n–3 PUFAs in cancer, surgery, and critical care: a systematic review on clinical effects, incorporation, and washout of oral or enteral compared with parenteral supplementation

Barbara S van der Meij, Marian AE van Bokhorst-de van der Schueren, Jacqueline AE Langius, Ingeborg A Brouwer, and Paul AM van Leeuwen

ABSTRACT

Background: n–3 (omega-3) Fatty acids (FAs) may have beneficial effects in patients with cancer or in patients who undergo surgery or critical care.

Objective: Our aim was to systematically review the effects of oral or enteral and parenteral n–3 FA supplementation on clinical outcomes and to describe the incorporation of n–3 FAs into phospholipids of plasma, blood cells, and mucosal tissue and the subsequent washout in these patients.

Design: We investigated the supplementation of n–3 FAs in these patients by using a systematic literature review.

Results: In cancer, the oral or enteral supplementation of n–3 FAs contributed to the maintenance of body weight and quality of life but not to survival. We did not find any studies on parenteral supplementation of n–3 FAs in cancer. In surgical oncology, we did not find any studies on enteral supplementation of n–3 FAs. However, postoperative parenteral supplementation in surgical oncology may reduce the length of a hospital stay. For general surgery, we did not find any studies on enteral supplementation of n–3 FAs, and evidence on parenteral supplementation was insufficient. In critical care, enteral supplementation of n–3 FAs had beneficial effects on clinical outcomes; evidence on parenteral supplementation in critical care was inconsistent. The incorporation of n–3 FAs in plasma and blood cells was slower with enteral supplementation (4–7 d) than with parenteral supplementation (1–3 d). The washout was 5–7 d.

Conclusions: This review shows the beneficial effects of n–3 FA supplementation in cancer, surgical oncology, and critical care patients. Supplementation in these specific patient populations could be considered with the route of administration taken into account.

INTRODUCTION

n–3 (omega-3) FAs frequently attract the attention of medical experts, scientists, and consumers. The main n–3 FAs are EPA (20:5 n–3), DHA (22:6n–3), and α-linolenic acid (18:3n–3). EPA and DHA are mainly in fish and seafood, and α-linolenic acid is in flaxseed, canola, soy, perilla, and walnut oils and is an essential FA for humans.

In several animal and human studies, an increased consumption of dietary n–3 FAs resulted in a decreased proportion of AA and an increased proportion of EPA in membrane phospholipids of immune cells (1, 2), which caused immunomodulation, less inflammation, and attenuation of cachexia (3, 4). In healthy volunteers, the immunomodulation of effects continued for ~10 wk after the end of supplementation (5).

Clinical antiinflammatory effects of n–3 FAs have been documented in several chronic inflammatory conditions including rheumatoid arthritis and inflammatory bowel diseases (6). In cancer, n–3 FAs may have positive effects on cachexia and survival (3, 4, 7, 8), but evidence from randomized clinical trial was equivocal and results of additional trials are awaited (9, 10).

Likewise, supplementation of n–3 FAs in other highly inflammatory circumstances, such as in surgery, sepsis, and ARDS, appears to have beneficial effects (11). Cancer, surgery, and critical care are areas with a high potential for the application of n–3 FAs in hospitals. Our objective was to systematically review effects of oral or enteral and parenteral n–3 FA supplementation on clinical outcomes in patients with cancer who underwent surgery or critical care. Second, knowledge on the incorporation into phospholipids of plasma, blood cells, and mucosal tissue and the subsequent washout after oral or enteral and parenteral n–3 FA supplementation in these patient populations is extremely limited. Therefore, we also reviewed this area.

METHODS

The PRISMA statement was followed (12).

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2 This project was partly carried out during an International Cancer Technology Transfer fellowship (application no. ICR/10/010/2010) funded by the Union for International Cancer Control. A part of the publication costs was funded by the Vivax foundation (Netherlands).

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4 Abbreviations used: AA, arachidonic acid; ARDS, acute respiratory distress syndrome; FA, fatty acid; ICU, intensive care unit; LBM, lean body mass; MeSH, medical subject headings; ONS, oral nutritional supplement; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RBC, red blood cell; RCT, randomized controlled trial; WBC, white blood cell.

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Eligibility criteria

Types of studies

To address the primary research objective to study the supplementation of enteral and parenteral n−3 FA supplementation, we included only RCTs. RCTs were either double blinded, single blinded, or nonblinded, performed in a hospital or community setting, and studied the supplementation of oral or enteral and parenteral n−3 FA supplementation. For the secondary research objective on the incorporation and washout of n−3 FAs, we included controlled and noncontrolled studies.

Types of participants

Types of participants included adult human subjects with any type of cancer who received chemotherapy and/or radiotherapy or palliative care; subjects who underwent elective surgery (abdominal, head and neck, or gastrointestinal), and subjects who received critical care (defined as admission to the medical ICU after a diagnosis of systemic inflammatory response syndrome, sepsis, ARDS, acute lung injury, or surgery).

Types of intervention

For the primary research objective, we included studies that compared supplementation of n−3 FAs to a control or placebo intervention. The means of n−3 FAs were fish-oil capsules, ONSs, and enteral or parenteral nutrition. We excluded studies with dietary interventions of multiple immune-enhancing compounds (eg, arginine, glutamine, nucleotides, and n−3 FAs) or studies with concurrent use of appetite stimulants.

For the secondary research objective, we included controlled and noncontrolled studies that investigated supplementation of n−3 FAs by fish-oil capsules, ONSs, and enteral or parenteral nutrition.

Types of outcome measures

For the primary research objective, we defined the following outcome measures: nutritional status (body weight, LBM, mid-upper arm circumference, and appetite), morbidity, mortality, length of hospital stay, length of ICU stay, and quality of life. Quality-of-life variables included symptoms (eg, fatigue), physical function, and performance status, which were measured by validated self-administered questionnaires or classification methods for clinicians.

For the second research objective, we included studies that reported on the incorporation and washout of n−3 FAs in phospholipids of plasma, blood cells, and mucosal tissue.

Search methods for identification of studies

We searched the electronic databases PubMed (www.pubmed.com) and EMBASE (www.embase.com). In PubMed, we used MeSH and key words to select relevant studies (Table 1; see the Appendix under “Supplemental data” in the online issue).

In PubMed, we applied limit criteria to search for publications in humans published in English. Subsequently, we searched EMBASE for additional publications that were not retrieved by PubMed. In EMBASE, we used Emtree expansion searches, key words, the map to preferred terminology option, explosion

<table>
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<tr>
<th>Subject</th>
<th>MeSH and key words</th>
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<tbody>
<tr>
<td>Cancer</td>
<td>“Neoplasms” [MeSH terms] OR neoplasm* OR malignan* OR cancer OR carcino* OR tumor OR tumour</td>
</tr>
<tr>
<td>Enteral nutrition</td>
<td>“enteral* OR supplement* OR sip OR feed OR formula* OR liquid OR tube OR nasogastric OR nasojejunal OR nasoduodenal OR gastrostomy OR jejunostomy OR Enteral Nutrition” [MeSH]</td>
</tr>
<tr>
<td>Morbidity</td>
<td>“Postoperative Complications” [MeSH] OR complications OR complication* OR “morbidity” [MeSH] OR morbidity*</td>
</tr>
<tr>
<td>Mortality</td>
<td>“mortality” [MeSH terms] OR “hospital mortality” [MeSH terms] OR mortalit* OR death* OR survival OR “survival” [MeSH terms]</td>
</tr>
<tr>
<td>Length of stay</td>
<td>length of stay OR LOS OR “length of stay” [MeSH terms]</td>
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</table>

1 MeSH, medical subject headings.
 searches, and the study-type filter (ie, RCT). We searched for studies published from the start date of the electronic databases (1948 for PubMed and 1986 for EMBASE) until 1 April 2011.

