Cancer cachexia: mediating factors and the effect of eicosapentaenoic acid dieting

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Abstract: Cancer cachexia is an involuntary weight loss of more than 10% of premorbid weight, caused by depletion of lipid stores, muscle wasting, anorexia and metabolic alterations. It results from a complex tumor-host interaction associated with an elevated production of cytokines (e.g. TNF-α, IL-1, IL-6) and release of tumour-derived catabolic factors (e.g. lipid-mobilizing factor, protein-mobilizing factor). In this paper we discuss data suggesting a potential role of ω-3 fatty acids, such as eicosapentaenoic acid (EPA) in the treatment of cancer cachexia. These data indicate that dietary EPA decreases production of cytokines, attenuates the lipolysis process and reduces activity of the proteolysis-inducing factor (PIF). In contrast to other therapeutic agents, which only improve appetite, it has been shown that EPA supplementation prolonged the survival of cancer cachexia patients.

Key words: cachexia, cytokines, tumour-derived factors, lipid mobilizing factor, protein mobilizing factor, proteolysis-inducing factor, ω-3 fatty acids, eicosapentaenoic acid

INTRODUCTION

Cachexia (from Greek kakos – “bad” and hexis – “condition”) is a nonspecific wasting syndrome associated with many types and forms of cancer disorders. Accompanied by anorexia, muscle and fat wasting, cancer cachexia arises from a complex interaction between the tumor and the host [1]. Cachexia syndrome occurs in the majority of cancer patients before death, and is responsible for the deaths of ca. 20% of cancer patients [2]. The degree of cachexia is inversely correlated with the survival time of the patient and always implies a poor prognosis [3]. In general, cancer cachexia is defined as a weight loss of more than 10% of premorbid body mass. This is caused mainly by depletion of lipid stores and muscle wasting [4] and is often associated with hypoproteinemia, elevation of acute phase proteins level, anorexia and anaemia, and also with alterations in carbohydrate, lipid and protein metabolism [5, 6].

Although the clinical aspects of cancer cachexia have been extensively investigated, its pathophysiological mechanism has not been fully clarified to date [7]. The development of cachectic state is associated with the presence and growth of the tumour, and contributes to the state of malnutrition due to the disease-associated anorexia and decreased food intake. In addition, the competition for nutrients between the tumour and the host leads to an accelerated starvation state which promotes severe metabolic disturbances in the host, including hypermetabolism which leads to an increased energetic inefficiency [8]. It is thought that one of the main pathogenetic mechanisms underlying cancer cachexia is an increased production of cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-1 (IL-1), as well as an elevated release of tumour-delivered catabolic factors, such as lipid mobilizing factors (LMFs) and protein mobilizing factors (PMFs) [9].

Endogenous mediators and factors of cancer cachexia. A significant number of cytokines and other factors may be responsible for the metabolic changes associated with cancer wasting. Among them are: TNF-α, IL-1, IL-6, IFN-γ, LMFs and PMFs.

TNF-α. In the early 1980s, Cerami and Beutler [5] identified a monocyte/macrophage lineage-derived TNF-α (17-kDa) as a first humoural factor which triggers a disease-associated body weight loss. Production of this factor is synergistically regulated by other cytokines, such as IL-1 and IFN-γ. TNF-α alone is also capable of inducing the production of cytokines IL-1 and IL-6 [5]. TNF-α alters the metabolism of adipose tissue, mainly through induction of lipolysis and inhibition of lipoprotein lipase (LPL) activity. Moreover, this cytokine reduces lipogenesis through an inhibition of enzymes involved in the lipid synthesis, such as fatty acid synthase and acetyl-CoA carboxylase [10, 11]. There are also data suggesting that chronic increases in the serum TNF-α produced by tumour cells are associated with muscle wasting. In studies using a murine model of muscle wasting [12] it has been demonstrated that TNF-α provoked an oxidative stress, together with an increase of the nitric oxide synthase (NOS) activity in skeletal muscle and a decrease in the myosin creatinine phosphokinase (MCK) expression. In the study by Buck and Chojkier [12], effects characteristic for cachexia in the TNF-α-treated mice were prevented by administration of antioxidants, such as D-a-tocopherol or the NOS inhibitor nitro-L-arginine.

