></td></tr>
<tr><td>Rejection episodes</td><td>Fish oil</td><td colspan="7">3 patients (out of 16 total) within month 1</td><td>ND</td></tr>
<tr><td></td><td>Control</td><td colspan="7">2 patients (out of 19 total) within month 1; 1 @ month 9</td></tr>
<tr><td>Mean number of HTN agents</td><td>Fish oil</td><td colspan="7">1.7 (range 0-4)</td><td>ND</td></tr>
<tr><td></td><td>Control</td><td colspan="7">1.8 (range 0-4)</td></tr>
</table>
No significant differences in systolic and diastolic blood pressure at any evaluation point in the two groups, number of antihypertensive agents per patients was similar in each group
No significant difference in total and CD4 cell counts between groups.
Five patients in treatment group did not complete study due to noncompliance (1), irreversible acute rejection (1), primary graft not function (1), death due to unrelated causes (hemorrhagic shock from removal of native polycystic kidney and intestinal infarction) (2).
Two patients in placebo group did not complete the study due to irreversible acute rejection (1) and late irreversible arterial graft
</td><td></td></tr>
<tr><td>Butani, 2000
10910466

Case report</td><td>Case report of a 12-year-old boy who underwent a renal treatment for IgA nephropathy . Patient was treated with Aza, corticosteroids and CsA. Two years after treatment, he developed new onset proteinuria and microscopic hematuria. Kidney biopsy showed recurrent IgA nephropathy. Patient treated with prednisone with partial response and side-effects. Thus, he was treated with Max EPA 6 g twice daily. Within 8 weeks, proteinuria declined. By one year, creatinine normalized, with normal urinary protein to creatinine ratio. Patient did not receive ACE inhibitor or NSAIDs.</td><td>Case report</td></tr>
</table>

Appendix C. Evidence Table Ie. Results for Omega-3 Fatty Acids and Kidney Transplantation

<table>
<tr><th>Author, year
UI#
Design</th><th>Results</th><th>Bias / Limitations / Comments</th></tr>
<tr><td>Castro, 1997
9351079

RCT: Parallel</td><td>
<table>
<tr><th>Outcome</th><th>Cohort</th><th>N</th><th>Baseline</th><th>Unit</th><th>SD /SE /range</th><th>Follow-up</th><th>P W/in</th><th>P Btw</th></tr>
<tr><td>Total cholesterol</td><td>Fish oil</td><td>18</td><td>266±25</td><td>mg/dl</td><td>SD</td><td>240±31</td><td><0.001</td><td>ND</td></tr>
<tr><td></td><td>Simvastatin</td><td>25</td><td>271±46</td><td></td><td></td><td>228±49</td><td><0.001</td><td></td></tr>
<tr><td>HDL</td><td>Fish oil</td><td>18</td><td>63±15</td><td>mg/dl</td><td>SD</td><td>53±12</td><td><0.01</td><td>ND</td></tr>
<tr><td></td><td>Simvastatin</td><td>25</td><td>58±14</td><td></td><td></td><td>56±16</td><td>NS</td><td></td></tr>
<tr><td>LDL</td><td>Fish oil</td><td>18</td><td>162±21</td><td>mg/dl</td><td>SD</td><td>158±30</td><td>NS</td><td>ND</td></tr>
<tr><td></td><td>Simvastatin</td><td>25</td><td>177±40</td><td></td><td></td><td>144±43</td><td><0.01</td><td></td></tr>
<tr><td>Tg</td><td>Fish oil</td><td>18</td><td>203±105</td><td>mg/dl</td><td>SD</td><td>156±72</td><td>0.02</td><td>ND</td></tr>
<tr><td></td><td>Simvastatin</td><td>25</td><td>180±78</td><td></td><td></td><td>134±45</td><td><0.01</td><td></td></tr>
<tr><td>Graft survival</td><td>Fish oil</td><td></td><td>18/18</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td></td><td>Simvastatin</td><td></td><td>25/25</td><td></td><td></td><td></td><td></td><td></td></tr>
</table>
In fish oil group, there was significant reduction in TC (9.8%), Tg (14.1%), HDL (16.9%). LDL, Lp(a), Apo A1, Apo B remained stable. In simvastatin group after 3 months, significant reductions in TC (15.9%), Tg (15.6%), LDL 18.6%), and Apo B (15.6%). Apo A1 increased(10.4%), no significant changes in HDL and Lp(a).
Mean body weight remained stable.
CPK and serum creatinine values remained stable.
No adverse events with respect to “digestive, musculoskeletal or respiratory systems, skin and skin appendages, special senses or bleeding episodes.”
</td><td>Not specifically designed to measure equivalence.
Compliance was not assessed.</td></tr>
<tr><td>Grekas, 2001
11474227

Single-arm cohort</td><td>
<table>
<tr><th>Outcome</th><th>Cohort</th><th>N</th><th>Baseline</th><th>Unit</th><th>SD /SE /range</th><th>Follow-up</th><th>P W/in</th><th>P Btw</th></tr>
<tr><td>Tg</td><td>Fish oil</td><td>24</td><td>169±49</td><td>mg/dl</td><td>SD</td><td>124±40</td><td>P<0.03</td><td>-</td></tr>
<tr><td>Total cholesterol</td><td>Fish oil</td><td>24</td><td>229±49</td><td>mg/dl</td><td>SD</td><td>187±70</td><td>P<0.02</td><td>-</td></tr>
<tr><td>LDL</td><td>Fish oil</td><td>24</td><td>151±67</td><td>mg/dl</td><td>SD</td><td>124±45</td><td><0.03</td><td>-</td></tr>
<tr><td>HDL</td><td>Fish oil</td><td>24</td><td>46±16</td><td>mg/dl</td><td>SD</td><td>49±12</td><td>NS</td><td>-</td></tr>
<tr><td>CsA level</td><td>Fish oil</td><td>24</td><td>120±50</td><td>ng/ml</td><td>SD</td><td>No change</td><td></td><td></td></tr>
<tr><td>MAP</td><td>Fish oil</td><td>24</td><td>107±3.2</td><td>mmHg</td><td>SD</td><td>No change</td><td></td><td></td></tr>
<tr><td>Graft survival</td><td>Fish oil</td><td></td><td>24/24</td><td></td><td></td><td></td><td></td><td></td></tr>
</table>
Diet and pravastatin significantly lowered total and LDL cholesterol. Diet plus pravastatin plus fish oil significantly lowered total cholesterol, triglycerides, LDL, Apo A1 and Apo B. After reapeated measures analysis of variance, only significant difference was in plasma triglyceride levels after addition of fish oil.
All patients able to complete the six-month study. None reported adverse effects with respect to the digestive, musculoskeletal and respiratory systems or bleeding episodes. No adverse hepatic effects seen.
Renal function and blood CSA levels were not changed during and after the study (DATA NOT SHOWN). CPK increased in only one patient.
</td><td>Same group of patients underwent 2 different treatment protocols with a 4 weeks washout period. May have cumulative therapeutic effects.
No data on the EPA and DHA contents of the fish oil (Prolipid) reported. Information was then obtained through personal communication with the primary author.</td></tr>
</table>

Appendix C. Evidence Table Ie. Results for Omega-3 Fatty Acids and Kidney Transplantation

<table>
<tr><th>Author, year
UI#
Design</th><th>Results</th><th>Bias / Limitations / Comments</th></tr>
<tr><td>Hansen, 1995a
8559499

Single-arm cohort</td><td>
<table>
<tr><th>Outcome</th><th>Cohort</th><th>N</th><th>Baseline</th><th>Unit</th><th>SD /SE /range</th><th>Follow-up</th><th>P W/in</th><th>P Btw</th></tr>
<tr><td>GFR</td><td>Fish oil</td><td>10</td><td>61.9±4.8</td><td>ml/min</td><td>SE</td><td>64.1±6.3</td><td>NS</td><td>-</td></tr>
<tr><td>ERPF</td><td>Fish oil</td><td>10</td><td>277±24</td><td>ml/min</td><td>SE</td><td>286±31</td><td>NS</td><td>-</td></tr>
<tr><td>MAP</td><td>Fish oil</td><td>10</td><td>106±2</td><td>mmHg</td><td>SE</td><td>106±2</td><td>NS</td><td>-</td></tr>
<tr><td>Heart rate</td><td>Fish oil</td><td>10</td><td>63±3</td><td>beats</td><td>SE</td><td>61±2</td><td>NS</td><td>-</td></tr>
<tr><td>CsA level</td><td>Fish oil</td><td>10</td><td>245±19</td><td>ng/ml</td><td>SE</td><td>237±19</td><td>NS</td><td>-</td></tr>
<tr><td>Fasting serum creatinine</td><td>Fish oil</td><td>10</td><td>124±7</td><td>mmol/L</td><td>SE</td><td>125±10</td><td>NS</td><td>-</td></tr>
</table>
Fish oil was well tolerated except for a fishy aftertaste.
ANOVA revealed an overall significant difference in the GFR and ERPF time response between the study days with CsA intake and the study day without CsA intake.
Two patients dropped out.
</td><td>Reasons for dropouts (2 patients) unclear</td></tr>
<tr><td>Hansen 1995b
7703381

