REVIEW ARTICLE

Cancer cachexia

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ABSTRACT

Cancer cachexia is a wasting syndrome characterized by weight loss, anorexia, asthenia and anemia. The pathogenicity of this syndrome is multifactorial, due to a complex interaction of tumor and host factors. The signs and symptoms of cachexia are considered as the prognostic parameters in cancer patients. This review gives an emphasis on the various mechanisms involved in cachexia and an insight into head and neck cancer cachexia.

Key words: Cachexia, head and neck cancer, tissue wasting, wasting syndrome

INTRODUCTION

Cachexia was described as a syndrome of irreversible wasting in the terminally ill patients. In Greek, 'kakos' means 'bad things,' and hexus, means 'state of being.' It is usually associated with chronic inflammatory conditions and cancer. Cancer cachexia is a multifactorial syndrome characterized by marked loss of body weight, anorexia, asthenia, and anemia; however, in early cases these factors manifest with variable extent.[1-4] It is the most common manifestation of the advanced malignant disease, leading to death. Cachexia is so destructive that it taps into other sources of energy, namely skeletal muscle and adipose tissue when the body senses a lack of nutrition. Nutritional status is compromised in direct response to tumor-induced alterations in the metabolism.^[5] Cachexia adversely affects the patients' ability to fight against infection and withstand treatment by chemotherapy and radiotherapy. As a result of all these negative effects, the body begins to waste away.^[2]

LOSS OF BODY WEIGHT

Weight loss in cancer cachexia and starvation, have different mechanisms. Weight loss in cancer patients is due to equal loss of both adipose tissue and skeletal muscle mass, whereas, in starvation or anorexia nervosa, weight loss is mainly from the fat and only a small amount from the muscle. In starvation, ketone bodies are produced from fat metabolism in the liver, and fat replaces glucose as an energy source and prevents loss

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of muscle mass. Depending upon the tumor type, weight loss occurs in 30 to 80% of cancer patients. Patients with pancreatic or gastric cancer have the highest frequency of weight loss, while patients with non-Hodgkin's lymphoma, breast cancer, acute non-lymphocytic leukemia, and sarcomas have the lowest frequency of weight loss.^[4,5] In head and neck cancer, dysphagia and alteration of taste also play a significant role in weight loss. [6] Weight loss is an important prognostic factor in cancer; the higher the extent of weight loss, the shorter the survival time. Reduction in food intake (>1500 kcal/day), together with a weight loss of 10% or greater and a systemic inflammatory response are considered prognostic parameters. Weight loss and the wasting process cannot be reversed by nutritional supplements in cancer patients. Patients with cancer cachexia die when there is 25 – 30% of total body weight loss, but weight loss alone cannot be a prognostic factor, because it cannot identify the complete effect of cachexia. Proteolysis-inducing factors have been identified, which cause wasting, and increased energy expenditure is also considered as a factor that contributes to the wasting process. [4,7]

ENERGY EXPENDITURE

Energy expenditure is a metabolic calculator determined by three factors: Basal metabolic rate, diet-induced thermogenesis, and physical activity. The best predictor for 24-hour energy expenditure is Resting Energy Expenditure (REE), which can be calculated by indirect calorimetery. It appears that about 70% of the total energy loss in sedantry individuals is from the resting energy expenditure. [8,9] REE in cancer patients varies with the type of malignancy. It is high in lung and pancreatic cancer and there is no increase in gastric and colorectal cancer patients. [7] Two main reasons for alteration REE are the acute phase response (APR) protein and thermogenesis. [10,11] APR is a series of changes in liver protein synthesis, where there is shift from production of albumin to acute phase proteins (APP) like C- reactive protein (CRP), fibrinogen, serum amyloids,

Cancer cachexia Dhanapal, et al. 258

2-macroglobulin, and α -1 antitrypin. In the head and neck squamous cell carcinoma an increase in CRP has been noted in patients with cachexia. [6] These substances are produced in response to tissue injury, infection, or inflammation. Acute phase response enhances the rate of loss of body mass. [10]