IL-1 and IL-6. It is thought that IL-1 and IL-6, well known inflammatory cytokines produced by macrophages and endothelial cells, are critical factors engaged in the onset and progress of cancer cachexia. These cytokines are known for their pyrogenic activity [13] and for induction of the acute-phase response [14]. Similar to the effects provoked by TNF-α, IL-1 also acts on adipose tissue by inhibiting LPL activity and stimulating lipolysis in cultured adipocytes [5]. In addition, IL-1 is capable of inducing the production of IL-6. It has been shown that IL-6 alike is a potent inhibitor of the LPL activity in adipose tissue, and also has a negative influence...
on skeletal muscle [5]. Therefore, it has been hypothesized that IL-6 acts via IL-1 in the process of cachexia; for example, Strassmann et al. [15, 16] have shown that in vitro murine colon-26 adenocarcinoma cells produced large quantities of IL-6 after stimulation with IL-1. In their in vivo studies, the IL-1 dependent production of IL-6 was also evident; namely, they demonstrated that administration of an anti-IL-6 monoclonal antibody suppressed the development of cachexia associated with colon tumour growth [15]. In subsequent studies, Strassmann et al. found that tumour-infiltrating macrophages produced IL-1 which, in turn, supposedly induced the production of IL-6 by the tumour cells [16].

LIF and IFN-γ. Leukemia inhibitory factor (LIF) has properties similar to IL-6 regarding the effects leading to cachexia syndrome. LIF – like IL-6 and IL-1 – is also an inhibitor of the LPL activity, although it is not as effective as TNF-α [11]. Mice inoculated with tumour hematopoietic cells over-expressing LIF developed a syndrome similar to that provoked by the administration of IL-6, characterized mainly by weight loss and abnormalities in calcium metabolism [17]. However, in a case of IFN-γ, a wider and potentially lethal spectrum of the cachexia mechanisms has been demonstrated in nude mice inoculated with cells overexpressing mouse IFN-γ gene [18]. In this study, the cachexia syndrome was evident by loss of body weight, depletion of fat stores, and reduction of food intake. The wasting state was proportional to the amount of cells producing IFN-γ, which were significantly reduced by treating the mice with antibodies to IFN-γ, and was accompanied by the IFN-γ-induced stimulation of lipolysis and inhibition of LPL activity [18]. Thus, IFN-γ is actually considered as one of the major players in cachexia associated with tumour disorder.

Tumour-derived factors. In addition to the cytokines presented above, tumour-derived molecules have also been proposed as mediators of cancer cachexia. These factors can be divided into two groups: those acting on adipose tissue (LMFs – lipid mobilizing factors), and those acting directly on skeletal muscle (PMFs – protein mobilizing factors). They are present in the circulation and appear to act in a hormone-like manner. Studies on human and animal models of cachexia provided evidence that LMFs produced by cachexia-inducing tumours act directly on adipocytes to stimulate lipolysis in a cyclic AMP-dependent manner by a mechanism similar to that of the lipolytic hormones [19]. This is different from the effect ascribed to the cytokines, which are thought to enhance lipolysis by inhibition of the clearing enzyme lipoprotein lipase. LMFs are involved in the degradation of adipose tissue with increased oxidation of the released fatty acids through an induction of uncoupling proteins (UCP) expression [20]. Indeed, recent studies have revealed that LMFs increased carbohydrate metabolism and whole body fatty acid oxidation associated with the induction of UCP [21]. PMFs, on the other hand, induce protein degradation in skeletal muscle through stimulation of ATP-ubiquitin-dependent pathway, one of the three major proteolytic pathways responsible for the catabolism of proteins in skeletal muscle. Muscle catabolism is also stimulated by the proteolysis-inducing factor (PIF) – the main protein mobilizing factor, which is produced by cachexia-inducing murine and human tumours [22]. PIF increases muscle catabolism by elevating the levels of ubiquitin mRNA, ubiquitin-carrier protein and proteasome subunits, and its action is associated with the activation of the transcription the factor NF-κB pathway [23].