Search terms for n−3 FAs and enteral and parenteral nutrition were combined with search terms for cancer, surgery, critical care, and the respective primary and secondary outcome variables (Table 1; see the Appendix under “Supplemental data” in the online issue).

In addition, reference lists of included publications were inspected for references that were not retrieved by the database search.

Data collection and analysis

Selection of studies

We excluded studies if the title and abstract were not relevant; to achieve consensus, researchers discussed all areas of disagreement.

Data extraction and management

Both reviewers read the selected articles. One reviewer extracted the following data from each study with the use of data-extraction forms: study design, characteristics of trial participants (number, condition, and treatment), and the type of n−3 FA supplementation or control intervention (duration, form and daily dose, and results on primary and secondary outcome measures). After extraction, a second reviewer checked the extracted data to minimize the possibility of errors. We only used data from original publications. For studies published more than once, we used the publication that reported at least one relevant outcome variable.

After extraction, a second reviewer checked the extracted data to minimize the possibility of errors. We only used data from original publications. For studies published more than once, we used the publication that reported at least one relevant outcome measure in the largest study population.

Assessment of risk bias in included studies

Two researchers independently, who were not blinded to authors or journals, assessed risk of bias in studies that met the inclusion criteria. We used the Jadad instrument (0–5-point rating scale, with 5 as the maximum score for methodologic quality) (13) and the Cochrane concealment assessment criteria for risk of bias, which included the following criteria: adequacy of randomization, sequence generation, and blinding of participants, personnel, and outcome assessors; addressing of incomplete outcome data; and allocation concealment. Each study was graded to be of poor (0 or 1 A–D), average (2 A–D), good (3 A–D), or excellent (4 or 5 A–D) quality (Table 2). For the literature study on primary outcome measures, studies with 0 points were excluded (13). Disagreements between researchers were discussed and solved by consensus.

RESULTS

Clinical outcome

Twenty-eight of 201 potential studies on effects of n−3 FA supplementation on clinical outcomes met our predefined inclusion criteria as follows: 8 RCTs in cancer patients, 13 RCTs in patients who underwent surgery, and 7 RCTs in patients who received critical care (Figure 1). Trials used fish-oil or placebo capsules (3, 14–16), ONSs (17–20), enteral nutrition (21–25), ONSs followed by enteral nutrition (26), or parenteral lipid emulsions as part of the total parenteral nutrition (27–40) (Tables 3–5).

Cancer (nonsurgical oncology)

Oral or enteral supplementation of n−3 FAs

We included the following 8 studies in cancer patients: 2 studies were performed during chemotherapy (15, 18), one study was performed during chemoradiotherapy (20), one study was performed after hospital discharge for oral or laryngeal cancer surgery (19), and 4 studies were performed in palliative-care patients (3, 14, 16, 17) (Table 3).

In one study in patients who received chemotherapy and bone marrow transplantations, the intervention consisted of fish-oil capsules (15), and in 3 studies (18–20), the intervention consisted of ONSs that contained n−3 FAs (~2 g EPA) compared with an isocaloric control supplement. In palliative-care patients, the intervention consisted of fish-oil capsules in 3 studies (3, 14, 16) and ONSs in one study (17).

Risk of bias in included studies

The quality of included studies was shown to range from poor to excellent; studies that were conducted during chemotherapy were both nonblinded and of poor (18) or average (15) quality. The one study conducted during chemoradiotherapy was of excellent quality (20). In palliative care, the quality was excellent in 2 large-scale studies (14, 17); 3 small, nonblinded studies were of average (16) and poor (3, 19) quality.

Clinical outcome

Seven studies reported on body-weight changes. One study showed a beneficial effect (20), whereas 4 studies did not show a beneficial effect (3, 16, 17, 19). A trend for a beneficial effect was observed in one study (14). Finally, one study reported

<table>
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<th>Table 2</th>
<th>Quality assessment and grading of clinical trials</th>
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<tbody>
<tr>
<td>Jadad instrument</td>
<td>Scoring points (total score: 0–5)</td>
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<tr>
<td>Was the study described as randomized?</td>
<td>Yes: +1</td>
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<tr>
<td>Was the study described as double blind?</td>
<td>Yes: +1</td>
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<tr>
<td>Was there a description of withdrawals and dropouts?</td>
<td>Yes: +1</td>
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<tr>
<td>Was the method to generate the sequence of randomization described and was it appropriate?</td>
<td>Yes: +1</td>
</tr>
<tr>
<td>Was the method of double blinding described and was it appropriate?</td>
<td>Yes: +1</td>
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<tr>
<td>Cochrane concealment assessment</td>
<td>A. Adequate</td>
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<tr>
<td>Quality grading</td>
<td>B. Uncertain</td>
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<td>0 or 1 A–D</td>
<td>C. Clearly inadequate</td>
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<tr>
<td>2 A–D</td>
<td>D. Not used</td>
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<td>3 A–D</td>
<td>Excellent</td>
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<td>4 or 5 A–D</td>
<td>Good</td>
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weight maintenance in the intervention group, whereas body weights in the control group decreased. However, this study failed to report changes compared with those with the placebo (18).

Five studies measured the effects of n-3 FA supplemented by ONSs on LBM. One small study observed a significant maintenance of LBM (20), and 2 studies showed a nonsignificant maintenance compared with that of a control intervention (14, 17); 2 studies showed no effects on LBM after supplementation of n-3 FAs during 2 (16) and 12 (19) wk.

Quality of life was an endpoint in 4 studies. In lung cancer patients, improvements of quality of life variables in the n-3 FA group were shown in time (18). In a large-scale, double-blinded RCT, patients who received n-3 FAs showed a tendency for a better maintenance of physical functioning than did control patients (14). In a post hoc analysis of the Fearon et al (14) study, weight gain was associated with an improved quality of life in the n-3 FA group (17). One trial of a 2-wk supplementation of n-3 FAs via fish-oil capsules did not find improvements in well-being, but there was a trend for a reduction of tiredness in the n-3 FA group (16).

With regard to Karnofsky Performance Status, no differences between n-3 FAs and control patients were observed in one large excellent-quality trial (14) and one small average-quality trial of 2 wk (16). One small poor-quality trial showed an increase of Karnofsky Performance Status in a subgroup of malnourished patients who received n-3 FAs (3).

Morbidity was studied in 2 trials; one study observed less graft than with host disease in patients who received n-3 FAs around bone marrow transplants (15), and a study in patients with head and neck cancer did not observe differences for complications between n-3 FAs and the control group (19).