Multiple-arm cohorts</td><td>
<table>
<tr><th>Outcome</th><th>Cohort</th><th>N</th><th>Baseline</th><th>Unit</th><th>SD /SE /range</th><th>Follow-up</th><th>P W/in</th><th>P Btw</th></tr>
<tr><td>CsA level</td><td>Fish oil + CsA
Fish oil + Aza</td><td>9
9</td><td>285±46</td><td>ng/ml</td><td>SD</td><td>302±32</td><td>NS</td><td>ND</td></tr>
<tr><td>MAP</td><td>Fish oil + CsA
Fish oil + Aza</td><td>9
9</td><td>121±9
110±14</td><td>mmHg</td><td>SD</td><td>119±9
103±12</td><td>NS
<0.05</td><td>ND</td></tr>
<tr><td>Graft survival</td><td>Fish oil + CsA
Fish oil + Aza</td><td></td><td>9/9
9/9</td><td></td><td></td><td></td><td></td><td></td></tr>
</table>
Fish oil had no effect on ERPF, GFR or clearance of lithium in any group
No significant difference in urinary excretion of sodium, potassium, creatinine, albumin, 6-Keto-prostaglandin F1a, or thromboxane B2 before and during supplementation.
No affect on bioavailability of CsA.
GFR and lithium clearance increased significantly to the same extent before and during fish oil supplementation.
Fish oils were well-tolerated, excellent compliance, fishy aftertaste only problem.
</td><td>Like their companion study, negative results may reflect that treatment was begun late rather than immediately after transplant.
Not randomized and no blinding.</td></tr>
</table>

Appendix C. Evidence Table Ie. Results for Omega-3 Fatty Acids and Kidney Transplantation

Author, year UI# Design	Results									Bias / Limitations / Comments
Hernandez 2002 11981081 RCT: Parallel	Outcome	Cohort	N	Baseline	Unit	SD /SE /range	Follow-up	P W/in	P Btw	ATg was used as induction therapy. Only patients who had surviving allografts at any time during the study were included in the final analysis of interleukin expression and renal function. 4 patients in the fish oil group were excluded from final analysis: 1 patient in the fish oil group lost the allograft due to acute postoperative arterial thrombosis and 3 additional patients lost their grafts due to acute rejection. 2 patients in the control group were excluded from the final analysis due to lost grafts as a consequence of acute rejection.
	GFR (Cr-EDTA)	Fish oil	45	50.8±17	ml/min/1.73m^2	SD	61±35	ND	ND	
		Soy oil	40	51.6±22			59±14.4	ND		
	Total cholesterol	Fish oil	45	187±49	mg/dl	SD	234.4±34	ND	ND	
		Soy oil	40	175.6±44			251.4±42.2	ND		
	Tg	Fish oil	45	203±102	mg/dl	SD	167±82	ND	ND	
		Soy oil	40	164±65.7			174±78.5	ND		
	MAP	Fish oil	45	106±8.9	mmHg	SD	105.3±11.8	ND	ND	
		Soy oil	40	109±9.3			110±11.7	ND		
	CsA dose	Fish oil	45	4.2±1.7	mg/kg/d	SD	3.8±1.4	ND	ND	
		Soy oil	40	4.1±1.3			4.1±1.7	ND		
	CsA levels	Fish oil	45	244.1±103	ng/ml	SD	239.1±87.1	ND	ND	
		Soy oil	40	263.7±104.7			258.2±63	ND		
	Rejection episodes	Fish oil	45	16 @ month 1, 4 b/w months 1 and 3; 0 b/w months 4 and 12					NS	
		Soy oil	40	12 @ month 1, 4 b/w months 1 and 3; 3 b/w months 4 and 12						
	1-year Graft survival	Fish oil		86% (39/45)					NS	
		Soy oil		89% (36/40)						
	Expression of TNF-alpha, IL-1beta and IL-2 mRNA in those without acute rejection did not differ. TNF alpha at rejection episodes significantly lower in fish oil group. IL-1 beta after rejection episodes (2 weeks) significantly lower in fish oil group. No differences in serum creatinine, GFR, or proteinuria in those with and without rejection episodes in fish oil or control groups. No major adverse events observed; only complaint was a fishy aftertaste. No clinical bleeding or any prolonged episode of hematuria following biopsy.									

Appendix C. Evidence Table Ie. Results for Omega-3 Fatty Acids and Kidney Transplantation

Author, year UI# Design	Results									Bias / Limitations / Comments
Homan van der Heide, 1990a 2271089 RCT: Parallel	Outcome	Cohort	N	Baseline	Unit	SD /SE /range	Follow-up	P W/in	P Btw	All renal hemodynamic studies were performed after 1 month of oil supplement. Multiple subgroup analyses, which appear to be post-hoc without appropriate adjustment. Randomization and blinding not described.
	GFR (^{125}I)	Fish oil	14	ND	ml/min	range	44 (26-60)	ND	ND	
		Coconut oil	17	ND			40 (10-80)	ND		
		Fish oil (no rej episode)	11	ND	ml/min	range	45 (26-60)	ND	ND	
		Coconut oil (no rej episode)	11	ND			51 (20-80)	ND		
	MAP	Fish oil	14	ND	ml/min	range	106 (82-137)	ND	ND	
		Coconut oil	17	ND			107 (80-132)	ND		
		Fish oil (no rej episode)	11	ND	mmHg	range	85 (60-115)	ND	ND	
		Coconut oil (no rej episode)	11	ND			90 (75-105)	ND		
	CsA levels	Fish oil	14	ND	ng/ml	range	207 (90-275)	ND	ND	
		Coconut oil	17	ND			180 (40-295)	ND		
		Fish oil (no rej episode)	11	ND	ng/ml	range	235 (135-275)	ND	ND	
		Coconut oil (no rej episode)	11	ND			200 (40-240)	ND		
	CsA dose	Fish oil	14	ND	mg/kg/d	range	5.8 (3-10)	ND	ND	
		Coconut oil	17	ND			6.0 (2-9)	ND		
		Fish oil (no rej episode)	11	ND	mg/kg/d	range	5.6 (3-8)	ND	ND	
		Coconut oil (no rej episode)	11	ND			6.0 (2-9)	ND		
	Rejection episodes	Fish oil	3 (out of 14) @ month 1						ND	
		Coconut oil	6 (out of 17) @ month 1							
	GFR, ERPF and FF were measured at 1-month post-treatment, after dopamine, following amino acids, and during the combination of both. No significant differences in GFR and ERPF. Same values provided after stratifying patients as having had a rejection episode or not. There was a significant difference in the increase in the GFR following amino acid infusion between the									
Homan van der Heide, 1990b 2316014 RCT: Parallel	Outcome	Cohort	N	Baseline	Unit	SD /SE /range	Follow-up	P W/in	P Btw	
	GFR (^{125}I)	Fish oil	11	56 (24-79)	ml/min	range	68 (29-93)	<0.01	<0.01	
		Corn oil	10	64.5 (30-92)			60 (32-84)	NS		
	MAP	Fish oil	11	106 (93-116)	mmHg	range	98 (76-106)	<0.01	<0.01	
		Corn oil	10	106.5 (103-116)			109 (103-116)	NS		
	CsA levels	Fish oil	11	90 (65-125)	ng/ml	range	90 (65-125)	ND	NS	
		Corn oil	10	133 (45-265)			136 (55-235)	ND		
	There was no change in platelet count. 2 of the 12 patients in the corn oil group withdrew from the study because they suffered from a histologically confirmed rejection episode. 1 of the 12 patients in the fish oil group was excluded from further analysis because of noncompliance.									

