Nutritional Support in Cancer

Topic 26

Module 26.1

Mechanisms of Wasting in Cancer Cachexia

Paula Ravasco

Learning Objectives

- Understanding the pathophysiology of cancer cachexia;
- Recognising the clinical and physical consequences and implications of cachexia;
- Understanding the metabolic pathways underlying cancer wasting and cachexia.

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Key Messages

- Cancer cachexia is a clinical syndrome as yet not totally understood;
- Muscle mass, adipose tissue, energy requirements and metabolic derangements are common;
- Cancer cachexia is associated with physical, symptomatic, metabolic and tumour-associated factors;
- Cachexia is prevalent and has profound adverse effects on patients' Quality of Life and survival;
- Evidence shows the need for the integration of nutrition as part of a team approach for cancer patients' treatment.

1. Malignancy

The word "cancer" is inclusive and comprises a wide range of different types of malignant tumours, which can develop in virtually every body tissue, thus determining diverse clinical manifestations (1). In 2001, the total number of incident cancer cases in Europe, for both men and women, was 1,480,110 with a 5-year prevalence of 4,049,077 (2). Cancer is a major cause of morbidity and mortality, being the second most frequent cause of death worldwide (2, 3). However, the advances in early diagnosis and sophisticated modalities of treatments increase the possibility of cure, or at least prolonged survival. It is thus to be expected that most cancer patients will be ambulatory with the desire for a "good" quality of life; the latter requires patient-centred multiprofessional management in which nutrition plays a central role (4-8).

1.1. The wasting spectrum in cancer

Cancer has been associated with protein-energy malnutrition, or simply malnutrition (9-11) that may evolve to cancer cachexia. Cancer cachexia has been defined as "a multi-factorial syndrome with loss of skeletal muscle mass (with or without loss of fat mass), not fully reversed by conventional nutritional support". It leads to progressive functional impairment. Its pathophysiology is characterized by negative protein and energy balance driven by a variable combination of reduced food intake and abnormal metabolism" (12). A series of studies already conducted in patients with cancer between 1932 and 1974, highlighted the syndrome of nutritional wasting apparently multifactorial in nature (13). Although many studies were undertaken in the early 20th century, publications in 1980s and 1990s showed that cachexia is still an unresolved phenomenon. Indeed, estimates of the prevalence of wasting in specific groups of cancer patients range from 8% to 84%, apparently depending on the cancer site, e.g. 80% in patients with gastrointestinal cancer (9, 14-18) and 70% in patients with head and neck cancer (19-23).

Cancer wasting is generally regarded as a physiological adaptation to stress: the body sacrifices large portions of the muscle mass to spare more immediate critical functions in visceral organs. There are however limitations to this adaptive response: contraction of the skeletal muscle mass leads to muscle weakness, decreased work tolerance and functional capacity (24). On the other hand, the most frequent manifestation of wasting reported by cancer patients is weight loss, which when exceeding 10% is of particular clinical and/or prognostic significance, because weight loss of this magnitude in the setting of any illness may lead to significant increases in morbidity and mortality (24, 25). At least some degree of weight loss has been registered in up to 75% of cancer patients prior to surgery, 57% prior to radiotherapy, 51% prior to chemotherapy, and in 80% of general cancer patients living in the community (25, 26). Despite the suggestion that the presence of nutritional wasting varies according to the cancer's anatomical location, the likelihood that a cancer patient will sustain substantial weight loss is likely to be related also to other factors, e.g. the aggressiveness of the cancer (stage and histological characteristics), anti-neoplastic treatments (radiotherapy, chemotherapy, surgery), age, and intervening emotional factors such as depression (5, 27-30).

