Metabolic and nutritional aspects of cancer

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Summary

Cancer, being in fact a generalized disease involving the whole organism, is most frequently associated with metabolic deregulation, a latent inflammatory state and anorexia of various degrees. The pathogenesis of this disorder is complex, with multiple dilemmas remaining unsolved.

The clinical consequences of the above-mentioned disturbances include cancer-related cachexia and anorexia-cachexia syndrome. These complex clinical entities worsen the prognosis, and lead to deterioration of the quality of life and performance status, and thus require multimodal treatment.

Optimal therapy should include nutritional support coupled with pharmacotherapy targeted at underlying pathomechanisms of cachexia. Nevertheless, many issues still need explanation, and efficacious and comprehensive therapy of cancer-related cachexia remains a future objective.

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INTRODUCTION

The malignant cell mass reaching about 1 kg is the threshold of death for the great majority of cancer patients. Yet, benign tumours may achieve a several or several dozen times higher mass without any significant impact on patient survival. Consequently, malignancies may lead to death not only due to the simple burden of excessive cellular mass.

The presence of a malignant neoplastic cell population in the body induces numerous metabolic disturbances, leading in turn to deregulation of systemic homeostasis, a chronic latent inflammatory state and appetite loss.

This process results in progressive and often irreversible cachexia.

Unfortunately, currently there are no acknowledged methods of nutrition which could reduce the treatment of cancer cachexia to simple supplementation of alimentary deficits caused by the presence of an additional "consumer" – the neoplastic disease.

This knowledge justifies implementation of complex therapy, encompassing proper nutritional interventions adjusted to actual metabolic disorders and appetite deficiency, as well as pharmacologic treatment targeted at cancer-related malnutrition.

Pathogenesis of metabolic deregulation

Metabolic and energetic disorders induced by malignancies are characterized by extremely complex pathogenesis with multiple elements remaining still unexplained. However, it is currently known that the cachectic metabolic deregulation is the result of action of a number of biologically active substances secreted both by neoplastic cells and by healthy tissues in response to cancer-related stimuli.

The key role is ascribed to low-molecular-weight regulatory proteins with multimodal properties – cytokines. The published data point to the progressive cancer-related imbalance between pro-inflammatory cytokines and their antagonists, resulting in a systemic latent inflammatory state and enhanced catabolism of body proteins [2,41,42,43,28].

The best documented pro-inflammatory cytokines implicated in the pathogenesis of cancer cachexia include tumour necrosis factor alpha (TNF-α, formerly known as cachectin), interleukin-1α and 1β (IL-1α, IL-1β), interleukin-6 (IL-6) and interferon gamma (IFN-γ). Their action at the level of target cells is mediated mainly by the nuclear transcription factor NF-κB and involves both direct and indirect stimulation of catabolism, as well as anti-anabolic, anorexigenic and pyrogenic effects [2,6,20,28,29,38,41,42,43,44,45].

Accumulating evidence indicates the major role of TNF-α in initiation of cancer-related cachexia. TNF-α increases the level of myostatin, a protein with anti-anabolic activity, belonging to the transforming growth factor beta (TGF-β) family. Myostatin in turn stimulates the activity of the ubiquitin-proteasome system, which is responsible for degradation of ubiquitin-labelled proteins and negatively interferes with the mammalian target of rapamycin (mTOR) signalling pathway, mediating anabolic stimuli [2,18,26,31,42,43,44,45].

Dysfunction of multiple regulatory mechanisms has also been confirmed. Deregulated signalling may involve not only cytokines, but also other substances, mainly neurotransmitters active in brain centres regulating appetite and metabolism. The most important examples are members of the melanocortin system and preproopiomelanocortin derivatives, members of the neuropeptide Y (NPY) and serotonin systems. Moreover, it has been documented that the pathogenesis of appetite and metabolism disorders involves protein and lipid mobilizing factors (PMF, LMF), dysfunctional leptin and ghrelin signalling, as well as the unfavourable influence of parathyroid hormone-related protein (PTHrP) [5,21,25,35,37,41,44].

Numerous and extremely complicated interactions between biologically active factors, acting on an endocrine, neurocrine, paracrine or occasionally autocrine basis, result in deregulation of the main intermediate metabolic and energetic pathways, as well as appetite inhibition.

Metabolism in cancer patients

Disturbances of protein, carbohydrate, and lipid metabolism, energetic imbalance, specific deficiency syndromes, as well as secondary metabolic disorders, are all described in cancer patients.

However, it should be emphasised that the deregulation of protein metabolism plays the crucial role in the development of cancer-related cachexia, encompassing the abnormal exacerbation of protein degradation, mainly involving the myofibrillar proteins of skeletal muscles, with concomitant inhibition of anabolic processes [17,23].