Appendix C. Evidence Table Ie. Results for Omega-3 Fatty Acids and Kidney Transplantation

Author, year UI# Design	Results									Bias / Limitations / Comments
Homan van der Heide, 1992 1496538 RCT: Parallel	Outcome	Cohort	N	Baseline	Unit	SD /SE /range	Follow-up Median value	P W/in	P Btw	Significant difference in the number of mismatches on HLA-A and B in the coconut oil-treated patients receiving more poorly matched grafts.
	GFR (Cr-clearance)	Fish oil	39	ND	ml/min	range	53 (22-80)	ND	ND	
		Coconut oil	47	ND			49 (12-88)	ND		
		Fish oil (rejection episode)	14	41.5	ml/min	range	43 (22-69)	NS	ND	
		Coconut oil (rej episode)	12	39			27 (12-50)	<0.05		
		Fish oil (no rej episode)	25	ND	ml/min	range	59 (25-80)	ND	ND	
		Coconut oil (no rej episode)	35	ND			58 (24-88)	ND		
	MAP	Fish oil	39	ND	mmHg	range	105 (76-137)	ND	ND	
		Coconut oil	47	ND			108 (76-142)	ND		
		Fish oil (rejection episode)	14	ND	mmHg	range	107 (90-120)	ND	ND	
		Coconut oil (rej episode)	12	ND			112 (100-130)	ND		
		Fish oil (no rej episode)	25	ND	mmHg	range	106 (76-137)	ND	ND	
		Coconut oil (no rej episode)	35	ND			106 (76-142)	ND		
	CsA levels	Fish oil	39	ND	ng/ml	range	222 (75-565)	ND	ND	
		Coconut oil	47	ND			200 (35-490)	ND		
		Fish oil (rejection episode)	14	ND	ng/ml	range	150 (75-390)	ND	ND	
		Coconut oil (rej episode)	12	ND			182 (70-295)	ND		
		Fish oil (no rej episode)	25	ND	ng/ml	range	251 (80-565)	ND	ND	
		Coconut oil (no rej episode)	35	ND			200 (35-490)	ND		
	CsA dose	Fish oil	39	ND	ng/ml	range	6 (3-9)	ND	ND	
		Coconut oil	47	ND			6 (2-9)	ND		
		Fish oil (rejection episode)	14	ND	mg/kg/d	range	6 (2-10)	ND	ND	
		Coconut oil (rej episode)	12	ND			5.5 (3-11)	ND		
		Fish oil (no rej episode)	25	ND	mg/kg/d	range	6 (2-10)	ND	ND	
		Coconut oil (no rej episode)	35	ND			6 (3-11)	ND		
	Graft survival	Fish oil	40	1/40 @ month 1					NS	
		Coconut oil	48	1/48 @ month 1						
	Rejection episodes	Fish oil	40	15/40 @ month 1					NS	
		Coconut oil	48	12/48 @ month 1						

Appendix C. Evidence Table Ie. Results for Omega-3 Fatty Acids and Kidney Transplantation

Author, year UI# Design	Results									Bias / Limitations / Comments
Homan van der Heide, 1993 8350886 RCT: Parallel	Outcome	Cohort	N	Baseline	Unit	SD /SE /range	Follow-up	P W/in	P Btw	In discussion section, authors note that the greatest difference in the incidence of acute rejection occurred between days 30 and 90, a fact that may be attributed to the time lag needed to incorporate n-3 fatty acids into the phospholipids of various cell membranes. Acute postoperative oliguria or anuria significantly less frequent in the fish oil group. Perhaps they had better grafts to begin with? In discussion section authors state that results were similar when such patients were excluded. Second part of study not placebo controlled. Outcomes such as need for rehospitalization may be subject to bias.
	GFR (^{125}I)	Fish oil	30	42	ml/min	ND	53	ND	ND	
		Coconut oil	28	32			40	ND		
	MAP	Fish oil	30	100 (75-138)	mmHg	range	103 (80-141)	ND	ND	
		Coconut oil	28	108 (89-135)			118 (98-131)	ND		
	CsA levels	Fish oil	30	245 (55-565)	ng/ml	range	140 (50-321)	ND	ND	
		Coconut oil	28	285 (90-490)			143 (80-245)	ND		
	CsA dose	Fish oil	30	6 (3-8)	mg/kg/d	range	5 (2-7)	ND	ND	
		Coconut oil	28	6 (3-8)			4 (1-10)	ND		
	Graf survival	Fish oil	33	30/31					0.097	
		Coconut oil	33	28/32						
	Rejection episodes	Fish oil	33	6 episodes @ month 1, 1 episode b/w month 2 and 3; 0 episode b/w month 4 and 6; 1 episode b/w month 6 and 12						
		Coconut oil	33	10 episodes @ month 1, 9 episodes b/w month 2 and 3; 0 episode b/w month 4 and 6; 1 episode b/w month 6 and 12						
	One-year graft survival tended to be better in fish oil group but results did not achieve statistical significance. Fish oil group had significantly lower MAP and required significantly less antihypertensive therapy at all times. Median length of hospitalization shorter in fish oil group but did not achieve statistical significance. Mean number of second admissions significantly less in fish oil group. One patient stopped because of pyrosis, swallowing problems and fishy aftertaste. All patient with surviving grafts were included in the analysis of renal function and MAP (n=58), whereas the analysis of graft survival included all patients (n=66). In the fish-oil group, 1 patient lost the renal graft because of acute postoperative arterial thrombosis, 1 patient stopped taking fish oil because of its fishy aftertaste, and 1 patient declined to undergo renal-function tests during follow-up. In the control group, 1 patient lost the graft because of a technical failure, 3 patients lost their grafts because of therapy-resistant rejection, and 1 patient died of myocardial infarction.									

Appendix C. Evidence Table Ie. Results for Omega-3 Fatty Acids and Kidney Transplantation

Author, year UI# Design	Results									Bias / Limitations / Comments
Kooijmans-Coutinho, 1996 8704119 RCT: Parallel	Outcome	Cohort	N	Baseline	Unit	SD /SE /range	Follow-up	P W/in	P Btw	Compliance was not measured. Of the 50 patients included in the trial, 31 were evaluated 12 months after transplantation. The 19 patients were lost to follow-up because of various reasons including graft loss, death, non-compliance, pregnancy or concomitant illness. Graft-survival analysis was based on the intention to treat (N=50)
	GFR (^{125}I)	Fish oil	14	46.1± 18.9	ml/min/1.73m^2	SD	54.4± 21.6	ND	ND	
		Coconut oil	17	43.2 ±16.9			52.5 ±18.9	ND		
	MAP	Fish oil	20	103.8 ±14.4	mmHg	SD	104.3 ±10.8	ND	ND	
		Coconut oil	18	106.8± 9.9			106.3 ±11.7	ND		
	CsA levels	Fish oil	20	288.3± 124.5	ng/ml	SD	109 ±37.6	ND	ND	
		Coconut oil	18	341.7 ±137.5			113.6± 31.6	ND		
	CsA dose	Fish oil	20	6.5± 1.8	mg/kg/d	SD	3.9 ±1.4	ND	ND	
		Coconut oil	18	7.2 ±2.6			4.4 ±1.6	ND		
	Graft survival	Fish oil		20/24					ND	
		Coconut oil		20/23						
	Incidence of acute rejection after one month same for both groups (fish oil vs. control: 11/25 vs. 11/25 respectively). Between months 1 and 3 significantly more patients in the fish oil group experience rejection (13/24 vs. 3/23 respectively, p=0.003). Between months 3 and 12, rejection occurred in 14% in both groups (3/22 vs. 3/22 respectively). Three patients stopped because of gastric complaints and swallowing problems. One complained of fishy aftertaste and stopped taking drug (on coconut oil, however). 5 patients in each group experienced graft loss within 1 yr of transplantation. In fish oil group, one graft was lost because of primary function failure, 3 were lost as a result of therapy-resistant rejection, and 1 patient died with a functional graft. In placebo group,									

Appendix C. Evidence Table Ie. Results for Omega-3 Fatty Acids and Kidney Transplantation

Author, year UI# Design	Results									Bias / Limitations / Comments
Maachi, 1995 7879202 RCT: Parallel	Outcome	Cohort	N	Baseline	Unit	SD /SE /range	Follow-up	P W/in	P Btw	No specific measurement of blood EPA or DHA to assure compliance. No placebo controlled arm.
	GFR	Fish oil	40	47.5±18.1 (3months)	ml/min/1.73m^2	SD	50.1±18.0	NS	ND	
		Control	40	42.5±18.1 (3months)			43.0±14.0	NS		
	CsA dose	Fish oil	40	5.7±1.8 (3months)	mg/kg/d	SD	4.5±1.4	NS	ND	
		Control	40	6.3±2.0 (3months)			5.1±1.6	NS		
	CsA levels	Fish oil	40	437.6±171 (3months)	ng/ml	SD	438.2±160	NS	ND	
		Control	40	420.0±142 (3months)			418.5±133	NS		
	Tg	Fish oil	40	1.55±0.71 (3months)	mmol/L	SD	1.34±0.62	ND	ND	
		Control	40	1.91±0.75 (3months)			2.00±1.14	ND		
	Total cholesterol	Fish oil	40	6.03±1.11 (3months)	mmol/L	SD	6.01±1.20	ND	ND	
		Control	40	5.66±1.15 (3months)			6.12±1.41	ND		
	Rejection episodes	Fish oil		29 episodes in 20 patients					NS	ND
		Control		32 episodes in 25 patients						
	Graft survival	Fish oil		35/40					ND	
		Control		35/40						
Ng 2003 12809474 Case report	Case report of a 34 year old man who had a kidney transplant in May 1996. He did well till 1991 when he developed IgA nephropathy. After 1 year 5 months peritoneal dialysis, he received a 2nd transplant. Immunosuppressive medications of prednisone and CsA were identical to his prior regimen. After 5 years his nephrotic syndrome recurred, verified by biopsy. Fish oil treatment commenced and stabilized his proteinuria. His kidney function is "well preserved". He began angiotensin-receptor blocker in 1999 but this did not further improve his proteinuria.									Case report

