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Editorial

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Cancer cachexia

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Abstract

In recent years many efforts of researchers and clinicians were made to improve our knowledge of cachexia syndrome. Not only cancer, but also many chronic or end-stage diseases such as AIDS, chronic obstructive pulmonary disease (COPD), rheumatoid arthritis, tuberculosis and Crohn's disease are associated with cachexia, a condition of abnormally low weight, weakness, and general bodily decline which deteriorates quality of life and reduces the prognosis of the patients who suffer from it. In the present editorial we will focus cachexia related on cancer and provide some insight into this prognosis-limiting syndrome.

Editorial

Cancer cachexia occurs most frequently in malignancy and is associated with more than 20% of cancer deaths [1]. Patients with upper gastrointestinal cancer are especially likely to suffer from substantial weight loss, and patients with pancreatic cancer have the highest frequency of developing a cachectic syndrome. Thus the research groups and physicians dealing with pancreatic cancer are very interested in finding an effective treatment for cachectic patients. But there is still little known about this clinical issue, and our knowledge grows slowly. Much more research and many more clinical trials are needed to increase our understanding of the syndrome and to develop therapeutic strategies for one of the major symptoms of cancer.

The word "cachexia" comes from the Greek words "kakos" and "hexis", meaning "bad conditions" [2]. Cachexia is a complex metabolic status with progressive weight loss and depletion of host reserves of adipose tissue and skeletal muscle. Cachexia should be suspected if involuntary weight loss of greater than five percent of premorbid weight occurs within a six-month period [3]. Cachexia represents the clinical consequence of a chronic, systemic inflammatory response, with high hepatic synthesis of acute-phase proteins resulting in depletion of essential amino acids [4]. In contrast, in starvation only fat metabolism is increased while the organism tries to conserve lean body mass [5].

In addition to metabolic changes, cachexia is often associated with anorexia. In cancer patients there can be mechanical interference such as obstructions, as well as treatment-related toxicity. In patients receiving chemotherapy or radiation, subsequent nausea, vomiting and diarrhea can contribute to weight loss. But the lack of nutrients alone cannot explain the metabolic changes seen in cachexia. In clinical trials, nutritional supplementation and dietary counseling failed to increase body weight [6]. Several appetite-stimulating drugs have been tested in an attempt to increase the food intake of cachexia

patients, but most of them had little or no effect on body weight [7].

Only limited treatment options exist for patients with clinical cancer cachexia. In one trial, corticosteroids improved the sensation of well-being and led to increased food intake, but this effect lasted only a few weeks [2]. Progestogens such as megestrol acetate and medroxyprogesterone acetate also failed to meet expectations [3,8]. Body composition analysis showed that the weight gain resulted only from increased body fat and fluid, with no change in lean body mass [2]. Additionally, therapy with progestogens led to a decline in the response rate to chemotherapy and an increase in the frequency of thrombembolic events [3,7].

Much research is currently focused on determining the mechanism of the development of cachexia. There are two main theories of the development of cancer cachexia.

The first theory is the pathological alteration of control cycles. Food-intake is regulated through a complex system of hormones and neuropeptides. Inui *et al*. demonstrated that Neuropeptid Y (NPY), the most potent feeding-stimulatory peptide in this cycle, is deregulated in the hypothalamic orexigenic network, leading to decreased energy intake but high metabolic demand for nutrients [9]. High levels of leptin, a hormone secreted by adipocytes, block the release of NPY. In cachexia the leptin feedback loop seems to become out of control, altering the neuropeptidergic control cycles [9].

The second theory is based on the idea that tumor-derived factors maintain the cachectic syndrome. Tisdale *et al*. postulated a factor that was extracted from the urine of cachectic patients and which induces protein degradation in skeletal muscle by upregulation of the ubiquitin-proteasome pathway. This proteolysis-inducing factor (PIF) is closely related to weight loss in cachexia, and in a recent study it was shown that PIF is produced in human colon cancer [1,10,11].

A second factor extracted from the urine of cachectic patients – lipid mobilizing factor (LMF) – is closely related to weight loss and induces lipolysis in murine adipocytes. A recent study showed that this lipolytic process is mediated through the β-3 adrenoceptors. LMF produces a significant increase in the UCPs in brown adipose tissue, skeletal muscle and liver [12].

Mitochondrial uncoupling proteins (UCPs) 1, 2, and 3 are involved in the control of energy metabolism through thermogenesis in brown adipose tissue and possibly in skeletal muscle tissue in humans. In many animal models, overexpression of UCPs (especially UCP 2) in white adipocytes and in muscle and liver tissue was associated with cachexia [6].

Both theories contribute to a better understanding of the development of cancer cachexia. However, it is still uncertain how they interact and whether they come into play at the beginning or at the end stage of the disease.

Despite the controversial discussion of cachexia-inducing mechanisms uncertainty over what causes cachexia, it is quite clear that proinflammatory cytokines are linked to all pathways that induce cachexia. As mentioned, cachexia is associated with a chronic systemic inflammatory response and the elevation of acute phase proteins. High serum levels of IL-1, IL-6 and INF gamma are present in many cancer patients, and the levels of these cytokines seem to correlate with tumor progression.

These cytokines stimulate the expression of leptin and/or mimic the hypothalamic effect of negative feedback from leptin by disarranging the signaling pathway of NPY, resulting in long-term inhibition of food intake. IL-1 antagonizes NPY – induced feeding in rats and disrupts the orexigenic pathway of NPY. On the other hand, central corticotropin-releasing factor (CRF), which is upregulated by IL-1, seems to influence satiety, and is a potent anorexigenic signal [13].

UCP expression is not only increased by LMF. Tumor necrosis factor alpha (TNF-α) also increases the mRNA levels of UCP2 and 3. In combination with INFγ TNF-α activates the transcription factor NFκB that leads to reduction of Myo D, a transcription factor essential for repairing damaged muscle tissue [14].

Although IL-6 is one of the key cytokines involved in the development of cachexia, the definite mechanisms have not yet been clarified. Improvements in appetite and weight gain through decreased cytokine expression after the application of corticosteroids or special antagonists like IL-6 antibodies were seen over short periods, but further investigations of the cytokine system are necessary to elucidate the interaction between host and tumor-derived cytokines and to determine their effect on biochemical mechanisms.

Conclusions

Many trials have been performed in the search for a treatment for cachexia, but most therapies have not fulfilled expectations. Currently, eicosapaentanoic acid is being tested in cachectic patients. Eicosapaentanoic acid seems to interfere with the signaling pathway of PIF, and first results are promising [4]. Future therapies may consist of anticatabolic and anabolic drugs in combination with appetite stimulants.

Although in recent years our understanding of cachexia has increased, we are still in the fledgling stages. The scientists and clinicians dedicated to finding an effective treatment for cachectic patients have their work cut out for them.

Author's contribution

MEM and PK drafted the paper. HF provided comments and suggestions for its finalization. All authors read and approved the final manuscript.

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