2. Tumour burden, metabolic dysfunction and symptoms

Whatever the disease, clinical practice suggests that loss of appetite is probably the most frequent cause of reduced food intake, deriving from both physical and psychosocial problems; hence, anorexia is a common contributor to wasting in cancer (31). Particularly in patients with cancers of the head and neck and of the gastrointestinal tract, due to the mechanical dysfunction or concurrent treatments, the act of eating may incite a variety of adverse symptoms including pain, dysphagia, vomiting, and diarrhoea. Therefore a "voluntary anorexia" develops in which the patients' learned food aversions

are a means of avoiding such symptoms (32). Moreover, food aversions may be present unrelated to any other symptom and even before the establishment of the diagnosis (27). In addition, the tumour mass alone may preclude adequate ingestion of food. The underlying factors contributing to reduced food intake include decreased central drive to eat, chemosensory disturbances (dysguesia and dysosmia), decreased upper gastrointestinal motility (e.g. early satiety, nausea, vomiting) and distal tract dysmotility (diarrhoea, constipation) (26). On the other hand, the emotional adjustment associated with dealing with cancer is *per se* a precipitant of depression and anxiety, which are known contributors to anorexia (33). Of note, different cancer types or locations may display different nutritional patterns (34); wasting and marked nutritional intake deficits have been associated with advanced disease (35, 36) and cancer aggressiveness (28-30); all factors are prone to exacerbate every organ/systemic physiological derangements.

Indeed, although anorexia frequently accompanies cachexia, the drop in caloric intake alone cannot account for the body-composition changes seen in cachexia, and, moreover, cachexia can occur even in the absence of anorexia. Norton et al (37) provided evidence for the parabiotic transfer of cachexia into rats, indicating that cachexia must be mediated at least in part by some circulating factor. Animal models of the condition have suggested several agents that may play a role in the tissue wasting of cachexia: 1) products of host tissues, such as tumour necrosis factor-α (TNF-α), interleukins (IL-1 and IL-6), interferon (IFN-γ), and leukaemia inhibitory factor (LIF); 2) tumour products with a direct catabolic effect on host tissues, such as lipid mobilizing factor (LMF) acting on adipose tissue, and proteolysis-inducing factor (PIF), which acts on skeletal muscle. Although evidence has been presented for circulatory levels of tumour catabolic products in humans, there is less evidence for cytokines. Some studies have shown an elevated TNF-α correlated with advanced disease stage, cancer aggressiveness and increased metabolic rate (38). In addition, some cytokines, such as IL-6, may not be capable of producing cachexia alone. Thus, in a phase I study, patients received between 1 and 10 µg/kg/day of IL-6, but weight loss was not a common side effect; rather, toxicities consisted mainly of flu-like symptoms and fatigue (39). It is possible that tumour catabolic products and cytokines work together, with the former inducing total changes in cytokine production that then contribute to the overall development of cachexia.

2.1. Acute phase response

The acute phase response (APR) refers to various physiologic and metabolic changes in response to tissue injury, infection, or inflammation. Liver protein synthesis shifts from synthesising albumin to producing acute phase proteins such as C-reactive protein (CRP), serum amyloid-A protein, β2-macroglobulin and α-1-antitrypsin. An APR has been associated with more rapid weight loss in patients with lung or pancreatic cancer, as well as in patients with melanoma (40). The presence of APR is also associated with a reduced survival in patients with renal, pancreatic, or colorectal cancer. Additionally, the APR is activated and modulated by cytokines (24). A significant positive association has been found between the severity of APR and serum levels of IL-6 and TNF-α (41). Tumour factors associated with cachexia, such as PIF, activate the transcription factor nuclear factor-kappa B (NF-κB), resulting in increased production of the pro-inflammatory cytokines IL-8, IL-6, and CRP and decreased production of transferring (42). The mechanism by which the APR is related to weight loss and survival in cancer patients is not known, but acute phase proteins have been suggested to scavenge amino acids leading to muscle protein degradation. However, APR alone is not sufficient to produce weight loss. Thus, ciliary neurotrophic factor (CNTF), a member of the IL-6 superfamily, produced profound anorexia and lean tissue wasting, associated with an APR, when administered to mice at the same dose. These results suggest that other factors are involved in the tissue wasting of cachexia.