Appendix C. Evidence Table Ie. Results for Omega-3 Fatty Acids and Kidney Transplantation

<table>
<tr><th>Author, year
UI#
Design</th><th>Results</th><th>Bias / Limitations / Comments</th></tr>
<tr><td>Rodriguez, 1997
Cochrane 00197406

RCT: Parallel</td><td>
<table>
<tr><th>Outcome</th><th>Cohort</th><th>N</th><th>Baseline</th><th>Unit</th><th>SD /SE /range</th><th>Follow-up</th><th>P W/in</th><th>P Btw</th></tr>
<tr><td>Tg</td><td>Fish oil</td><td>18</td><td>260.88±99.14</td><td>mg/dl</td><td>SD</td><td>197.37±90.15</td><td><0.01</td><td><0.05</td></tr>
<tr><td></td><td>lovastatin</td><td>16</td><td>235.26±102.5</td><td></td><td></td><td>199.7±96.3</td><td>NS</td><td></td></tr>
<tr><td>HDL</td><td>Fish oil</td><td>18</td><td>48.12±15.56</td><td>mg/dl</td><td>SD</td><td>49.23±11.14</td><td>NS</td><td>NS</td></tr>
<tr><td></td><td>lovastatin</td><td>16</td><td>60.23±15.77</td><td></td><td></td><td>60.36±13</td><td>NS</td><td></td></tr>
<tr><td>LDL</td><td>Fish oil</td><td>18</td><td>104.59±46.12</td><td>mg/dl</td><td>SD</td><td>97.86±52.94</td><td>NS</td><td><0.01</td></tr>
<tr><td></td><td>lovastatin</td><td>16</td><td>120.64±52.6</td><td></td><td></td><td>78.17±42.98</td><td><0.01</td><td></td></tr>
<tr><td>Total cholesterol</td><td>Fish oil</td><td>18</td><td>271.5±29.73</td><td>mg/dl</td><td>SD</td><td>237.25±33.77</td><td><0.001</td><td><0.01</td></tr>
<tr><td></td><td>lovastatin</td><td>16</td><td>278±43.15</td><td></td><td></td><td>221±38.38</td><td><0.001</td><td></td></tr>
</table>
Total cholesterol decreased significantly in both groups but to a greater extent and faster in the lovastatin group.
Both groups showed rise in HDL cholesterol ratio and a significant decrease in the Apo B/Apo A ratio. Only lovastatin group had a significant decrease of LDL-cholesterol. Only fish oil had significant decrease in Tg.
One dropout in fish oil group due to GI intolerance.
</td><td></td></tr>
</table>

Appendix C. Evidence Table Ie. Results for Omega-3 Fatty Acids and Kidney Transplantation

Author, year UI# Design	Results									Bias / Limitations / Comments
Santos, 2000 11134724 RCT: Parallel	Outcome	Cohort	N	Baseline	Unit	SD /SE /range	Follow-up change	P W/in	P Btw	Randomization and blinding methods not described explicitly.
	CsA levels	Fish oil	15	ND	ng/mL	SD	171± 31	ND	ND	
		Placebo	15	ND			151 ±32	ND		
	CsA dose	Fish oil	15	ND	mg/kg/d	SD	3.8 ± 0.6	ND	ND	
		Placebo	15	ND			4.0 ± 2.0	ND		
	GFR (Cr-EDTA)	Fish oil	15	ND	ml/min	SD	92.6±37.6	ND	ND	
		Placebo	15	ND			88.5±20.4	ND		
	Total cholesterol	Fish oil	15	155±35	mg/dl	SD	210±41	ND	ND	
		Placebo	15	150±33			218±43	ND		
	Tg	Fish oil	15	150±83	mg/dl	SD	165±46	ND	ND	
		Placebo	15	161±91			130±61	ND		
	LDL	Fish oil	15	100±37	mg/dl	SD	131±38	ND	ND	
		Placebo	15	118±29			140±38	ND		
	HDL	Fish oil	15	36±9	mg/dl	SD	5015	ND	ND	
		Placebo	15	39±9			46±13	ND		
	SBP	Fish oil	15	139.3±14.8	mmHg	SD	134±18	ND	ND	
		Placebo	15	143.8 ±21.2			133±20	ND		
	DBP	Fish oil	15	82.3 ±9.5	mmHg	SD	80±28	ND	ND	
		Placebo	15	83.5 ±13.2			78±12	ND		
	Rejection episodes	Fish oil	15	5 episodes in 4 patients					ND	
		Placebo	15	8 episodes in 6 patients						
	All grafts survived . Use of antihypertensives significantly less in fish oil group. None reported adverse effects with respect to digestive systems or bleeding episodes. There were no variations in the hematologic profile and glycemic control in both groups.									

Appendix C. Evidence Table Ie. Results for Omega-3 Fatty Acids and Kidney Transplantation

<table>
<tr><th>Author, year
UI#
Design</th><th>Results</th><th>Bias / Limitations / Comments</th></tr>
<tr><td>Schut, 1993
8210973

Schut, 1993
EMBASE
1993223288

Schut, 1992
14621869

Levi, 1992
1465791

RCT: Cross-over</td><td>
<table>
<tr><th>Outcome</th><th>Cohort</th><th>N</th><th>Baseline</th><th>Unit</th><th>SD /SE /range</th><th>Follow-up @ 4 months</th><th>Follow-up @ 8 months</th><th>P Win</th></tr>
<tr><td>GFR (^{125}I)</td><td>F-C + CsA</td><td>10</td><td>57 ±16</td><td>ml/min</td><td>SD</td><td>46±14</td><td>48± 21</td><td>NS</td></tr>
<tr><td></td><td>C-F + CsA</td><td>10</td><td>58± 19</td><td></td><td></td><td>57±16</td><td>65 ±19</td><td>NS</td></tr>
<tr><td></td><td>F-C + CsA + Pred</td><td>10</td><td>50±19</td><td>ml/min</td><td>SD</td><td>56±20</td><td>52± 20</td><td>NS</td></tr>
<tr><td></td><td>C-F + CsA + Pred</td><td>10</td><td>67± 7</td><td></td><td></td><td>70±8</td><td>73± 10</td><td>NS</td></tr>
<tr><td></td><td>F-C + Aza + Pred</td><td>9</td><td>62±11</td><td>ml/min</td><td>SD</td><td>63±7</td><td>65 ±11</td><td>NS</td></tr>
<tr><td></td><td>C-F + Aza + Pred</td><td>9</td><td>76±17</td><td></td><td></td><td>72±13</td><td>74 ±16</td><td>NS</td></tr>
</table>
F-C = subgroup which is supplemented first with fish oil, afterwards with corn oil; C-F = subgroup which is supplemented first with corn oil, afterwards with fish oil.

Blood pressure: In none of patients was antihypertensive treatment changed during the study.
Plasma phospholipids concentration showed significant increase in omega-3 fatty acids suggesting good compliance.
</td><td>Originally the study was crossover design (fish oil crossover to corn oil), but results were not analyzed properly.
No washout period (crossover @ 4months). Therefore, for the purpose of this review, only data from baseline to 4 months should be used. Data should be treated as a 4-month fish oil vs. corn oil parallel trial.</td></tr>
<tr><td>Sweny, 1993
8470281

Sweny, 1989
2517328

Single-arm cohort</td><td>
<table>
<tr><th>Outcome</th><th>Cohort</th><th>N</th><th>Baseline</th><th>Unit</th><th>SD /SE /range</th><th>Follow-up change</th><th>P W/in</th><th>P Btw</th></tr>
<tr><td>Tg</td><td>Fish oil</td><td>14</td><td>3.14±1.69</td><td>mmol/l</td><td>SD</td><td>1.98± 0.78</td><td><0.003</td><td>-</td></tr>
<tr><td>Total cholesterol</td><td>Fish oil</td><td>14</td><td>7.52±2.09</td><td>mmol/l</td><td>SD</td><td>7.99 ±2.05</td><td>NS</td><td>-</td></tr>
<tr><td>Proteinuria</td><td>Fish oil</td><td>14</td><td>1.21±1.78</td><td>g/24</td><td>SD</td><td>1.64±2.43</td><td>NS</td><td></td></tr>
</table>
Mean decline of renal function demonstrates a slowing of the rate of decline during the 6-month period on fish oil supplements.
Fish oil did not affect total platelet count but platelet aggregation reduced.
</td><td></td></tr>
</table>

Appendix C. Evidence Table Ie. Results for Omega-3 Fatty Acids and Kidney Transplantation

<table>
<tr><th>Author, year
UI#
Design</th><th>Results</th><th>Bias / Limitations / Comments</th></tr>
<tr><td>Urakaze, 1989
2812166