Another reason for an increased REE is due to an increased thermogenesis in brown adipose tissue or in skeletal muscle. brown adipose tissue (BAT) is increased in cachetic patients when compared to the age-matched control.[11] Although white adipose tissue acts as a fat store, brown adipose tissue's main function is thermogenesis. Thermogenesis or heat generation is proportional to the oxidation, thus it is related to respiration. Certain coupling (electron transport associated with oxidative phosphorylation) and uncoupling proteins present in the mitochondria are essential for cellular respiration.[12] The uncoupling proteins (UCP) mediate proton leakage across the inner mitochondrial membrane, decreasing the level in coupling of respiration to ADP phosphorylation. Three types of UCPs are identified: UCP1 is found only in brown adipose tissue, UCP2 is found in most of the tissues, and UCP3 is found in brown adipose tissue and muscle.[12] Levels of UPC3 mRNA increase in cancer and they are responsible for the enhanced energy expenditure and increased tissue catabolism. The increase in UCP is also associated with an increase in circulatory fatty acid. It appears that some cytokines and tumor lipid mobilizing factors (LMF) can increase the levels of UCP in both brown adipose tissue and skeletal muscle.[13,14]

ANOREXIA

Anorexia, the loss of desire to eat or loss of appetite, is an important component causing weight loss in cancer cachexia and it is unrelated to the effect of chemotherapy. In patients with cancer-induced anorexia, no beneficial effect is obtained even with food supplementation (increased caloric intake either by the oral route or by parenteral nutrition), and the stoppage of chemotherapeutic drug intake fails to counteract the wasting process. Thus, cancer-induced anorexia is an independent and irreversible process. The aberrant metabolic rate is the direct response by the tumor and the immune system to disrupt the pathways that regulate the homeostatic loop of body-weight regulation.^[15]

Early satiety, that is, feeling full after taking even a small amount of food is reported in cancer patients. It is considered either as a direct effect of the tumors in the gastrointestinal tract (GIT) obstructing the passage of food or due to altered mucosa leading to malabsorption. Cholecystokinin (CCK) was discovered in 1928, as one of the first satiety-inducing peptide in the gut. In addition to inhibiting food intake, CCK stimulates pancreatic secretion, gall bladder contraction, and intestinal motility, but it inhibits gastric mobility. It acts upon the lateral hypothalamus, medial pons, and lateral medulla, which have brain-sensitive CCK sites. CCK receptors are

of two types: CCK-A and CCK-B, which are coupled with G-proteins. CCK-A is involved in satiety and it is found on the afferent vagal neurons that regulate the diet intake. [16] Cholecystokinin administration in cachetic animal models exhibits reduced food intake in comparison to controls. [17] The mRNA levels of cholecystokinin in the hypothalamus is not altered, probably indicating a peripheral role in cachexia. [18]

Cancer patients have decreased taste and smell of food, which may be the effect of the tumors of the GIT or due to psychological depression. In addition, the release of chemicals by the tumor or host immune system may induce anorexia. Neuropeptides and cytokines play an important role in the induction of anorexia. [19]

Anorexia — Role of neuropeptides

Imbalance between orexigenic signals (increase appetite) by neuropeptide Y (NPY) and anorexigenic signals (decrease appetite) by Pro-opiomelanocortin (POMC) play a role in anorexia. NPY neurons increase the parasympathetic output and decrease the resting energy expenditure, whereas, POMC stimulates the sympathetic activity and increases the resting energy expenditure. Tumor products may inhibit NPY transport or release or interfere with the neuronal downstream of NPY. [20] Hypothalamic melanocortin α -MSH (a product of POMC) induces anorexia by activating two distinct melnocortin receptors, Mc3r and Mc4r. In cancer patients with anorexia, the NPY levels are lower than in the controls, and increased CNS melanocortin signaling is observed in cancer anorexia. [20-22]

Anorexia — Role of cytokines

Cancer and inflammation have been linked since the time of Virchow. Cancer cells are capable of producing cytokines constitutively. They may have an autocrine function, supporting tissues such as fibroblasts and blood vessels, thus producing a suitable environment for cancer growth. These cytokines also have an important role in inducing anorexia. [23] Macrophage inhibitory cytokine-1 (MIC-1), a member of the transforming growth factor (TGF) β superfamily, has been implicated in anorexia. Cytokines transport substrates across the blood brain barrier that interact with the brain endothelial cells to release cytokines like TNF- α and IL-1 in the region of the hypothalamus.^[24] In addition, interferon-γ (IFN-γ), produced by activated T and natural killer cells, possesses biological activities that overlap those of TNF-α. Other cytokines such as the leukemia inhibitory factor, transforming growth factor β, IL-1, and IL-6 also mediate anorexia. [6,23,25,26]

