Review Article

Adipose Tissue and Cancer Cachexia: What Nurses Need to Know

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ABSTRACT

The purpose of this article is to discuss the different types of adipose tissue involved in cachexia and describe their role in contributing to increased energy expenditure and negative energy balance. Armed with this knowledge, nurses will be better positioned to understand the clinical picture of cachexia, appreciate the rationale for proposed therapeutic interventions, and confidently dialogue with patients, families, and members of interdisciplinary health care teams about this prevalent condition.

Key words: Adipocyte, cachexia, metabolism

Cancer Cachexia

Patients with cancer-associated cachexia present with variable losses of skeletal muscle and adipose tissue.[1,2] The involuntary weight loss and marked depletion of skeletal muscle are highly recognizable in advanced cancer patients who resemble victims of famine.[3,4] In the face of such wasting, nurses may not consider the role of adipose tissue in cancer cachexia. Research demonstrates, however, that adipose tissue contributes to the metabolic dysfunction that occurs in primary cachexia and contributes to its development and progression.[5-8] It is thus important that nurses understand the contributions of adipose tissue to this condition. While pathophysiological processes are taught in nursing curricula, the literature suggests that nurses often lack confidence in both applying their general knowledge of pathophysiology to practice and discussing it with patients or other healthcare providers.[9,10] Cancer cachexia is a complex multifaceted syndrome characterized by a continuum of catabolism of skeletal muscle, loss of adipose tissue, elevated energy expenditure, fatigue, anorexia, reduced muscle strength, and systemic signs of inflammation.[2,11,12] Cachexia affects between 50% and 80% of those with cancer and accounts for one-quarter of all patient deaths.[13] Cachexia's prevalence in oncology populations means that nurses invariably will care for patients affected by it. Most commonly seen in individuals with bowel, liver, stomach, pancreatic, lung, and esophageal malignancies,[14] cachexia reduces quality of life,[15] is a poor prognostic indicator,[16] and negatively impacts the physical and psychosocial well-being of patients and family caregivers.[17-19] It cannot be fully reversed by nutritional support and effective medical or pharmacological interventions for cachexia remain elusive.[20]

Expert consensus definitions of cachexia characterize this syndrome on a three-stage continuum, reflecting variable degrees of weight loss, anorexia, sarcopenia, systemic inflammation, and metabolic derangement.[2] Research has also documented that the extreme muscle

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wasting that occurs in cachexia may be obscured in obese individuals.[21] It is estimated that this state, referred to as sarcopenic obesity impacts one in every four cancer patients with a body mass index >30 kg/m^2 negatively impacting survival,[21] increasing the risk of surgical complications,[22] and chemotherapy toxicity.[23]

Energy Balance, Functions of Adipose Tissue, and Contributions to Cachexia

The concept of energy balance is a critical concept in understanding cancer cachexia. Energy homeostasis is achieved in human beings when there is a balance between energy intake (calories) and expenditure.[24] Excessive caloric intake coupled with insufficient physical activity leads to the storage of extra calories in the form of adipose tissue.[25] Cancer cachexia occurs in the context of a sustained decreased energy intake and increased energy expenditure.[21] Early satiety,[26] chemosensory perturbations,[27] and malabsorption[28] may all contribute to decreased energy intake, while increased energy expenditure is driven by metabolic changes, including elevated energy expenditure, marked catabolism, and inflammation.[1,12]

White Adipose Tissue

Adipose tissue metabolism is highly salient to the pathophysiology of cachexia because of its contribution to metabolic dysfunction.[8] Three types of adipose tissue have been identified. White adipose tissue (WAT) accounts for most of the fatty tissue in humans and is found subcutaneously and intraabdominally.[29] It is composed of single lipid droplets (adipocytes) small numbers of mitochondria, inflammatory cells, immune cells, and fibroblasts.[29,30] WAT stores excess energy as triglycerides and mobilizes lipids through the process of lipolysis.[31,32] In addition to storing energy, white adipocytes synthesize and secrete proteins called adipokines which act both locally and distally, contributing to whole-body lipid metabolism.[32] Research suggests an association between altered adipose tissue secretion of adipokines and cachexia.[33-35]

A detailed examination of adipokines in cancer cachexia is beyond the scope of this paper and has been elegantly described elsewhere.[35] One of the more prominent adipokines, leptin, will be briefly mentioned here as it is representative of the kind of metabolic derangement that occurs in cachexia. Sometimes called the satiating hormone,[37] leptin has major receptors centrally in the hypothalamus and peripherally, in the liver, kidney, pancreas, lung, and skeletal muscle, and bone marrow.[38] It plays a major role in the regulation of body mass, and influences metabolic pathways, including growth hormone signaling, insulin sensitivity, and lipogenesis.[36] Leptin is a key hormone controlling how and when the body stores fat, and during times of starvation, works to prevent fat loss.[36-38] Higher levels of leptin promote the release of fat, increases energy expenditure, and decreases feelings of hunger. Conversely, low levels of leptin promote fat storage, decrease energy expenditure, and increases feelings of hunger.[39] Leptin levels are significantly decreased in cancer cachexia patients compared to both cancer patients without cancer and healthy individuals.[37] Given this feedback loop, we would expect to see increased hunger and decreased energy expenditure in that patients with cachexia with depleted fat stores. Such is not the case, however. Proinflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α,) and interleukin-1 (IL-1) and IL-6 are believed to contribute to this dysregulation.[34,39]