Mortality was reported on in 5 studies: 2 small RCTs (of poor and average quality) showed beneficial effects on survival in bone marrow–transplant patients (15) and in patients with various types of cancer (3), whereas 2 high-quality RCTs (14, 17) and one small study (19) did not show such beneficial effects.

In summary, we showed some evidence for beneficial effects of oral supplementation of n-3 FAs for 5–8 wk on body weight (but not on LBM) and quality of life in cancer patients during che-mo(radio)therapy and in palliative care. Effects on Karnofsky Performance Status and survival were inconsistent.

<table>
<thead>
<tr>
<th>First author, year (reference)</th>
<th>Design</th>
<th>Condition</th>
<th>n−3 (Duration, form, and daily dose)</th>
<th>Results</th>
<th>Quality</th>
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<tr>
<td>Guarcello, 2007 (18)</td>
<td>Nonblinded, randomized, and placebo controlled</td>
<td>n = 46 lung cancer patients who underwent chemotherapy&lt;br&gt;Baseline: &gt;10% weight loss in 6 mo</td>
<td>60 d&lt;br&gt;n = 26: n−3 FA ONSs (2.2 g EPA and 1.0 g DHA; Prosure, Abbott Laboratories)&lt;br&gt;n = 20: isonitrogenous control ONSs</td>
<td>Patients in the n−3 FA group showed significant increases in body weight, energy and protein intakes, quality of life, appetite, and prealbumin.</td>
<td>1B</td>
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<td>Takatsuka, 2001 (15)</td>
<td>Nonblinded, randomized, and controlled</td>
<td>n = 16 patients who underwent chemotherapy and allogeneic BMT from unrelated donors&lt;br&gt;Baseline: no details on nutritional status</td>
<td>21 d before BMT to 180 d after BMT&lt;br&gt;n = 7: 3 capsules (1.8 g EPA)&lt;br&gt;n = 9: no capsules</td>
<td>Significantly higher survival rate in EPA group (P &lt; 0.01); EPA reduced complications (graft compared with host disease; n = 2 grade III in the EPA group; n = 3 grade III or IV) (P value not reported)</td>
<td>2D</td>
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<td>Gogos, 1998 (3)</td>
<td>Nonblinded, randomized, and placebo controlled</td>
<td>n = 60 cancer patients (breast, gastrointestinal, lung, liver, and pancreas)&lt;br&gt;Baseline: 50% malnourished (defined by weight loss &gt;10% in 6 mo, serum albumin concentration &lt;30 g/L, serum transferrin concentration &lt;2.0 g/L, and KPS &lt;60)</td>
<td>40 d&lt;br&gt;n = 30: 18 fish-oil capsules (3.1 g EPA and 2.0 g DHA)&lt;br&gt;n = 30: control (sugar) tablets</td>
<td>n−3 FAs compared with control group: increased survival, no differences for body weight, serum albumin, or serum transferrin; malnourished n−3 FA subgroup compared with other subgroups: increase in KPS</td>
<td>1B</td>
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<td>Fearon, 2006 (14)</td>
<td>Double-blinded, randomized, and placebo controlled</td>
<td>n = 198 patients with gastrointestinal cancer&lt;br&gt;n = 231 lung cancer patients&lt;br&gt;Baseline: ≥5% loss of preillness stable weight</td>
<td>8 wk&lt;br&gt;n = 175: 2 g EPA (95% diester capsules)&lt;br&gt;n = 172: 4 g EPA (95% diester) capsules&lt;br&gt;n = 171: control capsules</td>
<td>Compared with placebo: 2 g EPA: positive trend for body weight after 8 wk (weight change +1.2 kg; P = 0.66). Mean weight change in 4-g EPA group was +0.3 kg. Physical function improved by 7% in 2-g EPA group (P = 0.04) and decreased by ~5% in the 4-g EPA group. Weakness tended to decrease in the 2-g EPA group at 4 and 8 wk, whereas there was little change in the 4-g EPA group; no significant differences between groups for albumin, KPS, survival, LBM, appetite, nausea, vomiting, diarrhea</td>
<td>5A</td>
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<tr>
<td>Buera, 2003 (16)</td>
<td>Nonblinded, randomized, and placebo controlled</td>
<td>n = 60 cancer patients&lt;br&gt;Baseline: anorexia and weight loss &gt;5%</td>
<td>14 d&lt;br&gt;n = 30: 18 fish-oil capsules (3.2 g EPA and 2.2 g DHA)&lt;br&gt;n = 30: 18 control (olive oil) capsules</td>
<td>No difference between groups for body weight, appetite, tiredness, nausea, well-being, energy intake, LBM, arm circumference, and triceps skinfold thickness.</td>
<td>2D</td>
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<tr>
<td>Fearon, 2003 (17)</td>
<td>Double-blinded, randomized, and placebo controlled</td>
<td>n = 200 pancreatic cancer patients Baseline: ≥5% weight loss in 6 mo</td>
<td>8 wk n = 95: n−3 FA ONSs (2.2 g EPA and 1.0 g DHA) n = 105: isonitrogenous control ONSs</td>
<td>No correlation between fish-oil doses and changes in effect variables between days 1 and 14 Body weight and LBM stabilized in both groups; no significant differences between groups in performance scores or any of the quality-of-life measures. Increased concentrations of plasma phospholipids EPA in the control group; noncompliance in both groups. Post hoc analysis showed a significant correlation between supplement intake and body weight and LBM in the n−3 FA group; significant correlation between plasma phospholipids EPA concentrations and LBM and body weight in the n−3 FA group. Weight gain was associated with improved quality of life in the n−3 FA group.</td>
<td>5A</td>
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<td>De Luis, 2008 (19)</td>
<td>Nonblinded, randomized, and placebo controlled</td>
<td>n = 65 patients with oral and laryngeal cancer Baseline: recent weight loss</td>
<td>12 wk postoperative (starting at hospital discharge) n = 31: ONSs with a high ratio (3.7) of n−3:n−6 FAs (2.0 g EPA and 0.9 g DHA) n = 34: control ONSs with a low ratio (0.99) of n−3:n−6 FAs (1.8 g EPA and 1.2 g DHA)</td>
<td>No differences in plasma proteins, anthropometric variables (weight, LBM, fat mass, triceps skinfold thickness, and arm circumference), postoperative infectious complications, or wound complications.</td>
<td>1C</td>
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<td>van der Meij, 2010 (20)</td>
<td>Double-blinded, randomized, and placebo controlled</td>
<td>n = 40 patients with lung cancer who underwent chemoradiotherapy Baseline: 20% malnourished</td>
<td>5 wk n = 20: n−3 FA ONSs (2.02 g EPA and 0.92 g DHA; Prosure) n = 20: isocaloric control ONSs (Ensure; Abbott Laboratories)</td>
<td>Differences compared with controls: after 4 wk, the n−3 FA group showed higher energy and protein intakes [2456 kJ (P = 0.03) and 25.0 g (P = 0.01), respectively]. The n−3 FA group had better weight maintenance after 1, 2, and 4 wk [1.1 kg (P = 0.07), 1.3 kg (P = 0.02), and 1.7 kg (P = 0.04), respectively] and less decrease in LBM [1.5 kg (P = 0.05) and 1.9 kg (P = 0.02)] after 3 and 5 wk, respectively. REE in n−3 FAs decreased by 16.7% of predicted (P = 0.01) compared with that in controls after 3 wk.</td>
<td>5A</td>
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1 BMT, bone marrow transplantation; FA, fatty acid; KPS, Karnofsky Performance Status; LBM, lean body mass; ONSs, oral nutritional supplements; REE, resting energy expenditure.
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<tr>
<td><strong>Enteral</strong> Surgical oncology</td>
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| Kenler, 1996 (24)             | Double-blinded, randomized, and placebo controlled | n = 50 patients with upper-gastrointestinal cancer | 7 days postoperative 
  n = 17: n−3 FA enteral nutrition (4.0 g EPA and 1.9 g DHA) 
  n = 18: isocaloric, isonitrogenous control enteral nutrition (Osmolite HN; Abbott Laboratories) | No differences between groups for number of infections, LoS, mortality, and nitrogen balance; fewer gastrointestinal complications in the n−3 FA group (P = 0.053); 50% reduction in the total number of infections in the n−3 FA group (P = 0.037); lower number of infected patients with more than one infection in the n−3 FA group (P = 0.09). | 2B |
| Swails, 1997 (25)             | Double-blinded, randomized, and placebo controlled | n = 20 patients with upper-gastrointestinal cancer | 7 days postoperative 
  n = 8: n−3 FA enteral nutrition (2.8 g EPA and 1.4 g DHA) 
  n = 10: isocaloric, isonitrogenous control enteral nutrition (Osmolite HN) | No differences between groups for number of infections (n−3 FA group: 6; control: 5; P > 0.05) or nitrogen balance; n−3 FA group: trend for fewer infections per infected patient (n−3 FA group: n = 1; control: n = 2; exact P values not reported). | 2B |
| Ryan, 2009 (26)              | Double-blinded, randomized, and placebo controlled | n = 53 cancer patients who underwent an esophagectomy 
  Baseline prevalence of malnutrition: ±63% | 5 days preoperative (ONSs) to 21 days postoperative (enteral nutrition) 
  n = 28: n−3 FA enteral nutrition (2.3 g EPA and 1.0 g DHA; ProSure, Abbott Laboratories) 
  n = 25: isocaloric, isonitrogenous control enteral nutrition (Ensure Plus; Abbott Laboratories) | n−3 FA group: lower number of patients with 5% weight loss at 1 month postoperative (n−3 FAs: n = 2; control: n = 10; P = 0.03); maintenance of LBM (perioperative LBM difference, n−3 FAs: 0.3 kg, P = 0.8; control: 1.9 kg, P = 0.03); no differences in incidence of major complications (n−3 FAs: n = 19; control: n = 24) or SIRS (n−3 FAs: 4%; control: 22%; P = 0.34). | 5A |
| **Parenteral** Surgical oncology |        |           |                                     |         |         |
| Heller, 2004 (28)            | Double-blinded, randomized, and placebo controlled | n = 44 gastrointestinal or pancreas cancer patients who underwent surgery | 5 days postoperative 
  n = 24: soya bean oil and fish oil (0.2 g/kg body weight) 
  Described as in the methods of Liang, 2008 (29); n−3:n−6 FA ratio of 1:4 (eg, body weight of 70 kg, 2.8 g EPA, and 3.2 g DHA) 
  n = 20: soya bean oil | No weight loss in fish-oil group (mean ± SD: fish oil, 0.0 ± 2.9 kg; soya bean oil, −1.1 ± 2.2 kg; NS); patients with increased risk of sepsis: tendency to shorter ICU stay, Complications and mortality: NS | 5A |
| Liang, 2008 (29)             | Double-blinded, randomized, and placebo controlled | n = 42 colorectal cancer patients who underwent surgery | 7 days postoperative 
  n = 21: n−3 lipid emulsion (0.2 g/kg body weight) and soya bean oil emulsion (1.0 g/kg body weight) 
  n−3:n−6 FA ratio of 1:3 (eg, body weight of 70 kg, 2.8 g EPA, and 3.2 g DHA) 
  n = 21: soya bean oil emulsion (1.2 g/kg body weight) | n−3 group: tendency to shorter postoperative hospital stay (mean ± SD: 17.45 ± 4.80 compared with 19.62 ± 5.59 d; P = 0.19) Complications and mortality: NS | 5A |