An overview of disturbances of the main intermediate metabolic pathways with a short commentary is presented below in tables 1-3 [14,19,23,24,30,40,45].

Clinical consequences of metabolic deregulation

Cancer has long been perceived as a disease leading to a progressive decrease of body weight, up to extreme prostration of the organism.

However, it should be stressed that cancer-related cachexia is not a synonym of simple malnutrition, and loss of body weight alone is not sufficient to establish the diagnosis.

According to the international consensus, cancer-related cachexia is defined as a compound syndrome of metabolic disorders leading to loss of lean body mass, mainly skeletal muscles, which is irreversible or not fully reversible by conventional nutritional support and leads to progressive functional impairment. It is most commonly associated with appetite loss, while both conditions together form the cancer anorexia-cachexia syndrome (CACS) [23].

A *sine qua non* condition for the diagnosis of cachexia or CACS is the loss of lean body mass, not necessarily accompanied by adipose tissue loss. Consequently, a normal total body mass according to the definition should not exclude the presence of cancer-related cachexia, whereas the most important predictor of prognosis is the lean body mass index.

Moreover, cachexia and CACS are among the most aggravating sequelae of malignancies in relation to quality of life, opportunity to treat the underlying disease and prognosis, which may be life threatening themselves. It is estimated that these clinical syndromes are the direct cause of death in ca. 20% of cancer patients. In addition, they remain the most important cause of impairment of the quality of life, worsen performance status and cause

Table 1. Protein metabolism

Process	Commentary
Negative protein balance	Predominance of catabolism-stimulating biologically active factors, especially proinflammatory cytokines
Increased endogenous protein catabolism, accelerated protein turnover	Applies mainly to skeletal muscles, which are the source of amino acids being the main substrates for gluconeogenesis (alanine, glycine)
Decreased anabolism	Plays an important role in the pathomechanism of cancer-related cachexia
Reduction of lean body weight	Adverse prognostic factor; among the main causes of reduced quality of life
Modified liver protein synthesis profile	Increased acute phase protein synthesis (secondary to IL-6), reduced synthesis of so-called negative acute phase proteins (for example albumin)

Table 2. Carbohydrate metabolism

Process	Commentary
Impaired glucose tolerance	Early metabolic disorder connected with insulin resistance of various degrees. The consequence is impaired intracellular glucose utilization
Insulin resistance	Result of action of multiple biologically active agents and (indirectly) latent inflammatory state
Increased glucose turnover	High glucose consumption is a characteristic feature of neoplastic cells, which function in relatively hypoxemic conditions and utilize substrates metabolized mainly in anaerobic pathways
Increased gluconeogenesis	Pathologic hyperactivation of endogenous glucose synthesis from non-carbohydrate-related substrates – mainly from glucogenic amino acids released in catabolic processes in skeletal muscles. Contrary to physiological conditions, glucose supply does not inhibit gluconeogenesis
Increased glycolysis	Anaerobic glucose metabolism is typical for neoplastic cells (see above).
Increased glycogenolysis	Increased glycogen breakdown.

Table 3. Lipid metabolism

Process	Commentary
Increased lipolysis	Increased turnover of endogenous and exogenous lipids in a subset of patients
Hypertriglyceridaemia	Occurs in a subset of patients; pathogenesis unclear
Decreased cholesterol level	Hypocholesterolaemia is a marker of malnourishment. It is connected with "reverse epidemiology" of risk factors: increased cardiovascular risk in patients with decreased cholesterol level.

ongoing functional disability. They are responsible for higher toxicity and lower efficacy of cancer treatment as well [4,5,15].

Not all neoplasms induce fully symptomatic cachexia or CACS with the same frequency. These syndromes are especially characteristic in patients with pancreatic cancer, malignancies of the upper alimentary tract, as well as lung cancer and tumours of the head and neck. Conversely, they are much less frequent in such tumours as colon and breast cancer.

This diversity is most likely attributable to cancer biology, or perhaps to not yet described personal factors. The tumour stage is also of utmost importance (resistant cachexia is a typical feature of disseminated disease), though CACS may develop even in patients with neoplasms weighing as low as 0.01% of the body mass, especially in pancreatic cancer.

Of note, cancer-induced metabolic disorders and their clinical consequences form a continuum of states and develop gradually. According to the international consensus, precachexia, cachexia and resistant cachexia should be discriminated (diagnostic criteria are shown in table 4) [23]. However, the SCRINO Working Group proposed a classification with 4 grades/classes: from asymptomatic precachexia (class 1 – loss of body mass <10%, no accompanying symptoms) to fully-developed cachexia (class 4 – loss of body mass >10%, anorexia –

intake of <1500 kcal/day, latent inflammatory state characterised by C-reactive protein concentration >10 mg/l) [12]. It is a useful tool to assess patients' prognosis and to make proper therapeutic decisions.

