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Applied nutritional investigation

Eicosapentaenoic acid in cancer improves body composition and modulates metabolism

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ABSTRACT

Objectives: The objective of this review article is to present the most recent intervention studies with EPA on nutritional outcomes in cancer patients, e.g. nutritional status, weight & lean body mass.
Methods: For this purpose a PubMed® and MedLine® search of the published literature up to and including January 2014 that contained the keywords: cancer, sarcopenia, EPA, ω-3 fatty acids, weight, intervention trial, muscle mass was conducted. The collected data was summarized and written in text format and in tables that contained: study design, patient' population, sample size, statistical significance and results of the intervention. The paper will cover malignancy, body composition, intervention with EPA, physiological mechanisms of action of EPA, effect of EPA on weight and body composition, future research.
Results: In cancer patients deterioration of muscle mass can be present regardless of body weight or Body Mass Index (BMI). Thus, sarcopenia in cancer patients with excessive fat mass (FM), entitled sarcopenic obesity, has gained greater relevance in clinical practice; it can negatively influence patients' functional status, tolerance to treatments & disease prognosis. The search for an effective nutritional intervention that improves body composition (preservation of muscle mass and muscle quality) is of utmost importance for clinicians and patients. The improvement of muscle quality is an even more recent area of interest because it has probable implications in patients' prognosis. Eicosapentaenoic acid (EPA) has been identified as a promising nutrient with the wide clinical benefits. Several mechanisms have been proposed to explain EPA potential benefits on body composition: inhibition of catabolic *stimuli* by modulating pro-inflammatory cytokines production and enhancing insulin sensitivity that induces protein synthesis; also, EPA may attenuate deterioration of nutritional status resulting from antineoplastic therapies by improving calorie and protein intake as well.
Conclusions: Indeed, cancer-related sarcopenia/cachexia is a multifactorial syndrome characterized by inflammation, anorexia, weight loss, and muscle/adipose tissue loss mediated by proinflammatory cytokines, e.g. TNF-α and IL-6, resulting in increased chemotherapy toxicity, costs, morbidity and mortality. With this review we found that EPA can reduce inflammation and has the potential to modulate nutritional status/body composition. In view of the modest survival benefits of chemotherapy/radiotherapy in some cancers, important issues for physicians are to optimize well-being, Quality of Life *via* nutritional status and adequate body composition. Thus, improvement in nutritional status is a central outcome.

Introduction

Cancer: Nutritional deterioration, sarcopenia and cachexia

Nutritional deterioration in cancer patients is a reality that continues untreated and is still a mystery for some clinicians. Cancer cachexia is defined as a "multifactorial syndrome characterized by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment" [1]. The diagnosis of cachexia is made according to the following criteria: Weight loss greater than 5% in the last 6 mo or weight loss greater than 2% in individuals already showing nutritional depletion according to current body weight and height (body mass index [BMI] < 20 kg/m^2) or reduced

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skeletal muscle mass (sarcopenia). Severity can be classified according to the degree of depletion of energy stores and of body protein, in combination with ongoing weight loss [1]. Patients who are cachectic may have anorexia, nausea, and other symptoms that may compromise food intake, reduce strength, impair functional capacity, and worsen their quality of life [2].

Although cancer treatments, such as chemotherapy or radiotherapy, may also cause weight loss and symptoms that may diminish nutritional status, the mechanisms associated with these clinical findings are totally different from those found in progressive tissue wasting [3–5]. Anorexia and increased energy expenditure may contribute to cancer cachexia; anorexia may be induced by proinflammatory cytokines (interleukin [IL]-1 α, IL-1 β, IL-6, and tumor necrosis factor [TNF]-α) released by both the tumor and the host's immune system. Conversely, the hypermetabolic state may result from the production of acute phase proteins (C-reactive protein, fibrinogen, and α-1 antitrypsin) by the liver. Still, anorexia alone is not responsible for the wasting process and not all cancer patients are hypermetabolic [6]. Therefore, there have to be other mechanisms behind metabolic alterations associated with cancer cachexia, namely tumor and host factors that may activate lipogenic and proteolytic pathways [7]. All of these observations justify the research to find and/or optimize nutritional intervention that improves body composition, particularly muscle mass and muscle quality [7,8].

Body composition assessment

Although patients' weight loss is a highly relevant parameter to be assessed and registered in the clinical routine, it does not allow us to distinguish body compartments, namely lean body mass (LBM) or fat mass (FM), and therefore to identify muscle and/or fat loss [3,9]. Moreover, clinical reports show that nutritional status in cancer patients is highly diverse: Studies show a high prevalence of overweight and obesity, even in patients with low muscle mass. This body composition pattern, designated as sarcopenic obesity, has been established as a predictor of poor functional status, worse quality of life and reduced survival [4,5].