Role of eicosanoids in the induction of cachexia. A large body of data indicates that eicosanoids – biologically active lipids derived from the arachidonic and other ω-6 unsaturated fatty acids – represent a potent factor involved in the induction of tumour and cancer cachexia [24-26]. The metabolism of arachidonic acid by cyclooxygenase (COX), lipoperoxidase (LOX) and P-450 epoxygenase pathways generates a substantial number of ω-6 eicosanoids, including prostanoids, leukotrienes, hydroxyeicosatetraenoic acids and epoxyeicosatrienoic acids. Both COX and LOX pathways are well known proinflammatory mechanisms provoked by cytokines. Epidemiological, clinical and animal studies provide evidence that activation of these particular pathways results in chronic inflammation and carcinogenesis, and may contribute to the cancer cachexia [27]. On the other hand, arachidonic acid is one of the major ingredients of the animal fats ingested; therefore, a major clinical hypothesis states that substantial dieting of arachidonic acid upon chronic inflammation may eventually result in the aberrant arachidonate metabolism [27] leading to, e.g. overproduction of prostaglandins. The overproduction of prostaglandins by inflammatory cells and tumour cells stands in negative feedback from the immune surveillance and the development of defence against malignant cells [25]. Accordingly, non-steroidal anti-inflammatory drugs that inhibit the COX pathway have been reported as having beneficial effects in reducing the risk of development of some tumours [28]. It has also been shown that COX inhibitors significantly reduce the metabolic rate of cachetic rats [29]. Other animal studies have shown that supplementation of the diet with ω-3 unsaturated fatty acids, e.g., eicosapentaenoic acid, may result in the substitution of the ω-6 unsaturated fats as substrates for the eicosanoid metabolism; in consequence, leading to the generation of a different class of eicosanoids.

Eicosapentaenoic acid in the treatment of cancer cachexia. The most common pharmacological agents used to treat cachexia syndrome include glucocorticoids, gestational and antiserotogenic drugs, or branched-chain amino acids [2, 30]. Although the treatment is focused on the inhibition of muscle wasting, as well as on the reduction of lipid depletion, its therapeutic effect, however, is considered rather insufficient [30]. Nowadays, eicosapentaenoic acid (EPA), an ω-3 fatty acid which occurs in oily cold-water fish, is receiving increased attention as a therapeutic factor for a number of disorders, including cancer cachexia syndrome. In the early 80s, of the 20th century, Karmali et al. [31] reported that diet enriched with EPA and DHA (docosahexaenoic acid, another ω-3 fatty acid that can be found in the fish oil) has an inhibitory effect on mammary tumorigenesis. More recent studies have shown that substantial supplementation of the diet with ω-3 fatty acids also decreases the risk of the onset of colorectal cancer [32].

The beneficial effect of ω-3 fatty acids on the risk of cancer may be associated with its effect on the process of inflammation. In accordance with this, it has been documented that supplementation of diet with ω-3 fatty acid results in the modulation of endotoxin, steroid abscnox-induced sickness behaviour, inflammation and fever [33]. Although the complete anti-inflammatory mechanism of EPA is under scientific debate, it is thought that ω-3 fatty acids may
interfere with the synthesis of certain eicosanoids, and may affect membrane-dependent receptor and enzyme functions [34]. According to this hypothesis, EPA maybe incorporated into the cellular membrane, substituting arachidonic acid in the glycerophosphatides, thereby reducing an arachidonate-dependent metabolism upon inflammation [33, 35]. The protective effect of EPA in cancer cachexia may also be related to its ability to modulate inflammatory and immunological pathways at the level of signal transduction and the synthesis of certain inflammatory mediators. For example, it has been shown in in vitro studies that EPA decreases TNF-α gene transcription by preventing NFκb-Iκb dissociation and NFκb translocation into the nucleus (Figure 1). In consequence, the synthesis and release of TNF-α and IL-1 are reduced [35, 36].