The breakdown of WAT through lipolysis is significant as it may precede the loss of skeletal muscle--an essential feature of consensus definitions of cancer cachexia.[2] Studies in mouse models document the occurrence of lipolysis in animals with tumors early in their disease trajectory that worsens over time and is associated with skeletal muscle atrophy.[39] Penet and Bhujwalla's[40] review of biomarkers and fat loss in cancer cachexia underscores the important role inflammation plays in lipolysis and skeletal muscle degradation. Adipose tissue contains lymphocytes and macrophages, both of which can secrete inflammatory cytokines such as TNF-α and IL-6, suggesting a relationship between lipolysis and increased inflammation.[36,41,42]

Brown Adipose Tissue

Brown adipose tissue (BAT) once thought to be present only in neonates to help maintain normal body temperature outside the womb, has been documented in adults in the supraclavicular region of the neck, and near the aorta.[43] Present in much smaller amounts compared to WAT, BAT is composed of numerous lipid droplets, multiple iron containing mitochondria resulting in its brownish color.[44] Research demonstrates that brown adipose helps regulate glucose balance and insulin sensitivity in both healthy individuals and Type 2 diabetics.[45,46] When activated in response to sustained exposure to cold or β3-adrenergic stimuli BAT burns lipids and glucose resulting in heat production and dissipation through a process known as non-shivering thermogenesis.[47]

In recent decades, a third kind of adipose tissue referred to as "beige," or "brite" (brown-in-white) has been identified.[48,49] Beige adipocytes have been detected in WAT, and can be induced through various genetic and metabolic activators to expend energy like brown adipocytes do through a process known as WAT browning.[49] The reduction of obesity in mice and the presence of lean body mass in humans correlates with brown and beige cell

activity.[50,51] And, because of its therapeutic potential to promote the reduction of body fat, and improve insulin sensitivity in metabolic diseases WAT browning has been heralded as beneficial.[52,53] Its benefits do not hold in the context of cancer cachexia, however. Increased resting energy expenditure has been documented in mouse tumor models and in human studies.[1] WAT browning is implicated in this process, thereby contributing to the development and progression of cachexia and hypercatabolism.[54] The pro-inflammatory cytokine interleukin-6 has been found to play an especially important role in the pathogenesis of WAT browning.[54,55]

Considerations of the role of adipose tissue in cachexia must also include some mention of the role fat is believed to play in fuelling the replication and spread of cancer cells.[56] Paget's[57] "seed and soil" hypothesis likens tumor cells to seeds and the microenvironment within the body and surrounding the tumor as the soil. Tumor cell proliferation and spread reflect that seeds are growing in and spreading to good soil. Cancer cells need an energy source to support their metabolic activity, and lipids produced by adipose tissue provide a potent energy source, creating "suitable soil" within which tumor cells can grow and spread.[57,58]

The literature indicates that adipose tissue can foster the proliferation of melanoma cancer cells and transfer lipids to them, altering their metabolism.[59,60] Lipids from fat cells also serve as significant sources of energy promoting the growth of cancer cells in ovarian,[61] breast,[62] pancreatic,[63] and prostate cancers.[64,65] These sites are located near depots of adipose tissue their proclivity to metastasize may be driven, in part because of proximity to fat stores and the energy they provide.[66] Research aimed at explicating the complex mechanisms underpinning the link between obesity and metastases is ongoing.

Limited Pharmacological Interventions

Because extant evidence is not sufficiently robust, the American Society of Clinical Oncology 2020 evidence-based guidelines do not recommend a pharmacological standard of care for individuals with cachexia.[20] Notable exceptions include the use of megestrol acetate and dexamethasone to stimulate appetite in cachectic patients, though their optimal dosage and duration of administration is not clearly known.[20,67] The cumulative evidence from a systematic review conducted in 2004 by Pascual Lopez and colleagues[68] to assess the efficacy and safety of megestrol acetate in anorexia-cachexia syndrome and a 2013 Cochrane review completed by Ruiz-Garcia *et al*.[69] both reported modest weight gain. Such weight gain is likely composed of fat and water, versus an increase in lean muscle mass, however.[70] Patients taking this medication were at risk of increased death, thromboembolism, and edema[20] underscoring the need for vigilant nursing assessment when administering this medication.

Oral administration of the corticosteroid dexamethasone has been shown to improve appetite and well-being in patients with cachexia, but neither significant increases in weight nor improvements in performance status occurred.[20] Improvements in appetite tend to be time limited, with diminishing effect beyond 4 weeks of administration.[71] There are a host of significant negative side-effects associated with corticosteroid therapy including but not limited to osteoporosis, bone fractures, elevated blood sugar levels, gastrointestinal bleeding, psychiatric disturbances, adrenal suppression, and increased susceptibility to infection.[72-75] Side-effects increase when patients receive this medication long term.[73]

Conclusions

Conceptualizations of adipose tissue as simply a type of connective tissue and storage depot for extra energy have evolved to a fuller appreciation of the role that it plays in regulating metabolic processes and contributing to metabolic dysfunction. Adipose tissue is now understood to be a complex endocrine organ that coordinates numerous biological processes including energy metabolism. Adipose tissue dysfunction can lead to metabolic disruption and systemic disease such as is seen in cancer cachexia. Nurses require a solid appreciation of the contributions of adipose tissue to cachexia. Such understanding provides a foundation from which to better understand this complex syndrome and understand the putative effect of therapeutic interventions.

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Conflicts of interest

There are no conflicts of interest.

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