ANEMIA

An anemia-inducing substance (AIS) in cancer cachexia had been reported in 1987. [27] It is a substance that made the Red Blood Cells (RBCs) osmotically fragile and decreased

Cancer cachexia Dhanapal, et al. 259

their deformability, in the plasma of the patient with terminal cancer. [28] It is a 50 kD protein secreted by the malignant cells that depresses erythrocyte and immune-competent cell functions. AIS binds to the cell membrane of the RBCs and lowers the glucose influx and pyruvate kinase activity, leading to RBC dysfunction and lysis, which leads to anemia. [29] AIS has been implicated in lipolysis, thus causing weight loss. [30] In addition to anemia the patients with head and neck cancer are severely malnourished. The clinician should also be aware of the re-feeding syndrome, a complication during nutrition supplementing, especially in the head and neck cancer patients. [31]

Treatment

The treatment modalities at present are appetite stimulants, drugs against cachetic signaling molecules, and mediators, which help prevent and treat wasting.^[7] The current trends still under trial are anti-inflammatory antibodies and small anabolic molecules.[32] Counteracting weight loss and anorexia is possible with central and peripheral appetite stimulants and nutritional supplements (omega 3 fatty acids and essential aminoacids). Central appetite stimulant-like megestrol acetate (synthetic progestin) acts on the hypothalamus through the oxygenic signal of neuropeptides Y (NPY). Ghrelin (peripheral agent) is a stomach neuropeptide, which increases the appetite. Resting energy expenditure (REE) is controlled by the reduction of acute phase response (ARP) proteins by the anti-inflammatory agent, ibuprofen. Protein wasting is inhibited by agents such as EPA fatty acid and infliximab (TNF- α inhibitor). In head and neck cancers the cytokine IL-6 has been suggested as a therapeutic target. [33] A combination approach is required for the treatment of cachexia.^[7,32,33]

CONCLUSION

The mechanism involved in cancer cachexia appears to be complex and multifactorial. Although the loss of body weight, anorexia, and anemia, leading to asthenia, characterizes the morbidity status of cancer cachexia, the main cause of death is due to respiratory failure. Many research studies aim to identify modalities to prevent the distressing state of morbidity in cachexia. The new therapeutic agents developed would contribute to improve the quality of life of cancer patients. Care should be taken to avoid the re-feeding syndrome.

REFERENCES

- Bosaeus I, Daneryd P, Svanberg E, Lundholm K. Dietary intake and resting energy expenditure in relation to weight loss in unselected cancer patients. Int J Cancer 2001;93:380-3.
- Theologides A. Cancer cachexia. Cancer 1979;43(5 Suppl):2004-12.
- Argilés JM, Busquets S, García-Martínez C, López-Soriano FJ. Mediators involved in the cancer anorexia-cachexia syndrome: Past, present, and future. Nutrition 2005;21:977-85.
- 4. Fearon KC, Voss AC, Hustead DS; Cancer Cachexia Study