2.2. Hypermetabolism

Weight loss can occur due to decreased energy intake, increased energy expenditure, or both. As already mentioned, anorexia is common in cancer patients already at diagnosis (32, 43). Yet, in studies of malnourished cancer patients, the measured food intake failed to correlate with the degree of malnutrition. In addition, in cachectic states, nutritional supplementation by either dietary counselling or parenteral nutrition (44), did not counteract the wasting process, even though patients received the adequate energy according to requirements. Weight gain was transitory and due to accumulation of fat and water rather than addition of lean body mass. A similar effect is seen with appetite stimulants, such as Megestrol Acetate and Medroxyprogesterone acetate, acting by downregulating the synthesis and release of pro-inflammatory cytokines. Although these drugs are associated with some weight gain in some patients, body-composition analysis shows that it is due to increased adipose tissue and possibly also increased in body fluid, but not in fat-free mass (45, 46). This suggests that caloric reduction may contribute to loss of adipose tissue, but not to loss of lean body mass, since muscle protein is conserved during prolonged starvation. During the first few days of starvation, glucose utilization by the brain and erythrocytes demands depletion of liver and muscle glycogen stores, and glucose production by the liver is increased via lactate and also gluconeogenic amino acids from muscle. But during prolonged starvation, the brain adapts to use ketone bodies, metabolites of fatty acids, reducing the requirements for glucose and preserving muscle mass. Thus, in anorexia *nervosa*, depletion of adipose tissue exceeds that of lean body mass, whereas in cancer cachexia there is approximately equal loss from both compartments. In addition, when a reduction in lean body mass eventually occurs during starvation, there is loss of visceral mass in proportion to loss of muscle mass, whereas in cachexia there is selective loss of skeletal muscle, with no change in the visceral protein compartment, even when the total weight loss reaches 30% (24). This confirms that loss of skeletal muscle is peculiar to cancer cachexia.

2.3. Wasting, carbohydrate metabolism and energy expenditure

The most commonly altered aspects of carbohydrate metabolism include increased rates of gluconeogenesis and glucose flux, and the development of some degree of impaired insulin secretion as well as insulin insensitivity. The latter induces impaired glucose utilisation in peripheral tissues and glucose intolerance (47). Similar alterations in glucose metabolism are observed in any condition associated with a systemic inflammatory response and are thought to be due to TNF-α (48). These changes contrast with weight loss unrelated to illness or cancer, where insulin sensitivity is maintained (49).

Higher resting energy expenditure (REE) has been observed in patients with lung and pancreatic cancer, whereas patients with gastric and colorectal cancer have shown no increase in REE, despite the presence of weight loss (50, 51). However, since energy expenditure normally decreases with a decrease in food intake, even if there is no increase in REE, this could be considered abnormal in the face of progressive anorexia. In addition, not all changes in energy expenditure are increases in REE. Thus, skeletal muscle of patients with gastrointestinal cancer weight loss showed a fivefold elevation of mRNA levels for the mitochondrial uncoupling protein-3 (UCP-3) *vs* controls and cancer patients with no weight loss, despite the reported lack of an increase in REE. UCP-2 and UCP-3 mRNA expression in muscle is increased by catabolic stimuli, such as denervation atrophy and exercise (52), whereas a very low calorie diet decreased UCP-3 mRNA expression in human adipose tissue, suggesting that it may play a role in the reduction of energy expenditure observed during energy restriction. Changes in UCP expression are also seen in animal models of cachexia and may provide an indication of the mechanisms involved. Increased mRNA content was associated with a twofold increase in fatty acid,

triglyceride, and cholesterol levels. Reduction of hyperlipaemia with nicotinic acid did not reduce UCP-3 expression in muscle. This suggests that circulating fatty acids may be involved in the regulation of UCP-3 gene expression in aerobic muscles during cancer cachexia. Cachexia is thought to be mediated by TNF-α, and rats receiving a single IV injection of TNF-α (100 µg/kg) showed a significant increase in both UCP-2 and UCP-3 in skeletal muscle (53). This suggests that either LMF or TNF-α may be responsible for the elevation in UCP-3 mRNA observed in skeletal muscle of cachectic cancer patients, possibly through elevation of serum lipid levels.