Urakaze, 1989
2652688

RCT: Parallel</td><td>
<table>
<tr><th>Outcome</th><th>Cohort</th><th>N</th><th>Baseline</th><th>Unit</th><th>SD /SE /range</th><th>Follow-up</th><th>P W/in</th><th>P Btw</th></tr>
<tr><td>Tg</td><td>Fish oil
Control</td><td>14
16</td><td>148 (96, 228)
137 (90, 211)</td><td>mg/dl</td><td>(-SD +SD)</td><td>116 (90, 151)
142 (104, 194)</td><td><0.05
NS</td><td>NS</td></tr>
<tr><td>SBP</td><td>Fish oil
Control</td><td>14
16</td><td>141± 11
147± 19</td><td>mmHg</td><td>SD</td><td>144± 13
149 ±24</td><td>NS
NS</td><td>NS</td></tr>
<tr><td>DBP</td><td>Fish oil
Control</td><td>14
16</td><td>85± 9
85 ±10</td><td>mmHg</td><td>SD</td><td>87 ±11
92±12</td><td><0.05
<0.05</td><td>NS</td></tr>
<tr><td>Serum Creatinine</td><td>Fish oil
Control</td><td>14
16</td><td>1.80 (1.35, 2.39)
1.78 (1.26, 2.52)</td><td>mg/dl</td><td>(-SD +SD)</td><td>1.78 (1.32, 2.23)
1.79 (1.22, 2.65)</td><td>NS
NS</td><td>NS</td></tr>
<tr><td>Rejection episodes</td><td>Fish oil
Control</td><td></td><td>0/14
0/16</td><td></td><td></td><td></td><td></td><td></td></tr>
</table>
The levels of total cholesterol were not changed in either group [data not shown].
“Good compliance in fish oil concentrate confirmed in each patient in treatment group by checking increase in EPA in RBC membrane lipids”. Values were not given.
Change in epinephrine-induced platelet aggregation (but not collagen or ADP induced platelet aggregation) significantly different.
RBC filterability increased significantly in treatment group.
Ratio of PGI-m to TXB-M significantly higher in treated versus control group.
No significant differences in those treated and not treated with CsA.
Patients complained of fishy eructation and one patient suffered from diarrhea for the first few days, but all soon began to tolerate the fish oil capsules well.
</td><td>Urakaze 1989 (UI#2652688) was published in Transplantation Proceedings.
Control received no placebo or treatment.</td></tr>
<tr><td>Yoa, 1994
EMBASE
1994288697

RCT: Parallel</td><td>
<table>
<tr><th>Outcome</th><th>Cohort</th><th>N</th><th>Baseline</th><th>Unit</th><th>SD /SE /range</th><th>Follow-up</th><th>P W/in</th><th>P Btw</th></tr>
<tr><td>Total cholesterol</td><td>Fish oil
Olive oil</td><td>12
11</td><td>208±65
235±36</td><td>mg/dl</td><td>SD</td><td>216±67
235±37</td><td>NS
NS</td><td>ND</td></tr>
<tr><td>HDL</td><td>Fish oil
Olive oil</td><td>12
11</td><td>62±30
53±14</td><td>mg/dl</td><td>SD</td><td>64±39
56±16</td><td>NS
NS</td><td>ND</td></tr>
<tr><td>LDL+VLDL</td><td>Fish oil
Olive oil</td><td>12
11</td><td>146±54
182±36</td><td>mg/dl</td><td>SD</td><td>153±49
178±32</td><td>NS
NS</td><td>ND</td></tr>
<tr><td>Tg</td><td>Fish oil
Olive oil</td><td>12
11</td><td>133±76
145±70</td><td>mg/dl</td><td>SD</td><td>119±66
122±46</td><td>NS
NS</td><td>ND</td></tr>
</table>
Apo A1 decreased after olive oil. Apo B increased after fish oil.
RBC deformability increased significantly after fish oil.
</td><td></td></tr>
</table>

Appendix C. Evidence Table Ie. Results for Omega-3 Fatty Acids and Kidney Transplantation

Author, year UI# Design	Results									Bias / Limitations / Comments
Zolotarski, 2003 12644071 Single-arm cohort	Outcome	Cohort	N	Baseline	Unit	SD /SE /range	Follow-up	P W/in	P Btw	Published in Transplantation Proceedings
	Serum Creatinine	Fish oil	8	4.35±1.2	mg/dl	ND	1.59±0.73	<0.05	-	
	BUN	Fish oil	8	122±61	mg/dl	ND	102±47	NS	-	
	Tg	Fish oil	8	159±101	mg/dl	ND	170±45	NS	-	

MAP = mean arterial pressure; SBP = systolic blood pressure; DBP = diastolic blood pressure; HDL = high density lipoprotein; LDL = low density lipoprotein; VLDL = very low density lipoprotein; HTN = hypertension; Tg = triglyceride

Appendix C. Evidence Table II. Studies for Omega-3 Fatty Acids and Heart Transplantation

1. Andreassen, 1997 (UI#9137231)

Part I. Study Characteristics

Study Characteristics	Eligibility Criteria	Omega-3 FA Intervention	Compliance	Control
N3 enrolled: 15 Control enrolled: 15 Age, N3: 29±2 SE (14 patients) Age, control: 33±3 SE (14 patients) % Male, N3: 73 (14 patients) % Male, control: 85 (14 patients) Duration: 6 months Country: Norway Site: 1 Study Design: RCT: Parallel	Inclusion criteria: consecutive orthotopic heart transplant recipients Exclusion criteria: ND	Omacor, Pronova AS, Oslo, Norway EPA: 1.86 g/day DHA: 1.512 g/day Start: day 4 posttransplant	Capsule counts and determination of serum phospholipid fatty acids	Corn oil

Part II. Concomitant Treatments and Outcomes Studied

Concomitant Treatments

Immunosuppressive therapy:

Induction therapy	Maintenance	Trough CsA levels	Anti-rejection therapy
CsA 6mg/kg body weight Aza 2mg/kg/day Prednisolone 0.2mg/kg/day	CsA tapered off according to the department rejection protocol. Prednisolone tapered off to 0.1mg/kg/day over 2 months	ND	boluses of methylprednisolone and, if necessary, rabbit anti-thymocyte globulin.

Anti-hypertensive Drugs:
Enalapril as needed Dose: ND

Lipid-lowering Drugs:
ND

Outcome Metric

A. Survival and rejection episodes:	Died of vascular rejection
B. Renal function:	Creatinine clearance
C. New onset diseases or conditions:	ND
D. CVD risk factors:	SBP (mm Hg), DBP (mm Hg)
	24-hr hypertensive load (mm Hg)
	Total cholesterol (mg/dl), HDL (mg/dl), TG (mg/dl)
E. Infections:	ND
F. Drug pharmacokinetics:	Additional antihypertensive treatment after 6 months treatment
	CsA dose
	Prednisolone dose
G. Other outcomes:	Hyperemia response, including rest perfusion, peak hyperemia, time to recovery, and perfusion debt repayment area.

Appendix C. Evidence Table II. Studies for Omega-3 Fatty Acids and Heart Transplantation

1. Andreassen, 1997 (UI#9137231)

Part III. Results

Results									Bias / Limitations / Comments
Outcome	Cohort	N	Baseline	Unit	SD /SE /range	Follow-up	P W/in	P Btw	
Cr clearance	Fish oil	14	57±5	ml/min	SE	81±5	P<0.05	ND	
	Corn oil	14	55±4			74±8	P<0.05		
SBP	Fish oil	14	134±5	mmHg	SE	135±5	ND	P<0.01	
	Corn oil	14	126±5			140±4	ND		
DBP	Fish oil	14	73±3	mmHg	SE	85±4	ND	P<0.01	
	Corn oil	14	70±2			89±3	ND		
Total cholesterol	Fish oil	14	193±15	mg/dl	SE	247±16	<0.01	NS	
	Corn oil	14	208±19			290±16	<0.01		
Triglycerides	Fish oil	14	181±29	mg/dl	SE	124±27	P<0.05	P<0.05	
	Corn oil	14	183±11			197±31	NS		
HDL	Fish oil	14	30±3	mg/dl	SE	52±5	P<0.01	NS	
	Corn oil	14	32±4			52±4	P<0.01		
CsA dose	Fish oil	14	5.1±0.3	mg/kg	SE	3.7±0.3	ND	NS	
	Corn oil	14	5.5±0.4			3.5±0.2	ND		
CsA level	Fish oil	14	342±12	ng/ml	SE	190±11	ND	NS	
	Corn oil	14	341±19			183±5	ND		
Graft survival	Fish oil	14/15							
	Corn oil	14/15							

One patient in each group (n=2) died of vascular rejection 7 and 8 weeks postoperatively and were therefore excluded from the final analyses.
One patient in treated group and three patients in placebo group experienced minor strokes.
The relation b/w the change in 24-hr BP and that in serum phospholipids was studied in the treatment group (n=14, but only 12 dots are shown in the figure 4). The change in 24-hr SBP were significantly related to those in EPA and DHA taken together (mg/L) (r=-0.69, p=0.04). There is no significant relationship b/w changes in the hyperemic response and changes in EPA+DHA (mg/L)