Moreover, EPA exerts an inhibitory effect on the ATP-ubiquitin-proteasome pathway, which is responsible for more than 80% of lean tissue wasting through cancer [37]. Whitehouse et al. [38] have demonstrated that treatment with EPA of mice bearing the cachexia-inducing tumour (MAC16) attenuated loss of body weight and significantly suppressed protein catabolism in the soleus muscles through an inhibition of an ATP-dependent proteolytic pathway. Although the treatment with EPA significantly reduced protein degradation, it had no effect on the protein synthesis. The combination of EPA with amino acids, such as leucine, arginine and methionine, almost doubled the increase in protein synthesis [39]. This suggests that the combination therapy for the cancer wasting syndrome, involving both inhibition of enhanced protein degradation and stimulation of the reduced protein synthesis, may be much more effective than either treatment alone [39].

Data suggest that EPA may also affect the activity of tumour-derived catabolic factors such as LMFs and PMFs. Price and Tisdale [40] observed that stimulation of the lipolysis and adenylate cyclase (an enzyme which stimulates cAMP production) by LMFs is significantly reduced in animals treated with EPA. Thus, it seems that the ability of EPA to preserve fat stores during the wasting process arise from the attenuation of the stimulation of adenylate cyclase activity [40]. EPA inhibits muscle protein degradation induced by PMFs, especially by the proteolysis-inducing factor (PIF). Smith et al. [36] have reported that with increasing concentrations of PIF, the rates of protein synthesis decreased in non-treated cultured cells. However, when EPA was administrated to the cells, the rate of protein synthesis remained elevated. These results suggest that EPA may maintain protein synthesis by suppressing the proteolytic effects of PIF [36].

**Preliminary clinical studies using eicosapentaenoic acid.** The role of eicosapentaenoic acid in counteraction against cachexia has been documented in numerous clinical studies conducted on cancer patients with progressive weight loss.

In 1996, Wigmore et al. evaluated the effects of EPA in 18 patients with cachexia due to unresectable pancreatic cancer. The patients received 2 g of EPA per day (12 g of fish oil daily) over 3 months. After this period, the cachexia process was arrested in more than a half of the patients in the group, due to a decrease in skeletal muscle degradation. A small proportion of patients gained weight [6, 34].

Contemporary methods of cachexia treatment with ω-3 fatty acids are based on a combination of eicosapentaenoic acid with nutrients. Barber et al. tested nutrition supplement enriched with fish oil on 20 patients with advanced pancreatic cancer who were losing weight at a median rate of 2.9 kg per month. After 7 weeks of treatment with 2 g of EPA and 600 kcal daily, the patients had gained a median of 2.5 kg. Body-composition analysis revealed a significant gain in lean body mass. The therapy improved nitrogen balance and appetite, suggesting that the supplement was not simply replacing normal food intake. Moreover, after this treatment, production of the potential mediators of cachexia: cytokines and the proteolysis-inducing factor, was decreased [34].

A recently published report suggests that administration of ω-3 fatty acids in doses of at least 1.5 g/day for a prolonged period of time to patients with advanced cancer disease is associated with an improvement of life expectancy, and a better reaction to clinical treatment [6].

**SUMMARY**

Although progress has been made in understanding the physiologic changes in advanced cancer that give rise to cachexia, it still remains a significant cause of morbidity and mortality in malignant disease. The metabolic alterations that occur in cachectic patients might be normalized by anti-inflammatory agents, such as eicosapentaenoic acid derived from fish oil.

In conclusion, EPA appeared to be a consistently logical treatment of choice for cancer cachexia. In contrast to other therapeutic agents, which only improve appetite, EPA prolongs the survival of cancer cachexia patients and has a potential for improvement of their quality of life [36].

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