2.4. Wasting, protein metabolism and skeletal muscle

Cachexia is characterized by selective loss of skeletal muscle mass, which can be reduced by 75% when weight loss approaches 30% (54), then close to death. Skeletal muscle is the body compartment where most of the contraction of lean body mass occurs (52). The overriding functional significance of this is underscored by the observation that the extent to which this compartment is diminished correlates with the likelihood of survival (55, 56). Loss of skeletal muscle is characterized by depression in protein synthesis and increased protein breakdown. There are also changes in the concentration of plasma amino acids, and most studies report a decrease in gluconeogenic amino acids, in contrast with severe malnutrition, where the concentration of branched-chain amino acids in plasma is normal or even increased. Protein degradation in muscle results in the release of amino acids, namely alanine and glutamine. The former is channelled to the liver for gluconeogenesis and acute phase proteins' synthesis, whereas glutamine is taken up by tumour cells to sustain energy and nitrogen demands.

The activities of hexokinase, phosphofructokinase, and cytochrome c-oxidase were found to be significantly lower in the skeletal muscle of cancer patients, whereas the activity of glucose-6-phosphate dehydrogenase was significantly higher (47), suggesting impaired energy production, which may account for muscle weakness. Changes in total body protein synthesis are often not observed in weight-losing cancer patients, since hepatic protein synthesis is markedly increased (twofold). However, in weight-losing cancer patients, muscle protein synthesis accounted for only approximately 8% of total body synthesis, compared with 53% of healthy controls (47). A number of studies have reported increased whole body protein turnover, suggesting that degradation rates are also increased. Intracellular protein breakdown is suggested to be due mostly to the ATP-ubiquitindependent proteolytic pathway (57). Intravenous administration of TNF-α, IL-1, and IFN-γ causes increased the expression of ubiquitin transcripts in skeletal muscle, but neither LIF nor IL-6 produces any change in gene expression. No studies demonstrate protein degradation by IL-1 or IFN-γ, but TNF-α has been shown to cause protein loss in murine myotubes (58) and induces red-type muscle tissue catabolism in rats. Thus, of the cytokines, only TNF-α has been demonstrated to induce muscle protein breakdown, although controversial, since *in vivo* studies on cancer patients suggest that TNF-α has no direct metabolic effect on muscle (41, 59).

Low muscle mass in advanced cancer is common frequent, being a predictor of immobility and mortality (60); of note, low muscle mass adversely affects prognosis also in obese patients with advanced pancreatic cancer (61). Sarcopenic patients are at higher risk of increased toxicity of anti-neoplastic treatments (55, 56, 62), requiring smaller doses or delays that may reduce treatment efficacy (55).

2.5. Wasting, lipid metabolism and adipose tissue

Lipids have a high caloric value, and mobilization of lipids is required to meet the increased energy demands of the cachectic patient. In cancer-related wasting, adipose tissue constitutes the major source of energy and a decrease in fat mass may be

observed (11). As much as 85% of adipose tissue may be lost during the cachectic process (63), either through increased lipolysis or decreased lipogenesis.