Appendix C. Evidence Table II. Studies for Omega-3 Fatty Acids and Heart Transplantation

2. Barbir, 1992 (UI#1466329)

Part I. Study Characteristics

Study Characteristics	Eligibility Criteria	Omega-3 FA Intervention	Compliance	Control
N3 enrolled: 44 Control enrolled: 43 Age, N3: 53±7 SE Age, control: 52±6 SE % Male, N3: 91 % Male, control: 88 Duration: 3 months Country: U.K. Site: 1 Study Design: non-RCT	Inclusion criteria: consecutive cardiac transplant recipients with hyperlipidemia (cholesterol > 6.5 or TG > 2.8 mmol/l or both). Exclusion criteria: DM, abnormal thyroid function, significant hepatic or renal dysfunction, or symptomatic gallbladder disease with or without cholelithiasis, or those receiving anticoagulants (excluding antiplatelet drugs) or therapy with diuretics or prednisolone where dosage had been changed in the 3 months prior to the study.	MaxEPA EPA: 1.8 g/day DHA: 1.2 g/day Start: ND	ND	Bezafibrate 400 mg/day

Part II. Concomitant Treatments and Outcomes Studied

Concomitant Treatments				Outcome Metric	
Immunosuppressive therapy:				A. Survival and rejection episodes:	Patient survival, Rejection episodes
Induction therapy	Maintenance	Trough CsA levels	Anti-rejection therapy	B. Renal function:	Serum creatinine
ND	CsA+Aza N3: 37/44 Control: 38/43 CsA+Aza+ Prednisone N3: 2/44 Control: 2/43 Aza+ Prednisone N3: 5/44 Control: 3/43	ND	ND		Serum alkaline phosphatase, AST, Urea, Hemoglobin: hemostatic variables, Fibrinogen, Factor II, VII, VIII, IX, X, Antithrombin, Euglobin clot lysis time, TPA, PTA
				C. New onset diseases or conditions:	ND
				D. CVD risk factors:	Total cholesterol, TG, HDL, LDL Apo B, Apo B1, Lpa
				E. Infections:	
				F. Drug pharmacokinetics:	CsA blood levels
Anti-hypertensive Drugs: ND				G. Other outcomes:	
Lipid-lowering Drugs: ND					

Appendix C. Evidence Table II. Studies for Omega-3 Fatty Acids and Heart Transplantation

2. Barbir, 1992 (UI#1466329)

Part III. Results

Results										Bias / Limitations / Comments
Outcome	Cohort	N	Baseline	Unit	SD /SE /range	Follow-up % change	Follow-up	P W/in	P Btw	"open, controlled study"
Total cholesterol	Fish oil	44	7.4±0.2	mmol/l	SE	0%	ND	ND	0.0003	
	Bezafibrate	43	7.2±0.2			-12%	ND	ND		
TG	Fish oil	44	3.3±0.2	mmol/l	SE	-33%	ND	ND	0.61	
	Bezafibrate	43	2.9±0.2			-33%	ND	ND		
HDL	Fish oil	44	1.07±0.1	mmol/l	SE	0%	ND	ND	0.0023	
	Bezafibrate	43	1.05±0.1			+30%	ND	ND		
LDL	Fish oil	44	5.2±0.2	mmol/l	SE	0%	ND	ND	0.0002	
	Bezafibrate	43	5.0±0.1			-18%	ND	ND		
CsA levels	Fish oil	44	199±16	ng/mll	SE	ND	183±12	ND	0.12	
	Bezafibrate	43	198±12			ND	144.2±12	ND		
Serum Creatinine	Fish oil	44	139±4	mmol/l	SE	ND	140±5	ND	<0.0001	
	Bezafibrate	43	140±4			ND	176±4	ND		
1 patient died from CHD and 13 patients reported adverse events in fish oil group. Adverse events included dizziness, gastric intolerance, skin irritation, tonsilitis and fatigue. 2 withdrawals because of nausea.										
1 acute rejection episode in the Bezafibrate group. 15 of the 43 patients reported adverse events, including nausea, leg cramps, headaches,										

Appendix C. Evidence Table II. Studies for Omega-3 Fatty Acids and Heart Transplantation

3. Fleischhauer, 1993 (UI#8450169)

Part I. Study Characteristics

Study Characteristics	Eligibility Criteria	Omega-3 FA Intervention	Compliance	Control
N3 enrolled: 9 Control enrolled: 7 Age, N3: 46.7±3.6SE (7pts) Age, control: 48.7±2.4SE % Male, N3: 86 % Male, control: 100 Duration: 3 weeks Country: USA Site: 1 Study Design: non-RCT	Inclusion criteria: serum creatinine <2mg/dl. No prior evidence of coronary artery disease, clinically stable condition without evidence of recent rejection, infection or other illness. No history of a bleeding diathesis. Control group consisted of 7 heart transplant recipients selected to match the treatment group with respect to the age of the cardiac allograft and baseline clinical and lipid profiles. Exclusion criteria: ND	Viking Cod Liver Oil or Multi-EPA caps, Multiway Associates EPA: 3.4 g/day DHA: 2.3 g/day start: 1-6 years posttransplant N3: 1.1±0.1 SE control: 1.4±0.2 SE	Bottle and capsule counts and was determined to be >=90% ingested.	No fish oil

Part II. Concomitant Treatments and Outcomes Studied

Concomitant Treatments				Outcome Metric	
Immunosuppressive therapy:				A. Survival and rejection episodes:	ND
Induction therapy	Maintenance	Trough CsA levels	Anti-rejection therapy	B. Renal functions:	ND
ND	Prednisone mg/day N3: 9.0±2SE Control: 12.3±5.8 Immuran mg/day N3: 182±29 Control: 162±22 CsA mg/day N3: 246±49 Control: 316±86	ND	ND	C. New onset diseases or conditions:	ND
				D. CVD risk factors:	Blood pressure (BP) Heart rate
				E. Infections:	ND
				F. Drug pharmacokinetics:	
				G. Other outcomes:	% change mean left anterior descending artery diameter vs. baseline: Serial biplane angiography. Compare acetylcholine infused segment with control segment.
Anti-hypertensive Drugs: Diltiazem mg/day (N3: 3/7pts 200±30SE; control: 2/7pts 180±0) Hydralazine mg/day (N3: 3/7pts 183±60;) control: 3/7pts 133±17 Enalapril mg/day (N3: 1/7pt 180±0; control: 2/7pts 65±35) Captopril mg/day (N3: 2/7pts 88±13; control: 0/7) Clonidine mg/day (N3: 3/7pts 0.3±0; control: 2/7pts 0.3±0)					
Lipid-lowering Drugs: ND					

Appendix C. Evidence Table II. Studies for Omega-3 Fatty Acids and Heart Transplantation

3. Fleischhauer, 1993 (UI#8450169)

Part III. Results

Results									Bias / Limitations / Comments
Outcome	Cohort	N	Baseline	Unit	SD /SE /range	Follow-up	P W/in	P Btw	Control group consisted of 7 heart transplant recipients selected to match the treatment group with respect to the age of the cardiac allograft and baseline clinical and lipid profiles.
MAP	Fish oil	7	116±4	mmHg	SE	107±3	NS	NS	
	Control	7	114±4			109±3	NS		
Heart rate	Fish oil	7	98±6	beats/min	SE	88±4	NS	NS	
	Control	7	93±3			89±3	NS		
Mean left anterior descending artery diameter	Fish oil	7							
	Control	7				31% less	P<0.01		

2 patients in fish oil group were excluded because they had angiographically evident transplant coronary artery disease precluding acetylcholine infusion.