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<tr>
<td>Jiang, 2010 (39)</td>
<td>Randomized, double-blinded, and placebo controlled</td>
<td>206 gastrointestinal or colonic cancer surgery patients</td>
<td>7 d postoperative n = 100: soybean-oil plus n-3 FA emulsion (1.0 and 0.2 g/kg body weight, respectively) n = 103: soybean-oil emulsion (1.2 g/kg body weight)</td>
<td>Fewer infectious complications (4 compared with 12 on day 8; ( P = 0.066 )) and SIRS (4 compared with 13; ( P = 0.039 )). Hospital stay was significantly shorter (mean ± SD: 15 ± 5 compared with 17 ± 8 d; ( P = 0.041 )) in the n-3 FA group. Total postoperative medical costs were comparable in the 2 groups (mean ± SD: 1269 ± 254 and 1302 ± 324 US$ in n-3 FA and control groups, respectively; ( P = 0.424 )).</td>
<td>4B</td>
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<td>Wachtler, 1997 (30)</td>
<td>Double-blinded, randomized, and placebo controlled</td>
<td>40 patients with cancer who underwent major intestinal surgery</td>
<td>5 d postoperatively n = 19: 20% n-3 FA lipid emulsion (LipoPlus; B Braun) n = 21: 20% isocaloric MCT and LCT lipid emulsion</td>
<td>Intervention group compared with control group: no clinically significant changes in postoperative infections, Acute Physiology and Chronic Health Evaluation II scores, and LoS in the hospital or ICU.</td>
<td>3A</td>
</tr>
<tr>
<td>Badia-Tahull, 2010 (38)</td>
<td>Randomized, double-blinded, and placebo controlled</td>
<td>27 patients with high-risk elective major gastrointestinal surgery that required TPN</td>
<td>5 d n = 13: olive oil emulsion, partially replaced with FO (16.6%, w/w) n = 14: olive oil emulsion</td>
<td>Significantly lower incidence of infections in the n-3 FA group (23.1% compared with 78.6%; ( P = 0.007 )). No differences in mortality, sepsis, LoS in hospital, prealbumin, and safety variables.</td>
<td>2B</td>
</tr>
<tr>
<td>Grimm, 2006 (27)</td>
<td>Double blinded, randomized, and placebo controlled</td>
<td>33 patients with major abdominal surgery</td>
<td>5 d postoperative n = 19: 20% n-3 FA lipid emulsion (SMOFlipid; Fresenius Kabi) (4.7 g EPA/L and 5.3 g DHA/L) n = 14: control soybean-oil emulsion (Lipovenoes 20%; Fresenius Kabi)</td>
<td>n-3 FAs compared with soybean oil on day 6: shorter LoS (mean ± SD: 13.4 ± 2.0 compared with 20.4 ± 10.0 d; ( P &lt; 0.05 )).</td>
<td>1B</td>
</tr>
<tr>
<td>Mertes, 2006 (31)</td>
<td>Double-blinded, randomized, and placebo controlled</td>
<td>199 elective abdominal surgeries</td>
<td>5 d postoperative n = 99: 20% n-3 FA lipid emulsion (SMOFlipid) n = 100: control lipid emulsion (Lipovenoes; Fresenius Kabi)</td>
<td>No difference in mortality, tolerance, or safety. Tendency for shorter LoS in per protocol patients in the n-3 FA group (n-3 FAs: 15.7 ± 6.3d; control: 17.8 ± 13.2 d; ( P ) values not reported).</td>
<td>4A</td>
</tr>
<tr>
<td>Wichmann, 2007 (32)</td>
<td>Double-blinded, randomized, and placebo controlled</td>
<td>256 elective abdominal surgeries</td>
<td>5 d postoperative n = 127: 10% fish oil, 50% MCTs, and 40% LCTs (LipoPlus) n = 129: 100% LCT lipid emulsion (Intralipid; Fresenius Kabi)</td>
<td>Significantly shorter LoS in hospital (n-3 FAs: 17.2 d; control: 21.9 d; ( P = 0.0061 )) in fish-oil group; no differences for routine laboratory variables. No significant differences for complications, LoS in ICU, or mortality.</td>
<td>3A</td>
</tr>
</tbody>
</table>
Parenteral supplementation of \(n^-3\) FAs

