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Review

Should omega-3 fatty acids be used for adjuvant treatment of cancer cachexia?

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SUMMARY

Objectives: Cancer cachexia is characterised by a progressive loss of muscle, resulting in functional impairment and shorter survival. Therefore, omega-3 has been studied for its role as an anti-cachectic therapy. This systematic review identified studies published on use of omega-3 in cancer cachexia in order to examine the potential benefit.

Methods: A systematic review of the literature using PubMed and B-on databases was conducted to identify clinical trials published between 2000 and 2015, to evaluate the effect of n-3 PUFAs on nutritional features and Quality of Life in cancer cachexia. Of 140 publications, 7 were selected on the basis of their methodological quality, according to the *Delphi List*. The collected data was summarized and written in text format and in tables.

Results: Only one study, made in pre-cachectic population, show statistically and clinically positive intervention. No benefits were observed with the 4 g EPA/day, but a potentially clinically relevant treatment effect with 2 g EPA/day. Lung tumours showed the highest CRP levels and while the weight of patients with gastrointestinal cancer increased significantly, patients with lung cancer showed no significant response.

Conclusions: Future cachexia trials would likely benefit from studying a single tumour type with earlier stage disease, with probably different dosage depending on the cancer type and its inflammatory profile.

1. Introduction

Fatty acids, once solely thought as an energy source, have been shown to be highly active substances. They can act as transcription factors that regulate protein synthesis as ligands in signal transduction, and as membrane components that regulate the fluidity, permeability, and dynamics of cell membranes [2]. There are 3 types of naturally occurring fats: saturated, monounsaturated and polyunsaturated [1]. Polyunsaturated fats can be classified into 2 groups based on the position of the first double bond site: omega-3 fatty acids or omega-6 fatty acids [1,6]. Major dietary sources of omega-3 are fatty fish such as mackerel, herring, salmon, sardines, pilchards and kippers containing eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) [5], as well as nuts, seeds, and vegetable oils containing α-linolenic acid (ALA) that can be converted into EPA and then DHA by a desaturase enzyme. Isotope-labelled ALA feeding trials have shown the conversion of ALA to EPA to vary from 0.2% to 21% and that of ALA into DHA to vary between 0% and to 9% [1]. ALA does not usually accumulate to particularly high concentrations even when ingested at relatively high dietary levels. This is partly due to the fact that much of the dietary ALA undergoes β-oxidation in the mitochondria and very limited amount is available for its conversion to EPA and DHA [3].

The ratio of omega-6/omega-3 intake is estimated to be 20 to 1 in the modern "western diet", compared with that of our palaeolithic ancestors who ate a diet much richer in omega-3's: estimated omega-3/omega-6 ratio of 2:1 [1]. About 95–99% of the population has a poor intake of ω-3 fatty acids as compared with the recommendation [3]. The metabolism of omega-3's and omega-6's leads to the production of eicosanoids, which include prostaglandins, thromboxanes (secondary to COX activity) and leukotrienes

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(secondary to LOX activity) [1,5]. Eicosanoids derived from omega-6 are prostanoids (thromboxane A2, prostaglandin E2 and prostacyclin2) and 4-series leukotrienes (leukotriene B4 and leukotriene C4) and are associated with pro-inflammatory and pro-aggregator properties *vs* those derived from omega-3 fatty acids, that are 3-series prostanoids and 5-series leukotrienes and are predominantly anti-inflammatory and inhibit platelet aggregation [1,4–8].

Interest around n-3 fatty acids in cancer is enormous, as their impact in cancer patients' outcomes are both possible and highly relevant. Omega-3 fatty acids are known to reduce synthesis and secretion of cytokines, attenuate protein degradation by preventing NF-kB accumulation in the nucleus and inhibit the effects of PIF. Therefore, their supplementation could be useful in the nutritional support of cancer patients, eventually modulating nutritional and Quality of Life parameters in cancer cachexia. Yet, discussion and controversy still exist on this subject. Based on this framework, we conducted the present systematic review in order to evaluate the effect of n-3 PUFAs on nutritional parameters, Quality of Life and functional status in cancer cachexia.

2. Methods

A systematic review of the literature performed using the PubMed database and B-on database was conducted to identify clinical trials published between 2000 and 2015, to evaluate the effect of n-3 PUFAs on nutritional parameters, Quality of Life and functional status in cancer cachexia. Of 140 publications, 7 were selected on the basis of their methodological quality, according to the *Delphi List*. The collected data was summarized and written in text format and in tables.