The main therapeutic goal should be to prevent the development of fully symptomatic cachexia or at least to stop its progression. It has been shown that the greatest benefits for patients may be achieved by faster initiation of interventions from the field of broadly defined supportive treatment, perhaps also including anti-cytokine therapy (anti-IL-6 or anti-TNF-α monoclonal antibodies). Even if in the precachectic stage nutritional interventions may prove satisfactory, fully developed cachexia by definition is irreversible by means of sole augmentation of the supply of nutritional elements.

The optimal therapy of cachexia has not been precisely established as yet. The best method would be to cure the underlying malignancy, but this remains impossible in the majority of cases. Thus, the most reasonable mode of action is to combine the nutritional support with targeted pharmacologic treatment, directed at the pathogenesis of metabolic deregulation, as well as at the latent inflammatory state and appetite deficiency.

Unfortunately, multiple issues in the field of pharmacologic modulation of metabolism and efficacy of nutritional interventions still remain unsolved and are the subject of clinical trials in different phases. Nevertheless, even isolated nutritional interventions in cachectic patients may contribute to preservation or improvement of the current quality of life and delay the progressive loss of functional independence. This is especially important in view of the limited options of causative treatment of numerous advanced tumours.

Nutrition of cancer patients – nutritional support in oncology

Appetite deficiency is one of the most important components leading to the negative protein and energy balance that is a hallmark of cancer-related cachexia.

The anorexigenic influence of multiple biologically active agents, as well as gastrointestinal adverse effects of oncological treatment, results in reduction of food intake. Moreover, altered anatomical conditions due to extensive surgery and enzymatic deficiencies frequently observed in cancer patients hinder effective digestion of food and proper absorption of nutritional elements.

However, proper nourishment is especially important for the quality of life and prognosis, and the necessity of nutrition is very deep-rooted in the common awareness of patients and their relatives.

Nutritional guidance undoubtedly plays a major role, though a special and universal diet for cancer patients has not been developed yet. It is agreed that such nutrition should allow for undesirable effects of oncologic treatment, avoid too rich food (e.g. fat or fried dishes, mushrooms, leguminous plants) or meals poorly tolerated by individuals.

Recommendations include the augmentation of protein supply up to ~1.0-1.2 g/kg BW/day and the increase of fat/carbohydrate ratio in covering the daily energy demand, which typically varies between 25 and 30 kcal/kg BW/day. Enhancement of daily consumption of several nutritional elements may prove beneficial, especially of omega-3 fatty acids contained in saltwater fish. There are attempts to exploit their anti-cachectic properties, especially in pancreatic cancer patients [16].

Secondary lactase deficiency and secondary lactose intolerance are quite frequently observed (11-35% of patients undergoing chemotherapy); thus this subgroup of patients benefits from limited unprocessed milk intake, that is in amounts not exceeding 200 ml daily. Moreover, drinking of grapefruit juice is definitely contraindicated as long as systemic therapy is administered, as it contains active ingredients influencing the activity of the cytochrome P-450 enzyme group, which are responsible for metabolism of several cytotoxic agents.

Unfortunately, nutrition of oncological patients by means of natural products may prove insufficient due to abnormalities of appetite, digestion and absorption. Consequently, they often require additional administration of nutritional support.

Table 4. Diagnostic criteria of precachexia, cachexia, and resistant cachexia [23]

Precachexia*	Cachexia**	Resistant cachexia*
1. Unintended loss of body weight not exceeding 5% of basal body weight over past 6 months	1. Unintended loss of body weight >5% of basal body weight over past 6 months	
2. Continuous or periodic anorexia or occurrence of metabolic abnormalities, for example in carbohydrate metabolism	2. BMI <20 kg/m^2 and any degree of weight loss >2%	1. Cachexia
		2. Poor performance status – WHO/ECOG 3 and 4
	3. Sarcopenia and any degree of weight loss >2%	3. Predicted survival <3 months

* Necessary fulfilment of all conditions
** Necessary fulfilment of at least one condition

According to the European Society for Clinical Nutrition and Metabolism (ESPEN), the main methods of nutritional support include enteral nutrition, that is nutrition via the gastrointestinal tract by means of so-called industrial diets administered orally, directly to the stomach or enterally, as well as parenteral nutrition [11,33].

Particular application in oncology is reserved for oral nutritional supplements (ONS), namely industrial diets for oral intake. They ensure the delivery of a sufficient amount of proper nutritional ingredients in a small volume as well as in an easily ingestible and easily absorbable form. Products designed for cancer patients frequently contain increased amounts of protein (15-20%) and supplementation of special substrates (with immunomodulatory properties) – mainly omega-3 fatty acids, but also glutamine, arginine and nucleotides. They are available in powder or liquid form and are commonly used as supplements to the nutrition with natural products.