We showed no RCTs that investigated the effects of parenteral supplementation of \(n^-3\) FAs in nonsurgical oncology.

Surgery: surgical oncology

Oral or enteral supplementation of \(n^-3\) FAs

We identified 3 studies that applied enteral supplementation of \(n^-3\) FAs in surgical oncology in patients with gastrointestinal (24, 25) and esophageal cancer (26) (Table 4). Studies applied ONSs (26) and/or enteral nutrition (24–26).

Risk of bias in included studies

In a quality appraisal, we showed 2 trials to be of average (24, 25) methodologic quality because of a lack of details on randomization (24) and blinding (24) procedures or details on withdrawals and dropouts (24, 25). Only the study in esophageal cancer patients was shown to be of excellent methodologic quality (26).

Clinical outcome

One study reported on perioperative body weight and LBM changes in esophageal cancer patients and showed a postoperative maintenance of body weight and LBM, whereas this effect decreased in the control group (26).

Three studies measured morbidity in terms of postoperative complications; the number of complications between \(n^-3\) FAs and control groups after 7 d of postoperative enteral nutrition (25).

In summary, there was no evidence for beneficial effects of postoperative enteral supplementation of \(n^-3\) FAs on nutritional status, length of stay, infectious complications, and mortality in surgical oncology.

Parenteral supplementation of \(n^-3\) FAs

In 5 studies that involved patients with pancreas or colorectal cancer, \(n^-3\) FAs were parenterally supplemented during 5–7 d postoperatively (28–30, 38, 39) (Table 4).

Risk of bias in included studies

Three studies were rated of excellent quality (28, 29, 39). In the good-quality study, blinding was not described and probably not carried out (30). In the average-quality study, concealment was unsure because of the use of a randomization table with odd and even numbers (38).
<table>
<thead>
<tr>
<th>First author, year (reference)</th>
<th>Design</th>
<th>Condition</th>
<th>n−3 (Duration, form, and daily dose)</th>
<th>Results</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Enteral</strong></td>
<td></td>
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</tr>
</tbody>
</table>
| Pontes-Arruda, 2006 (21)      | Randomized, double-blinded, and placebo controlled | n = 165 patients with severe sepsis or septic shock who required mechanical ventilation | 28 d  
 n = 55: n−3 FA enteral nutrition  
 (4.9 g EPA, 2.2 g DHA, 4.6 g GLA, and antioxidant vitamins)  
 n = 48: isonitrogenous, isocaloric control enteral nutrition | Intervention compared with control: significant reduction in mortality rate (19.4%; 95% CI: 0.3%, 36.7%; P = 0.037); significant improvements in oxygenation status, more ventilator-free days and ICU-free days, and less development of new organ dysfunctions. | 2B      |
| Singer, 2006 (22)             | Randomized, nonblinded, and placebo controlled | n = 95 patients with acute lung injury | 14 d  
 n = 46: n−3 FA enteral nutrition  
 (5.4 g EPA, 2.5 g DHA, 5.1 g GLA, and antioxidant vitamins; Oxepa; Ross Laboratories)  
 n = 49: isonitrogenous, isocaloric control enteral nutrition | No significant differences in body weight at days 1 and 7; significant shorter length of ventilation (P < 0.04); no difference in survival. | 3D      |
| Gadek, 1999 (23)              | Randomized, double-blinded, and placebo controlled | n = 146 ARDS caused by sepsis or pneumonia, trauma, or aspiration injury | ≥4–7 d  
 n = 51: n−3 FA enteral nutrition (6.9 g EPA, 2.9 g DHA, and 5.8 GLA)  
 n = 47: isonitrogenous, isocaloric control enteral nutrition | Intervention compared with control: significant improvements in oxygenation; fewer days of ventilatory support (11 compared with 16.3 d; P = 0.011); decreased LoS in ICU (12.8 compared with 17.5 d; P = 0.016); fewer patients with new organ failure (8% compared with 28%; P = 0.015). | 3B      |
| Parenteral                   |        |           |                                     |         |         |
| Sabater, 2008 (34)            | Double-blinded, randomized, and placebo controlled | n = 16 patients with ARDS and intolerance to enteral nutrition | 12 h  
 n = 8: Lipophus 20% (B Braun)  
 (50% MCTs, 40% LCTs, and 10% n−3 FAs)  
 n = 8: Intralipid (Fresenius Kabi)  
 (100% LCTs)  
 Dose: 1.44 g fat/kg body weight | Significantly lower pulmonary capillary pressure in the n−3 group. No differences between groups for hemodynamics, gas-exchange variables, adverse events, or survival. | 2B      |
| Friesecke, 2008 (35)          | Double-blinded, randomized, and placebo controlled | n = 166 patients admitted to medical ICU | 7 d  
 n = 83: 10% n−3 FA lipid emulsion  
 (Omegaven; Fresenius Kabi)  
 TPN n−3:n−6 ratio of 1:2  
 n = 82: 20% MCT and LCT lipid emulsion (Lipofundin; B Braun)  
 TPN n−3:n−6 ratio of 1:7  
 Daily dose: minimum of 0.5 g fat/kg body weight | No differences between groups for nosocomial infections, duration of mechanical ventilation, LoS in ICU, 28-d mortality, and organ failures. | 4A      |

(Continued)
### TABLE 5 (Continued)

<table>
<thead>
<tr>
<th>First author, year (reference)</th>
<th>Design</th>
<th>Condition</th>
<th>n = 3 (Duration, form, and daily dose)</th>
<th>Results</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berger, 2008 (40)</td>
<td>Double-blinded, randomized, and placebo controlled</td>
<td>n = 24 patients admitted to the surgical ICU after abdominal aorta aneurysm surgery</td>
<td>4 d</td>
<td>Temperature increased in both groups, with a trend to lower values in the n–3 FA group (P = 0.09). Non-significant shorter ICU stay (P = 0.22) and hospital stay (P = 0.19) in the n–3 FA group. REE increased in both groups (NS).</td>
<td>2B</td>
</tr>
<tr>
<td>Barbosa, 2010 (37)</td>
<td>Randomized, single-blinded, and placebo controlled</td>
<td>n = 25 patients with sepsis</td>
<td>6 d</td>
<td>Ratio of P0\textsubscript{2}:FiO\textsubscript{2} was significantly higher in the fish-oil group (P = 0.047). The n–3 FA group tended to have a shorter LoS (mean ± SD: 22 ± 7 compared with 55 ± 16 d; P = 0.079). No differences in days on ventilation, LoS in ICU, and mortality between groups.</td>
<td>2A</td>
</tr>
</tbody>
</table>