The method of this systematic review and meta-analysis was prepared in accordance with the PRISMA statement (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) [22].

2.1. Search strategy

Systematic research of trials published between 2000 and 2015 was conducted on MEDLINE (via PubMed; National Library of Medicine, Bethesda, Maryland) and B-On via Web of Knowledge (via Web of Science, Thomson Reuters, New York, USA), using the combination of the categories of search terms shown in Table 1. The search was elaborated according to PICO strategy considering: patients/population: cancer patients; Intervention: n-3 PUFA; Comparisons: parallel group did not receive n-n-3 PUFA as intervention; and Outcomes: nutritional parameters functional status and Quality of Life. The search in databases was done using Boolean operators (OR and AND), parentheses, quotation marks and asterisks. Quotation marks were used to search for exact terms or expressions; parentheses were used to indicate a group of search terms or combine two or more groups of search terms enabling all possible combinations of sentences; asterisks (*) or cipher symbol ($) were used to search all words derived of the precedent inflected part. Any filters to refine search were not added. Additionally, reference lists of all identified studies and important reviews about the theme were hand-searched for relevant trials. The searches were conducted in the online database and the results exported to the reference manager software EndNote® version X7 (Thomson Reuters, New York, USA).

2.2. Selection criteria

Titles and abstracts of the articles, and when clear information was not presented, the full text, were reviewed in order to choose those which were eligible. The eligibility criteria were: controlled or randomized clinical trials performed in humans; use of n-3 polyunsaturated fatty acids as intervention, isolated or added in dietary formulas or as lipid emulsion; sample composed of subjects with over 18 years of age and, only affected by malignant neoplasm; and those trials that had assessed nutritional parameters, Quality of Life and functional status in cancer patients. Trials that did not meet the inclusion criteria, duplicated or triplicate publications from the same trial, as well as, trials that were originally published in languages other than English, Spanish or Portuguese, were excluded.

2.3. Data extraction

Data were extracted from eligible articles independently by two reviewers and cross-checked. Articles were consulted again in case of divergence of opinions. For qualitative synthesis, the following data were extracted: locality, methodological characteristics (study design, blinding, randomization technique), patient characteristics (mean age, Body Mass Index -BMI, cancer stage), sample size enrolled, anti-cancer treatment adopted, intervention characteristics (formulation, dose, duration of supplementation and route of administration), and, proportion of loss to follow-up. For the presentation of results, we considered mean and standard deviation of the nutritional parameters, Quality of Life scores and functional status values at the final moment of supplementation or at any other moment during the supplementation period, which could be significantly lower or higher than control. For trials that did not present the mean and standard deviation values for any outcome of interest, the corresponding authors were contacted to request these values, and only articles from authors who provided these data were included. From trials that presented the mean and their respective standard deviation in graphic format, the values were estimated by inspection of their spatial distribution in the graphic area. The data were organized in a Microsoft Office Excel® 2013 document (Microsoft Corporation, Washington, USA).

2.4. Validity assessment

An evaluation of quality was conducted by two independent reviewers, according to Cochrane Collaboration's tool for assessing quality and risk of bias [23] and CONSORT-based checklist [24]. The

Table 1
Groups of search terms (PICO strategy) used for search strategy.

PICO's criteria	Descriptions and search terms used for each criteria
Patient/population	Patients with cancer (cancer OR neoplasm OR tumor)
Intervention	n-3 polyunsaturated fatty acids (EPA and DHA) ("fish oil" OR "n-3 polyunsaturated fatty acids" OR "Omega-3" OR "eicosapentaenoic acid" OR "EPA" OR "docosahexaenoic acid" OR "DHA" OR "linolenic acid" OR polyunsaturated fatty acids" OR "Immunonutrition")
Comparisons	Parallel group did not receive n-3 polyunsaturated fatty acids ("controlled clinical trial" OR "randomized clinical trial")
Outcomes	Nutritional parameters ("body composition" OR "muscle mass"; "weight" OR body weight" OR resting energy expenditure" Functional status and Quality of life ("Quality of life" OR Karnofsky Performance Status" OR physical activity" OR "functional capacity" OR "functional status" OR "handgrip strength")