The net efflux of glycerol and fatty acids from adipose tissue that is observed in cancer wasting appears to be due to at least three factors: 1) increased lipolysis in adipose tissue, apparently mediated by TNF-α and lipid mobilising factor (LMF); 2) a decrease in *de novo* lipogenesis in the adipose tissue, suggested to be mediated by TNF-α and Interleukin-1 (59, 64); and 3) diminished activity of lipoprotein lipase (11). The latter enzyme is necessary for the uptake of fatty acids from circulating lipoproteins and the diminished activity in cancer appears to be mediated by TNF-α, Interleukin-6 and Interferon-γ (11). Although some reports suggest reduced plasma levels of lipoprotein lipase (LPL) in cachectic patients, which is important in triglyceride synthesis, others (65) have found no change in the total LPL enzyme activity or the relative levels of the mRNA for LPL and fatty acid synthase between adipose tissue of cancer patients and controls. However, the latter study did find a twofold increase in the relative level of mRNA for hormone-sensitive lipase involved in the cyclic AMP-dependent lipolytic cascade. Cancer patients have a high turnover of both glycerol and free fatty acids (66), and the elevated mobilization of lipids is often evident before weight loss becomes established. Computed tomography scanning shows intra-abdominal fat in cancer patients to be relatively preserved, compared with the intra-abdominal fat in subjects with anorexia nervosa (67). There is some evidence that fatty acid mobilization may arise, in part, from increased b-adrenergic receptor activity, since oral administration of b-receptor blockers atenolol and propranolol significantly reduced energy expenditure, whole body oxygen uptake, and CO2 production in cancer patients suffering weight loss (68). Patients with weight loss also showed increased levels of plasma and urinary catecholamines, an elevated heart rate, and increased fat oxidation. One of the characteristics of the cytokines TNF-α, IL-6, IL-1, IFN-γ, and LIF is that they inhibit the enzyme LPL (41, 59), thus inhibiting lipogenesis in adipose tissue, although a recent report (69) showed TNF-α to stimulate lipolysis in human adipocytes by activation of mitogen-activated protein kinase (MEK) and extracellular signal-related kinase (ERK) and by an elevation of intracellular cyclic AMP. In contrast, LMF isolated either from a cachexia-inducing murine tumor (MAC16) or from the urine of patients with cancer cachexia directly stimulates lipolysis through interaction with adenylate cyclase in a GTP-dependent process (70).

3. The impact of cancer wasting

Regardless of the underlying mechanisms, cancer-related wasting is multidimensional and worsens patients' well-being (40), tolerance to antineoplastic therapies and prognosis (19, 55, 56, 60). Specifically, weight loss decreases immunological responses to tumour cells (71) and resistance to infection (43), enhances susceptibility to postoperative complications (36, 72), and increases disability and overall cost of care (73). Also, in experimental conditions, both short term starvation (water only) as well as prolonged semi-starvation in healthy volunteers has been reported to reduce physical activity (43, 74, 75). In the landmark semi-starvation study of Keys et al, in which healthy subjects lost 25% of their body weight over 6 months, there was a reduction in both resting energy expenditure and physical activity (76). Feelings of tiredness and lethargy can further contribute to impaired physical activity. Marked decreases in physical activity that occur in severe disease-associated malnutrition may predispose to increased morbidity, in parallel to a reduced capacity to maintain daily activities and undertake work (74). Thus, mental function may be influenced by nutrition in several ways. Starvation and partial food deprivation in adults lead to anxiety, depression and/or other mental changes, which may in part be associated with micronutrient deficiencies. Cognitive function may also be adversely affected. In Keys' et al study, healthy volunteers who underwent partial starvation for 24 weeks, resulting in loss of 25% of body weight had a concomitant increase in their depression score (76).

4. Summary

Cachexia remains a challenging clinical syndrome, the importance of which lies in its prevalence and profound adverse effect on patients' Quality of Life and survival (9, 77, 78). It is now clear that cachexia is not due solely to a nutrient deficit or tumour/host competition for essential nutrients, but to complex metabolic changes in tissues arising from anorexia, tumour progression, systemic inflammation, reduced muscle mass *and* function, tumour catabolic factors, increased by pro-inflammatory cytokines, as well as the psychosocial sequelae. Knowledge of the wasting mechanisms may lead to improved treatments, which hopefully will extend lifespan, as well as improve Quality of Life. It is likely that further developments will concentrate on inhibitors of protein degradation together with protein synthesis stimulation. Inhibition of the increased energy demands will also restore adipose tissue reserves.

Evidence argues for the integration of nutrition as part of a team approach for cancer treatment and patient' management and to recognise the importance and necessity of good nutrition as therapy, strengthening the recognition of patients' rights to adequate nutrition care, mandatory to sustain life throughout the disease journey.

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