1AA, arachidonic acid; ARDS, acute respiratory distress syndrome; FA, fatty acid; GLA, γ-linolenic acid; ICU, intensive care unit; LCT, long-chain triglyceride; LoS, length of stay; MCT, medium-chain triglyceride; REE, resting energy expenditure; TPN, total parenteral nutrition.
Oral or enteral supplementation of n–3 FAs

Critical care

Oral or enteral supplementation of n–3 FAs

Reviewed publications in critical care included 3 studies on enteral supplementation of n–3 FAs, one study in patients with sepsis (21), and 2 studies in patients with Acute Lung Injury (22) or ARDS (23) (Table 5). All studies applied enteral nutrition.

Risk of bias in included studies

Large groups of patients were included, and the methodologic quality was judged average (21) or good (22, 23). One trial did not describe blinding and randomization procedures (21), one study was nonblinded (22), and one study did not describe a blinding procedure (23).

Clinical outcome

One study in acute lung injury described body-weight development over 7 d of intervention; no differences between n–3 FAs and control groups were observed (22). Two studies assessed new organ failures, and showed a lower incidence in n–3 FA groups with sepsis (21) or ARDS (23).

Significant improvements in oxygenation were shown in patients who received enteral nutrition that contained n–3 FAs in patients with acute lung injury (22), ARDS (23), and severe sepsis (21) after 4–7 d (23), 14 d (22), and 4 wk (21) of supplementation, respectively. One study in patients with acute lung injury showed a better respiratory function and lower requirements for mechanical ventilation in the group that received enteral nutrition that contained n–3 FAs (22).

Ventilator-free days increased in patients with sepsis, acute lung injury, and ARDS who received enteral nutrition that contained n–3 FAs (21–23). Two of these studies reported on ICU stay, which was decreased in n–3 FA groups (21, 23). The length of hospital stay was not different between n–3 FA or control groups after 4–7 d of supplementation (22).

Mortality decreased in the n–3 FA group in the study in sepsis patients (21), but in one study in ARDS patients there was no between-group difference for mortality (22).

In summary, enteral nutrition that contained n–3 FAs in critical care, especially in patients with sepsis, acute lung injury, or ARDS, resulted in a reduction of the length of ICU stay, mechanical ventilation, and, in sepsis patients, a reduced mortality rate.

Parenteral supplementation of n–3 FAs

Four studies on parenteral supplementation of n–3 FAs (during 12 h to 7 d) in patients who received critical care were reviewed in patients with sepsis (37), ARDS (34), ICU patients (35), and patients admitted to the ICU after abdominal aorta aneurysm surgery (40) (Table 5).

Risk of bias in included studies

One study was rated of excellent quality (35), and 3 studies were rated of average quality (34, 37, 40). Of the 3 studies of average quality, 2 studies did not describe blinding and randomization procedures (34, 40), and one study was single blinded (37). Two studies did not describe details on withdrawals and dropouts (34, 37).

Clinical outcome

None of the studies reported on nutritional status variables. One excellent study in patients admitted to the medical ICU did not observe any differences between groups after 7 d of parenteral nutrition (n–3 FAs or control) for the infection rate or organ failures (35). In one study in ICU patients who underwent abdominal aorta aneurysm surgery, body temperatures in the n–3 FA group tended to be lower than in the control group (40).

Other variables included gas variables and the duration of ventilation. One of the 2 studies showed improvements in gas-exchange variables in sepsis patients (37); in a small 12-h intervention study in ARDS patients, there were no differences in gas-exchange variables between n–3 FA and control groups (34). Two studies reported on the duration of mechanical ventilation and did not find any differences between n–3 FA and control groups (35, 37).

The length of hospital stay was not significantly different between n–3 FA and control groups in ICU patients (35). In 2 studies, one study in patients admitted to the ICU after abdominal aorta aneurysm surgery (40) and one study in sepsis patients (37), the length of hospital stay tended to be shorter. Hospital mortality was measured in 3 studies, none of which observed significant differences between n–3 FA and control groups (35, 37).

In summary, there was insufficient evidence for effects of parenteral supplementation of n–3 FAs on the clinical outcome in critical care.

Incorporation and washout of n–3 FAs after supplementation

The second aim of this review was to investigate the dose-dependent incorporation of n–3 FAs into phospholipids of plasma, blood cells, and mucosal tissue and the subsequent washout after n–3 FA supplementation (Figure 2). In total, we...
retrieved 23 RCTs and 13 open-label studies that reported incorporation or washout in cancer, surgery, and critical care after supplementation of n–3 FAs via fish-oil capsules (7, 41–59), ONSs (4, 17, 20, 26, 60), and/or enteral nutrition (23, 24, 26), or n–3 FA lipid emulsions for parenteral administration (27, 32, 33, 37, 40, 61–64) (see Supplemental Tables 1–3 under “Supplemental data” in the online issue). The following paragraphs summarize the most important findings.

Cancer

The findings of 23 clinical studies that investigated the incorporation of n–3 FAs in different tissues after supplementation by fish-oil capsules or ONSs are summarized in Supplemental Table 1 under “Supplemental data” in the online issue. The studies were performed in patients with cancer or in subjects with a high risk or history of cancer. We included 10 RCTs (17, 20, 41–44, 55, 57–59) and 13 open-label prospective studies (4, 7, 45–49, 51–55, 60). The doses of supplementation ranged from 0.47 to 9 g EPA/d and from 0.24 to 3.6 g DHA/d. The duration of supplementation ranged from 14 d to 2 y.

Oral or enteral supplementation of n–3 FAs

In general, oral or enteral supplementation of 1.5–3 g EPA (either combined with DHA or not) increased the average concentration of EPA in plasma phospholipids from ≤2.0% to 2.5–6.5% of total FAs, which was a 2.5–10-fold increase in the plasma EPA concentration (4, 7, 17, 20, 23, 24, 26, 44, 45, 47, 48, 50–55, 57, 60), and decreased the concentration of the n–6 FA AA (24, 57). The concentration of DHA in phospholipids increased in most studies after supplementation of EPA and DHA (4, 20, 44, 45, 47, 48, 50, 51, 54, 55, 60). Two studies reported unchanged plasma phospholipids concentrations of DHA after supplementation of EPA and DHA (24, 57).

Studies showed variable increases of plasma n–3 FAs after supplementation of 0.5–6.9 g EPA and 0.2–3.6 g DHA during variable periods as follows: short-term [4 d (23), 7 d (23, 24), and 2 wk (55, 65), respectively] and long-term [2–6 mo (42, 44, 45,
supplementation of n-3 FAs. In a few dose-escalation studies, a plateau of the maximal incorporation into plasma phospholipids was reached at doses \( \geq 2 \) g EPA: 2.1 g EPA (46) and 2.8–4.2 g EPA (41) did not further increase plasma EPA concentrations after 15 d and 6 mo, respectively.

