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Effects of Omega-3 Fatty Acids on Organ Transplantation

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.

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