There is common agreement that despite unquestionable advantages, ONS should not be administered routinely in all cancer patients. Indications for treatment with ONS correspond to ESPEN guidelines concerning the nutritional support in oncology (Table 5) [1,11].

In cases where efficient oral nutrition is impossible, nutrition should be delivered directly to the stomach or to the small intestine via a gastric or jejunal tube or feeding gastrostomy with application of specially prepared industrial diets. However, in cases with contraindications to feeding via the gastrointestinal tract, parenteral nutrition remains the only option. However, commencement of parenteral nutrition should be avoided in terminally ill cancer patients.

PHARMACOTHERAPY SUPPLEMENTING NUTRITIONAL TREATMENT

Multiple agents with a mechanism of action targeted at the underlying pathomechanism of cachexia and CACS are being studied in preclinical animal models and in clinical trials in different phases. There are attempts to exploit the anti-catabolic, anti-anorexigenic, anabolic and anti-inflammatory potential of various novel compounds, described in detail in Table 6 [3,8,9,10,13,18,26,27,36,39,47]. They are innovative tools to counteract cancer-related cachexia, though the majority of them lack sufficient clinical efficacy data justifying their wide application in everyday practice. The attempts to adjust dysfunctional metabolic pathways in cancer patients did not give sufficient clinical results to establish decisive recommendations for treatment or prophylaxis of CACS with any of these compounds. However, it is agreed that combined therapy should be preferred to cover the complex pathogenesis of CACS.

Agents most frequently used in current clinical practice are characterized by prevailing orexigenic activity

Table 5. Indications for nutritional support

Indications for nutritional support in oncology according to ESPEN*
Already existing under nutrition irrespective of stage
Anticipated inability to eat lasting >7 days
Insufficient nutritional intake ensuring <60% of demand for >10 days
Prior to major surgery
- patients with severe nutritional risk (SNR) —> about 10 days of nutritional treatment
- major abdominal surgery and surgery of the neck —> „immunonutrition" (arginine, nucleotides, omega-3 fatty acids) – 5-7 days of treatment continuation

* The European Society for Clinical Nutrition and Metabolism

Table 6. Possible pharmacologic interventions in cancer-related cachexia and anorexia

Agents neutralising metabolic disorders induced by pro-inflammatory cytokines	Anti-cytokine monoclonal antibodies and soluble cytokine receptors (anti-TNF-α, anti-IL-6, anti-IL-1, anti-IFN-γ, IL-1 soluble receptor) Myostatin inhibitors Anti-inflammatory and anabolic cytokines: IL-4, IL-10, IL-12, IL-15
Appetite stimulants	megestrol acetate and medroxyprogesterone acetate, cyproheptadine, cannabinoids, corticosteroids, ghrelin, melanocortin receptor antagonists
Agents with different or complex mode of action	Anabolic steroids – nandrolone, insulin, insulin-like growth factor (IGF-1), β2-adrenoreceptor agonists – formoterol, omega-3 fatty acids, branched chain amino acids (leucine, isoleucine, valine), glutamine, proteasome inhibitors (bortezomib), erythropoietin, creatine, immunomodulatory drugs (thalidomide, lenalidomide), non-steroidal anti-inflammatory drugs, selective cyclooxygenase 2 (COX-2) inhibitors.

(appetite stimulants). The most frequently used agents are synthetic progestins, such as megestrol acetate and medroxyprogesterone acetate [22].

These agents are assumed to effectively stimulate appetite and contribute to the increase of the total body weight in about 20-30% of patients, though mainly through the increase of adipose tissue mass. Unfortunately, there are insufficient data to support their influence on the most important aspect of cachexia, namely the loss of lean body mass. Moreover, until now they have never been proved to improve the prognosis in cancer patients, and their potentially positive influence on the quality of life remains controversial [32].

No precise guidelines concerning the clinical use of metabolic modulators have ever been proposed. When deciding to administer this form of therapy, physicians should consider adverse reactions, especially the increased risk of thromboembolic events. It is even more important because of the prothrombotic propensity accompanying multiple malignancies, particularly those with secondary cachexia (including pancreatic and gastric cancer).

Conclusion

Neoplastic disease, as a generalized multi-organ disease, requires complex multimodal treatment, including special consideration of metabolic and nutritional aspects. It is essential in malignancies irrespective of clinical stage and treatment phase – from diagnosis to palliative care.

The knowledge about the influence of cancer on metabolism and nutrition, as well as about the impact of proper nutrition augmented by targeted pharmacological treatment on the quality of life and prognosis, should urge earlier commencement of proper management.

In view of the increasing burden of cancer in the population, it would be wise to quote the following notion: "*oncological treatment today may allow patients with incurable cancer disease to survive up to a point at which further survival is significantly affected by the nutritional state*" [34].

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