With regard to membrane phospholipids of blood cells, one study showed the incorporation of EPA, DPA, and DHA in RBCs after supplementation of 1.2 g EPA + 0.9 g DHA during 2 mo (46) but not in WBCs. A second study showed the incorporation of EPA and DHA and a decrease of AA in RBCs (41). One study did not find an increase of the EPA concentration of neutrophils after 2 wk of supplementation of 3.2 g EPA + 2.2 g DHA (55).

In addition, oral supplementation of EPA (1.4–4 g) during \( \geq 1 \) mo, either combined with DHA or not, resulted in increased concentrations of EPA in colorectal mucosa (42, 58, 59). One of these studies observed a dose-dependent increase in EPA and DHA in rectal mucosa and a decrease in mucosal AA in groups that received 1.4, 2.7, or 4.1 g EPA combined with 1.1, 2.4 or 3.6 g DHA, respectively (59). None of the studies described a washout of n-3 FAs from plasma, blood cells, or mucosal tissue. In summary, there is a large body of evidence that showed increases of EPA and DHA concentrations in plasma phospholipids and colorectal mucosa after supplementation of EPA and DHA, which demonstrating incorporation to occur after short- and long-term oral or enteral supplementation in patients with cancer. Supplementation of 3 g EPA/d seemed to suffice to reach maximal incorporation. Too few studies have been performed to conclude on incorporation in other blood compartments (eg, RBCs and WBCs). Moreover, the duration of washout of n-3 FAs from plasma and cell membranes in patients with cancer is unknown to our knowledge.

Parenteral supplementation of n-3 FAs

We retrieved no studies that investigated incorporation or washout after parenteral supplementation in cancer patients.

Surgery

Eight RCTs reported on the incorporation and washout in patients who underwent surgery after enteral supplementation (24, 26, 56) or parenteral supplementation of n-3 FAs (27, 32, 33, 61, 62) (see Supplemental Table 2 under “Supplemental data” in the online issue).

Oral or enteral supplementation of n-3 FAs

Perioperative enteral supplementation of n-3 FAs was applied in 3 studies; the methodologic quality was rated to be excellent (26), good (56), and average (24). One study applied fish-oil capsules (56), and the other studies used ONSs and/or enteral nutrition that contained n-3 FAs (24, 26).

Two studies showed a significant increase in the concentration of plasma or serum EPA (24, 26). Seven days of postoperative supplementation of 4.0 g EPA and 1.9 g DHA in gastrointestinal cancer surgery resulted in increased plasma phospholipid EPA concentrations (0.6–11.3%); DHA concentrations did not significantly change (24). An excellent-quality study in esophageal cancer surgery applied 7-d preoperative ONSs and 3-wk postoperative enteral nutrition (2.3 g EPA and 0.95 g DHA) and showed the incorporation of EPA in serum (1.2–3.2%) (26). These studies also observed an increase of EPA concentrations in RBCs (24) and peripheral blood mononuclear cells (26). One study observed an increase of EPA, but not of DHA, in colonic mucosa after 7–21 d of preoperative supplementation of 1.4 g EPA and 1.0 g DHA with fish-oil capsules (56).

In summary, perioperative enteral supplementation of n-3 FAs only increased EPA, but not DHA, concentrations of plasma phospholipids and colonic mucosa. The washout after perioperative enteral supplementation of n-3 FAs is unknown.

Parenteral supplementation of n-3 FAs

A short-term (5–7 d) parenteral supplementation of n-3 FAs in surgery was applied in 5 studies; 2 studies of which were of poor and average quality in cancer surgery (61, 62) and 3 studies of which were of poor, good, and excellent quality in general surgery (27, 32, 33). Most studies only described the type of lipid emulsion and the daily dose of fat administered during the study and not the exact dose of EPA and DHA.

One study in gastrointestinal cancer surgery showed increases of plasma EPA, not DHA, after 5 d postoperative parenteral supplementation of n-3 FAs (61). Blood samples after 1 d of infusion did not show increases of plasma EPA and DHA (27).

In general surgery, plasma EPA and DHA increased after 5 d of supplementation (27, 33), whereas at the same time, plasma AA decreased in one of the studies (27); the other study did not find a decrease of AA (33). In the latter study, FA concentrations of RBCs were also measured; EPA increased, but there were no significant changes in DHA and AA concentrations in RBCs (33). A study in esophageal surgery also measured the incorporation in platelet FAs; after 7 d of supplementation, a peak in EPA was reached at day 8. For DHA, no significant changes in platelets were observed (62).

Two studies reported on the washout after cessation of supplementation. In patients who underwent an esophagectomy, the washout of EPA and DHA from platelet phospholipids was >7 d (62). In patients with colorectal surgery, the washout of EPA and DHA from plasma free FAs was >5 d (33).

In summary, the short-term (5–7 d) postoperative parenteral supplementation of n-3 FAs increased EPA in plasma and cell membranes (platelets and RBCs) and also, in some studies, plasma DHA. The washout from plasma and platelets after postoperative parenteral supplementation of n-3 FAs appeared to be >5–7 d.

Critical care

Five RCTs on incorporation of n-3 FAs in critical care were retrieved, of which 4 RCTs on parenteral supplementation of n-3 FAs (37, 40, 63, 64) (see Supplemental Table 3 under “Supplemental data” in the online issue).

Oral or enteral supplementation of n-3 FAs

One good-quality study investigated plasma incorporation after 4–7 d of enteral nutrition (7 g EPA and 3 g DHA) in patients with ARDS; EPA was incorporated after 4 d and further increased after 7 d (23).

In summary, enteral supplementation of n-3 FAs in critical care resulted in the incorporation of EPA in plasma phospholipids
and sometimes of DHA. After 4–7 d of supplementation, incorporation was observed. The washout after enteral supplementation of n-3 FAs in critical care is unknown.

**Parenteral supplementation of n-3 FAs**

A short-term (4–10 d) parenteral supplementation of n-3 FAs was applied in patients with sepsis (37, 63, 64) and patients after aorta aneurysm surgery (40). The methodologic quality was average (37, 63, 64) and poor (40). Doses of n-3 FA supplementation were ~7 g EPA + 6 g DHA (63, 64), 6 g EPA + DHA (40) and 2.3 g EPA + DHA (37).

All studies investigated plasma incorporation; 4 studies showed an increase in the concentrations of plasma EPA (37, 40, 63, 64), and 3 studies showed an increase in plasma DHA (37, 63, 64).

Two studies, one study in patients with sepsis (63) and one study after abdominal aorta aneurysm surgery (40), showed an increase of EPA and DHA in plasma-free FAs and phospholipids, respectively, after 1 d of infusion, which reached a peak concentration of EPA after 3 d. For AA, no significant changes in plasma free FAs were observed in the study in sepsis patients (63). Another study in sepsis patients observed increases of EPA and DHA in mononuclear leukocyte membranes; EPA already increased after 1 d. Concentrations of AA did not significantly change (64).

After the cessation of infusion, the washout of EPA and DHA from plasma and mononuclear leukocyte membranes occurred within 5 d (63).