Significant gastrointestinal distress and frequent belching in 1 patient

Appendix C. Evidence Table II. Studies for Omega-3 Fatty Acids and Heart Transplantation

4. Holm, 2001 (UI#11544435; EMBASE2001241336)

Part I. Study Characteristics

Study Characteristics	Eligibility Criteria	Omega-3 FA Intervention	Compliance	Control
N3 enrolled: 23 Control enrolled: 22 Age, N3: 57±2 SE (21pts) Age, control: 57±2 SE (20pts) % Male, N3: 95 (21pts) % Male, control: 95 (20pts) Duration: 12 months Country: Norway Site: 1 Study Design: RCT Parallel	Inclusion criteria: heart transplant patients who were clinically and hemodynamically stable in New York Heart Association functional class I without signs of ongoing rejection or significant concomitant disease. Exclusion criteria: ND	Omacor, Pronova AS, Oslo, Norway EPA: 1.86 g/day DHA: 1.512 g/day start: mean 6 years post-transplant, range 1-12 y	Capsule counts and determination of serum phospholipid fatty acids	Corn oil

Part II. Concomitant Treatments and Outcomes Studied

Concomitant Treatments				Outcome Metric	
Immunosuppressive therapy:				A. Survival and rejection episodes:	ND
Induction therapy	Maintenance	Trough CsA levels	Anti-rejection therapy	B. Renal functions:	Serum creatinine (mmol/L) GFR (ml/min): Calculated according to Cockroft and Gaults formula
ND	CsA mg/kg/day N3: 2.4±0.1 control: 2.3±0.1 Aza mg/kg/day N3: 1.2±0.1 control: 1.1±0.1 Prednisolone mg/kg/day N3: 0.1±0.01 control: 0.1±0.02	ND	ND	C. New onset diseases or conditions:	% normotensive after 12-month Rx
				D. CVD markers:	SBP (mm Hg), DBP (mm Hg), Systemic vascular resistance, TG (mmol/L), Total cholesterol (mmol/L), HDL-c (mmol/L), LDL-c (mmol/L), Hemodynamics (Including SVR, LVEF, LVEDPm MAP, PCW and CI) , TNF-α, IL-10,
Anti-hypertensive Drugs: ACE inhibitors, calcium-channel antagonist, beta blockers, diuretics				E. Infections:	ND
Lipid-lowering Drugs: Statins				F. Drug pharmacokinetics:	CsA dose
				G. Other outcomes:	Echocardiography (Including LVEDD, FS, septal thickness, posterior wall, E/A ratio, and deceleration time) Endothelium-dependent and –independent vasodilation

Appendix C. Evidence Table II. Studies for Omega-3 Fatty Acids and Heart Transplantation

4. Holm, 2001 (UI#11544435; EMBASE2001241336)

Part III. Results

Results									Bias / Limitations / Comments
Outcome	Cohort	N	Baseline	Unit	SD /SE /range	Follow-up	P W/in	P Btw	
SBP	Fish oil	21	138±3	mmHg	SE	No change	NS	0.02	
	Corn oil	20	139±3			+8±2	0.01		
DBP	Fish oil	21	89±1	mmHg	SE	No change	NS	0.07	
	Corn oil	20	90±2			+3±2	0.1		
TG	Fish oil	21	2.2±0.3	mmol/l	SE	1.7±0.2	<0.001	0.07	
	Corn oil	20	1.9±0.3			2.0±0.3	NS		
Total cholesterol	Fish oil	21	6.9±0.3	mmol/l	SE	6.8±0.3	NS	0.5	
	Corn oil	20	6.2±0.2			6.1±0.2	NS		
HDL	Fish oil	21	1.3±0.1	mmol/l	SE	1.5±0.1	NS	0.38	
	Corn oil	20	1.4±0.1			1.4±0.1	NS		
LDL	Fish oil	21	4.4±0.1	mmol/l	SE	4.4±0.1	NS	057	
	Corn oil	20	3.9±0.1			3.9±0.1	NS		
% normaltensive after 12-month Rx	Fish oil	9/21							
	Corn oil	0/20							
Graft survival	Fish oil	21/23							
	Corn oil	20/22							

Adverse effects were not described. Three patients died: 2 in the placebo group (cerebral infarction and amyotrophic lateral sclerosis) and 1 in the treatment group (prostate cancer) and one patient in the treatment group withdrew for personal reasons.

None of the patients withdrew from the study because of side effects.

There is a significant relationship b/w changes in SBP and serum EPA and DHA in 21 heart transplant recipients during 12 months Rx with omega-3 fatty acids (r= -0.52, p=0.02)

Serum creatinine increased significantly (121±6 to 130±5 mmol/l, p<0.01) in the placebo group but there was no increase in the fish oil group (data in figure 4)

Calculated GFR decreased significantly (74±5 to 68±4 ml/min, p=0.02 in the placebo group but there was no increase in the fish oil group

Appendix C. Evidence Table II. Studies for Omega-3 Fatty Acids and Heart Transplantation

5. Salen, 1994 (EMBASE1994139060)

Part I. Study Characteristics

Study Characteristics	Eligibility Criteria	Omega-3 FA Intervention	Compliance	Control
N3: enrolled: 41 Age, N3: 50±9 SE % Male: 100 Duration: 1 year Country: France Site: 1 Study Design: Single-arm cohort	Inclusion criteria: heart transplant patients with hypercholesterolemia (total cholesterol >6.5 mmol/L) Exclusion criteria: ND	French Meditteranean diet N3: 0.24±0.02 After 1 year: 0.63±0.08 P=0.0001 Start: ND	Dietary surveys and counseling	ND

Part II. Concomitant Treatments and Outcomes Studied

Concomitant Treatments				Outcome Metric	
Immunosuppressive therapy:				A. Survival and rejection episodes:	ND
Induction therapy	Maintenance	Trough CsA levels	Anti-rejection therapy	B. Renal functions:	ND
ND	Corticosteroid dose baseline 17.6±1.0 mg/day after 1 year 12.5±0.8 (p=0.0001)	ND	ND	C. New onset diseases or conditions:	ND
				D. CVD risk factors:	Total cholesterol, TG, HDL, LDL, Apo B-100, Apo A-1, Lipoprotein (a), Uric acid, Thrombin-induced platelet aggregation (Only performed in the last 25 consecutive patients)
Anti-hypertensive Drugs: ND				E. Infections:	ND
Lipid-lowering Drugs: ND				F. Drug pharmacokinetics:	CsA dose, Corticosteroid dose
				G. Other outcomes:	ND

Appendix C. Evidence Table II. Studies for Omega-3 Fatty Acids and Heart Transplantation

5. Salen, 1994 (EMBASE1994139060)

Part III. Results

Results									Bias / Limitations / Comments
Outcome	Cohort	N	Baseline	Unit	SD /SE /range	Follow-up change	P W/in	P Btw	Diet composition was estimated from 24-hour recall. Although the intake of linolenic acid increased, total calories and % saturated fats from calories were significantly decreased at the same time. The observed effects could not be solely attributed to ALA. Platelet aggregation analyses were only performed in the last 25 consecutive patients without further explanation.
Total cholesterol	ALA	41	8.2±1.6	mmol/L	SE	7.2±1.5	P=0.005	-	
Triglycerides	ALA	41	3.1±2.2	mmol/L	SE	2.9±2.5	NS	-	
HDL	ALA	41	1.4±0.4	mmol/L	SE	1.42±0.5	NS	-	
LDL	ALA	41	6.2±1.5	mmol/L	SE	5.3±1.3	P=0.004	-	
Weight	ALA	41	75.5±1.8	kg	SE	74.0±1.6	NS	-	
Platelet aggregation	ALA	41	19.1±1.4%		SE	13.5±1.7%	P=0.02	-	
Uric acid	ALA	41	333±20.1	umol/L	SE	399±19.8	P=0.02	-	
CsA dose	ALA	41	392±29	mg/day	SE	338±25	NS	-	
Arterial pressure did not decrease significantly, although immunosuppressive treatment was progressively reduced (p<0.0001) There was an inverse correlation between linolenic acid intake and platelet aggregation (r=-0.44; p=0.03) after the diet intervention. This analysis was only performed in the last 25 consecutive patients. All grafts survived.									

Appendix C. Evidence Table II. Studies for Omega-3 Fatty Acids and Heart Transplantation

6. Ventura, 1993 (UI#8222166)

Part I. Study Characteristics

Study Characteristics	Eligibility Criteria	Omega-3 FA Intervention	Compliance	Control
N3: enrolled: 10 Control enrolled: 10 Age, N3: 53±7 Age, control: 52±7 51±6 (6 pts) % Male, N3: 90 % Male, control: 90 83 (6 pts) Duration: 12 weeks Country: USA Site: 1 Study Design: RCT Parallel	Inclusion criteria: hypertensive orthotopic cardiac transplant recipients Exclusion criteria: ND	EPA+DHA: 3 g/day start: 3.5±1.5months posttransplant	ND	Corn oil

Part II. Concomitant Treatments and Outcomes Studied

Concomitant Treatments				Outcome Metric	
Immunosuppressive therapy:				A. Survival and rejection episodes:	ND
Induction therapy	Maintenance	Trough CsA levels	Anti-rejection therapy	B. Renal functions:	ND
ND	CsA Prednisone Aza	ND	ND	C. New onset diseases or conditions:	ND
Anti-hypertensive Drugs: Calcium-channel blocking agent, ACE inhibitor, or both				D. CVD risk factors:	MAP Systemic vascular resistance (SVR)
Lipid-lowering Drugs: ND				E. Infections:	ND
				F. Drug pharmacokinetics:	ND
				G. Other outcomes:	Echocardiographic indexes of myocardial structure and function: Septal thickness, posterior wall thickness, left ventricular end-diastolic diameter, left ventricular mass, ejection fraction %

Appendix C. Evidence Table II. Studies for Omega-3 Fatty Acids and Heart Transplantation