Body weight comprises two main compartments: fat free mass (FFM) and fat mass (FM); FFM includes mineral tissue and muscle mass, e.g., extracellular and intracellular water and metabolically active tissues: skeletal muscle and internal organs. According to the method used, different body composition compartments may be measured. Although simple and practical methods such as bioelectrical impedance analysis (BIA) do not distinguish skeletal muscle from other metabolically active tissues, image-based body composition methods like computed tomography (CT), allow a precise evaluation of the quantity and quality of skeletal muscle [10,11].

Recently, CT images at the level of the third lumbar vertebrae have been validated in oncology for body composition analysis, by comparison with the gold standard method: dual energy x-ray absorptiometry [11]. Studies have already used CT images to identify sarcopenic cancer patients and did find significant associations with disease prognosis and survival. Fearon et al [6]. found a prevalence of sarcopenia of 56% in pancreatic cancer patients by analyzing their CT images; sarcopenia was present in all BMI categories, including overweight/obese patients; these patients had the overall worst prognosis, even when compared with patients who were only sarcopenic and underweight [4, 9]. The fact is the presence of overweight/obesity may mask the presence of reduced muscle mass, and in the absence of imaging body composition methods, sarcopenia may be underdiagnosed and undertreated [12].

Eicosapentaenoic acid

Polyunsaturated fatty acids include two classes of fatty acids, ω-6 and ω-3 fatty acids. The ω-6 series includes linoleic acid (LA, 18:2 ω-6), arachidonic acid (AA, 20:4 ω-6), and gamma-linoleic acid (GLA, 18:3 ω-6); all can be found in foods of animal origin, some vegetables, sunflower, soybeans, and grape seed oils. The ω-3 series includes the alfa-linoleic acid (ALA, 18:3 ω-3) present in green vegetables, in rapeseed and soybean oils; eicosapentaenoic acid (EPA, 20:5 ω-3) and docosahexaenoic acid (DHA, 22:6 ω-3) are ubiquitous in mammals, seafood, and marine products. ω-3 polyunsaturated fatty acids are essential nutrients for humans, because humans lack the delta to 15 desaturase that converts ω-6 fatty acids into ω-3 fatty acids [5]. Although the use of vitamins, minerals, and other dietary supplements during cancer treatment remains controversial [11], it has been suggested that the supplementation with either fish oil or EPA alone in patients with advanced cancer and cachexia, may contribute to skeletal muscle preservation, improved appetite and weight gain [9].

EPA has different effects on LBM via two main mechanisms: reduced muscle degradation and increased muscle synthesis. EPA influences proteolysis by down regulating the acute phase response, by reducing serum concentration of C-reactive protein (CRP) and by suppressing IL-6 production [13]. On the other hand, EPA may decrease muscle wasting by down regulating the ubiquitin proteasome pathway that is the central pathway in muscle loss. Additionally, EPA reduces muscle apoptosis by reducing TNF-α [12,14]. EPA increases muscle insulin sensitivity, thus improving protein and calorie intake [13]. EPA also has indirect effects on nutritional status because it was demonstrated it reduces chemotherapy side effects and enhances tumor response to antineoplastic treatments [7]. Moreover, EPA may attenuate side effects from antineoplastic therapies, by improving calorie and protein intake [15]. It is worth mentioning that recent trials corroborate EPA's potential benefits on muscle mass preservation [5,12,15–17].

EPA, weight and body composition

The potential antiinflammatory effects of EPA and their influence on weight and body composition have already been shown in several studies (Table 1). Early reports did show positive and promising results: Maintenance or even improvement of weight and LBM. Wigmore et al. [14] reported that EPA supplementation had a positive effect on weight losing pancreatic cancer patients: 61% of patients experienced weight gain, whereas 17% became weight stable and 22% reduced the rate of weight loss. Even though no changes were found in anthropometric measures, after 1 mo of supplementation, a significant, although temporary, reduction in CRP concentration was found ($P < 0.002$), as well as a stabilization of resting energy expenditure. Similarly, in a study by Barber et al. [8] that enrolled weight losing pancreatic cancer patients, beneficial effects of EPA were described on weight and LBM. Daily energy intake was significantly increased ($P = 0.002$), whereas both performance status and appetite significantly improved after 3 wk of supplementation ($P < 0.005$ and $P < 0.01$, respectively).

Although EPA supplementation had positive effects on weight and LBM maintenance in the previously mentioned studies, these were uncontrolled, not-randomized, and enrolled a small