In summary, parenteral supplementation of n-3 FAs in critical care resulted in the incorporation of EPA in plasma phospholipids, and sometimes of DHA, after 1–3 d of supplementation. The washout in patients who received critical care occurred in ≤5 d.

**DISCUSSION**

The use of n-3 FA supplementations in clinical practice is still a subject of debate. What is the preferred supplementation method (oral or enteral compared with parenteral), which patients should be supplemented, when, and for how long?

The current systematic literature review included 28 RCTs that evaluated the clinical effects of n-3 FAs in patients with cancer who underwent surgery or received critical care. The following conclusions and recommendations were elaborated from the results of this literature review.

**Nonsurgical oncology**

Earlier reviews have stated that evidence for the recommendation of n-3 FAs for their beneficial effects in cancer patients with weight loss and cachexia was too weak (9, 66). The current review, which included 4 new studies that were not discussed in the earlier reviews, showed that 6–8 wk of supplementation of n-3 FAs by capsules or ONSs may have had beneficial effects on body weight and the quality of life in cancer patients who received chemo(radio)therapy or palliative care.

Because of the absence of RCTs on parenteral supplementation of n-3 FAs in nonsurgical oncology, no recommendation on this subject can be made. Studies in patients who regularly receive parenteral nutrition, in particular, in patients with hematologic malignancies, would be useful.

**Surgery**

There is no evidence for any beneficial effects for enteral supplementation of n-3 FAs on nutritional status, postoperative complications, or mortality for surgery patients. Five to 7 d of perioperative parenteral supplementation of n-3 FAs might have reduced the length of postoperative hospital or ICU stays but did not improve other clinical variables. The effect on the length of hospital stay was confirmed by a recent meta-analysis, which also showed fewer infectious complications in patients who received perioperative parenteral n-3 FA supplementation (67). Therefore, supplementation of n-3 FAs may be considered in patients who receive perioperative parenteral nutrition.

**Critical care**

There are convincing results of the beneficial effects of enteral supplementation of n-3 FAs on the morbidity and mortality in critical care patients, especially in patients with sepsis, ARDS, or acute lung injury. Benefits were observed after 4–7 d and 2 and 4 wk. These results were in line with those in earlier meta-analyses (68). Therefore, we recommend enteral nutrition that contains n-3 FAs for ≥4 d for patients with sepsis, ARDS, or acute lung injury.

Studies on the parenteral supplementation of n-3 FAs in critical care did not consistently show any beneficial effects on the clinical outcome. Before applying parenteral n-3 FAs in critical care, more research that shows clinical benefits would be required.

**Incorporation and washout**

A second aim of this review was to provide an overview of the incorporation into phospholipids of plasma, blood cells, and mucosal tissue and the subsequent washout after n-3 FA supplementation.

The studies included 23 RCTs and 13 open-labeled trials in cancer, surgery, and critical care and showed that the supplementation of n-3 FAs by oral or enteral or parenteral nutrition resulted in the incorporation of EPA, and sometimes of DHA, in plasma, serum, blood cells, and mucosal tissues. The incorporation after enteral supplementation of n-3 FAs occurred after 4–7 d. In a few studies that measured the incorporation on the first days after parenteral supplementation of n-3 FAs, concentrations increased within 1–3 d. Studies administered variable doses of EPA and DHA and measured the FA composition of various tissues. Because of the heterogeneity of study designs, it was hard to draw conclusions for a dose-effect relation of n-3 FA incorporation in plasma, blood cells, and mucosal tissue. In general, any dose between 0.5 and 4 g of EPA was expected to result in incorporation in a dose- and time-dependent manner.

The washout from plasma and blood cells after the cessation of supplementation has been studied only after the short-term parenteral administration of n-3 FAs. It should be noted that the washout might involve complex pathways. After long-term supplementation, n-3 FAs accumulate in adipose tissue and, after reaching a new steady state, there may be a prolonged washout period because of the release of n-3 FAs during subsequent postabsorptive periods (69). This pathway was not unraveled by the current review.
To our knowledge, the duration of the washout of $n$–3 FAs from plasma and cell membranes in patients with cancer is unknown, but in surgical oncology, the washout from plasma and platelets after postoperative parenteral supplementation appeared to be $\geq 5$–7 d. The washout of $n$–3 FAs from plasma and cell membranes of platelets and leukocytes after parenteral supplementation of $n$–3 FAs appeared to be somewhat longer after surgery ($> 5$ d) than in patients with sepsis ($< 5$ d), which we could not explain after having reviewed the underlying literature. Rapid washout might be related to the disease severity.

**Strengths and limitations of the review**

The strength of our review was the systematic inclusion of RCTs for the evaluation of clinical evidence by following the PRISMA statement, added by studies on the incorporation and washout of FAs.

This review had a number of potential limitations. At first, we focused on only one type of nutritional formula; we selected studies that investigated only the supplementation of $n$–3 FAs, thereby excluding studies on immune-modulating formulas. Immune-modulating formulas contain a mix of immune-modulating nutrients, such as glutamine, arginine, ribonucleic acids, and $n$–3 FAs. Meta-analyses have shown positive effects of immune-modulating formulas on the postoperative infection rate and length of hospital stay in patients who undergo gastrointestinal surgery (70). A combination of immune-modulating nutrients is probably more effective than the exclusive supplementation of $n$–3 FAs. In patients with critical illnesses, $n$–3 FAs alone proved to have beneficial effects above arginine and glutamine (71).

This review restricted itself to $n$–3 FA supplementation in patients with cancer (who received no treatment, any cancer treatment, or palliative care) around surgery or in patients who underwent critical care at the ICU (eg, because of sepsis, ARDS, or post-surgery). No conclusions can be drawn from this literature study on the effects of $n$–3 FAs in patients with, eg, inflammatory bowel diseases or HIV. We were particularly interested in differences between oral or enteral and parenteral supplementation of $n$–3 FAs. Unfortunately, no studies that compared these areas were shown.

For the successful application of $n$–3 FA supplementation, it is important to evaluate the safety and feasibility of parenteral and enteral supplementation. Only a few well-designed studies reported possible adverse effects. The supplementation of $n$–3 FAs (with doses of $\approx 2$ g EPA/d or $\leq 0.2$ g $n$–3 FAs/kg body weight) appeared to be safe in the patient populations of our interest (3, 14, 16–18, 20, 26). Oral or enteral supplementation of $n$–3 FAs may cause diarrhea or a fishy taste.

**Implications for practice**

This systematic review provided a summary and update of the evidence for effects of supplementation of $n$–3 FAs in patients with cancer around surgery and in critical care. Although studies were heterogeneous with regard to the $n$–3 FA dose, supplementation method, endpoints, and quality, we believe there is enough evidence to advise the oral or enteral supplementation of $n$–3 FA supplementation in cancer patients with a high risk of weight loss and in critical care patients (provided that the digestive tract is functioning and platelet and coagulation function are adequate). Parenteral supplementation might be considered around surgery.

Supplementation of the optimal dose should be continued as long as the initial indication for $n$–3 FA supplementation exists, taking the incorporation period (which is a few days longer for enteral than parenteral supplementation) and the relative short washout period into account. During the washout period, clinical beneficial effects of $n$–3 FAs probably extinguish.

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