6. Ventura, 1993 (UI#8222166)

Part III. Results

Results									Bias / Limitations / Comments
Outcome	Cohort	N	Baseline	Unit	SD /SE /range	Follow-up	P W/in	P Btw	
MAP	Fish oil	10	120±7	mmHg	SE	102±7	<0.01	ND	
	Corn oil	6	121±4			No change	NS		
Systemic vascular resistance	Fish oil	10	2107±45	dynes.sec.cm-5	SE	1426±60	<0.0001	ND	
	Corn oil	6	ND			No change	NS		
Septal thickness	Fish oil	10	1.0±0.2	cm	SE	1.0±0.2	NS	ND	
	Corn oil	6	0.9±0.1			0.9±0.1	NS		
Posterior wall thickness	Fish oil	10	0.98±0.1	cm	SE	0.96±0.1	NS	ND	
	Corn oil	6	0.8±0.1			0.8±0.1	NS		
Left ventricular end-diastolic diameter	Fish oil	10	4.5±0.1	cm	SE	4.4±0.1	NS	ND	
	Corn oil	6	3.9±0.2			4.0±0.1	NS		
Left ventricular mass	Fish oil	10	210±10	g	SE	182±12	P=0.1	ND	
	Corn oil	6	173±9			169±10	NS		
Left ventricular mass/height	Fish oil	10	117±5	g/m	SE	102±4	NS	ND	
	Corn oil	6	97±4			95±5	NS		
Total cholesterol	Fish oil	10	275±15	mg/dl	SE	264±14	NS	ND	
	Corn oil	6	265±16			286±15	NS		
Triglycerides	Fish oil	10	157±20	mg/dl	SE	149±12.1	NS	ND	
	Corn oil	6	180±172			178±14	NS		
HDL	Fish oil	10	47±4	mg/dl	SE	47±4	NS	ND	
	Corn oil	6	42±14			44±12	NS		
LDL	Fish oil	10	185±14	mg/dl	SE	176±14	NS	ND	
	Corn oil	6	174±14			187±14	NS		
Four patients in the placebo group did not finish the study: 2 because of acute allograft rejection and 2 because of an intolerance to omega-6 fatty acids.									
Three patients who continued oral supplementation with fish oil after completion of the study were able to discontinue antihypertensive agents.									

Appendix C. Evidence Table III. Study for Omega-3 Fatty Acids and Bone Marrow Transplantation

1. Takatsuka, 2001 (UI#11781629); Takatsuka, 2002 (EMBASE 2003001292)

Part I. Study Characteristics

Study Characteristics	Eligibility Criteria	Omega-3 FA Intervention	Compliance	Control
N3: enrolled: 8 Control enrolled: 9 Age, N3: 25.9 Age, control: 31.1 % Male, N3: 62.5 % Male, control: 11.1 Duration: 201 days Country: Japan Site: 1 Study Design: RCT Parallel	Inclusion criteria: consecutive patients who underwent unrelated allogeneic bone marrow transplant Exclusion criteria: ND	EPA: 1.8 g/day ethyl icosapentate, Mochida Pharmaceutical Co., Ltd., Tokyo, Japan start: day 21 before BMT	ND	No placebo

Part II. Concomitant Treatments and Outcomes Studied

Concomitant Treatments				Outcome Metric	
Immunosuppressive therapy:				A. Survival and rejection episodes:	Patient survival
Induction therapy	Maintenance	Trough CsA levels	Anti-rejection therapy	B. Renal functions:	ND
ND	CsA methotrexate methylprednisolone	400-600 ng/ml	ND If GVHD worsened, CsA and methylprednisolone increased, or CsA replaced by FK506	C. New onset diseases or conditions:	ND
				D. CVD risk factors:	LTB4 TNF-alpha IFN-gamma IL-2
Anti-hypertensive Drugs: ND				E. Infections:	ND
Lipid-lowering Drugs: ND				F. Drug pharmacokinetics:	ND
				G. Other outcomes:	The risk of graft-versus-host disease (GVHD): High-risk: LTB4 >= 20 FU/ml, Moderate-risk: 6 <= LTB4 < 20 FU/ml, Low-risk: LTB4 < 6 FU/ml

Appendix C. Evidence Table III. Study for Omega-3 Fatty Acids and Bone Marrow Transplantation

1. Takatsuka, 2001 (UI#11781629); Takatsuka, 2002 (EMBASE 2003001292)

Part III. Results

Results	Bias / Limitations / Comments
In the non-EPA group, 5 out of 9 patients died whereas all of the patients in the EPA group survived ($p<0.01$, log-rank test) There was a significant difference between the two groups with respect to the severity of colonic GVHD ($p=0.041$). No control patients changed in the risk levels after BMT, while 3 EPA treated patients were in the moderate-risk group became low-risk group after BMT. Compared to controls, there was a significant decrease in LTB4 and TNF-alpha in EPA-treated group ($p<0.05$) Compared to controls, there was a significant decrease IFN-gamma in EPA-treated group ($p<0.05$) during recovery phase only. Compared to controls, there was no significant change.	No blinding. No description of how the 17 consecutive patients were selected.

Appendix C. Evidence Table IV. Study for Omega-3 Fatty Acids and Liver Transplantation

1. Badalamenti, 1995 (UI#7489976)

Part I. Study Characteristics

Study Characteristics	Eligibility Criteria	Omega-3 FA Intervention	Compliance	Control
N3 enrolled: 14 Control enrolled: 13 Age, N3: 44.8±9SE (13pts) Age, control: 47.8±3 SE % Male N-3: 62 (13pts) % Male control: 54 Duration: 2 months Country: Italy Site: 1 Study Design: RCT Parallel	Inclusion criteria: stable normal serum creatinine and urine analyses before transplantation; time since OLT>6 months; stable liver function and serum creatinine and stable CsA dosage for at least 3 months before the study Exclusion criteria: ND	Total: 12 gram/day Max-Epa, Zyma, Saronno, Italy EPA: 2.16 g/day DHA: 1.44 g/day Start: ND	measure the plasma fatty acid	Corn oil

Part II. Concomitant Treatments and Outcomes Studied

Concomitant Treatments

Immunosuppressive therapy:

Induction therapy	Maintenance	Trough CsA levels	Anti-rejection therapy
ND	8 patients (4 from fish oil group and 4 from corn oil group) received only CsA. 4 patients (1 and 3) received CsA plus prednisone (5 to 10 mg/day), 7 patients (4 and 3) received CsA plus Aza (50 to 100 mg/day) 7 patients (5 and 2) received CsA plus prednisone (5 to 12.5 mg/day) plus Aza (50 to 100 mg/day)	ND	ND

Anti-hypertensive Drugs:
ND

Lipid-lowering Drugs:
ND

Outcome Metric

A. Survival and rejection episodes:	ND
B. Renal functions:	ND
C. New onset diseases or conditions:	ND
D. CVD risk factors:	LTB4 TNF-alpha IFN-gamma IL-2
E. Infections:	ND
F. Drug pharmacokinetics:	ND
G. Other outcomes:	The risk of graft-versus-host disease (GVHD): High-risk: LTB4 >= 20 FU/ml, Moderate-risk: 6 <= LTB4 < 20 FU/ml, Low-risk: LTB4 < 6 FU/ml

Appendix C. Evidence Table IV. Study for Omega-3 Fatty Acids and Liver Transplantation

1. Badalamenti, 1995 (UI#7489976)

Part III. Results

Results									Bias / Limitations / Comments
Outcome	Cohort	N	Baseline	Unit	SD /SE /range	Follow-up	P W/in	P Btw	
GFR	Fish oil	13	71±6	mL/min	SE	86.5±6.6	NS	ND	
	Corn oil	13	70.4±11			65.5±8	NS		
MAP	Fish oil	13	101±3	mmHg	SE	99±3	NS	ND	
	Corn oil	13	94±2			95±2	NS		
Blood CsA	Fish oil	13	480±18	ng/mL	SE	450±22	NS	ND	
	Corn oil	13	523±43			471±29	NS		
RBF	Fish oil	13	0.54±0.07	L/min	SE	0.64±0.07	P<0.03	ND	
	Corn oil	13	0.54±0.05			0.51±0.03	NS		
PA	Fish oil	13	140±29	pg/ml	SE	145±25	NS	ND	
	Corn oil	13	228±78			300±99	NS		
Bilirubin	Fish oil	13	0.9±0.1	mg/dL	SE	0.9±0.1	NS	ND	
	Corn oil	13	1.4±0.2			1.6±0.3	NS		
Prothrombin	Fish oil	13	92±4.1	%	SE	99.7±0.3	NS	ND	
	Corn oil	13	86±5			86.1±3.5	NS		
Serum albumin	Fish oil	13	3.65±0.15	g/dL	SE	3.67±0.11	NS	ND	
	Corn oil	13	3.42±0.2			3.45±0.2	NS		
Urine urea	Fish oil	13	19.3±2.6	g/24hr	SE	18.1±2.2	NS	ND	
	Corn oil	13	19.3±2.7			19.3±3	NS		
Urine TxB2	Fish oil	13	707±192	pg/hr	SE	276±76	P<0.03	ND	
	Corn oil	13	428±195			870±310	P<0.03		
Fishy taste, leading to unblinding									

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