- Group. Definition of cancer cachexia: Effect of weight loss, reduced food intake, and systemic inflammation on functional status and prognosis. Am J Clin Nutr 2006;83:1345-50.
- DeWys WD. Weight loss and nutritional abnormalities in cancer patients: Incidence, severity and significance. In: Calman KC, Fearon KC, editors. *Clinics in Oncology*. Vol. 5, no. 2. London: Saunders, 1986. p. 251-61.
- Richey LM, George JR, Couch ME, Kanapkey BK, Yin X, Cannon T, et al. Defining cancer cachexia in head and neck squamous cell carcinoma. Clin Cancer Res 2007;13:6561-7.
- Tisdale MJ. Mechanism of Cancer Cachexia. Physiol Rev 2009;89:381-410.
- Available from: http://www.rowett.ac.uk/edu_web/sec_pup/energy expenditure.pdf [Last accessed on 2011 March 03].
- Mifflin MD, St Jeor ST, Hill LA, Scott BJ, Daugherty SA, Koh YO. A new predictive equation for resting energy expenditure in healthy individuals. Am J Clin Nutr 1990;51:241-7.
- Falconer JS, Fearon KC, Plester CE, Ross JA, Carter DC. Cytokines, the acute phase response, and resting energy expenditure in cachectic patients with pancreatic cancer. Ann Surg 1994;219:325-31.
- Shellock FG, Riedinger MS, Fishbein MC. Brown adipose tissue in cancer patients: Possible cause of cancer-induced cachexia. J Cancer Res Clin Oncol 1986;111:82-5.
- 12. Robert M. Adipose tissue. In: Malina RM, Bouchard C, Oded Bar-or, editors. Growth, Maturation, and physical activity. 2nd ed. Illinois: Human Kinetics; 2004. p. 163-4.
- 13. Collins P, Bing C, McColloch P, Williams G. Muscle UCP-3 mRNA levels are elevated in weight loss associated with gastrointestinal adenocarcinoma in humans. Br J Cancer 2002;86:372-5.
- Busquets S, Carbo N, Almendro V, Figueras M, Lopez-Soriano FJ, Argiles JM. Hyperlipemia: A role in regulating UCP3 gene expression in skeletal muscle during cancer cachexia? FEBS Lett 2001;505:255-8.
- Ramos EJ, Suzuki S, Marks D, Inui A, Asakawa A, Meguid MM. Cancer anorexia-cachexia syndrome: Cytokines and neuropeptides. Curr Opin Clin Nutr Metab Care 2004;7:427-34.
- Austin J, Marks D. Hormonal regulators of appetite. Int J Pediatr Endocrinol 2009;2009:141753.
- 17. Willis GL, Sleeman M, Smith GC. Facilitation of cancer-associated anorexia by cholecystokinin. Regul Pept 1988;20:119-24.
- 18. Nara-ashizawa N, Tsukada T, Maruyama K, Akiyama Y, Kajimura N, Nagasaki K, *et al.* Hypothalamic appetite-regulating neuropeptide mRNA levels in cachectic nude mice bearing human tumor cells. Metabolism 2001;50:1213-9.
- Ramos EJ, Suzuki S, Marks D, Inui A, Asakawa A, Meguid MM. Cancer anorexia-cachexia syndrome: Cytokines and neuropeptides. Curr Opin Clin Nutr Metab Care 2004;7:427-34.
- Bing C, Taylor S, Tisdale MJ, Williams G. Cachexia in MAC16 adenocarcinoma: Suppression of hunger despite normal regulation of leptin, insulin and hypothalamic neuropeptoide Y. J Neurochem 2001;79:1004-12.
- Wisse BE, Frayo RS, Schwartz MW, Cummings DE. Reversal of cancer anorexia by blockade of central melanocortin receptors in rats. Endocrinology 2001;142:3292-301.
- 22. Inui A. Cancer anorexia-cachexia syndrome: Are neuropeptides the key? Cancer Res 1999;59:4493-501.
- Durham WJ, Dillon EL, Sheffield-Moore M. Inflammatory burden and amino acid metabolism in cancer cachexia. Curr Opin Clin Nutr Metab Care 2009;12:72-7.
- 24. Banks WA. Anorectic effects of calculating cytokines: Role of

Cancer cachexia Dhanapal, et al. 260

- the vascular blood-brain barrier. Nutrition 2001;17:434-7.
- Argilés JM, Busquets S, García-Martínez C, López-Soriano FJ. Mediators involved in the cancer anorexia-cachexia syndrome: Past, present, and future. Nutrition 2005;21:977-85.
- Matthys P, Billiau A. Cytokines and cachexia. Nutrition 1997;13:763-70.
- 27. Ishiko O, Sugawa T, Tatsuta I, Shimura K, Naka K, Deguchi M, et al. Anemia-inducing substance (AIS) in advanced cancer: Inhibitory effect of AIS on the function of erythrocytes and immunocompetent cells. Jpn J Cancer Res 1987;78:596-606.
- 28. Honda K, Ishiko O, Tatsuta I, Deguchi M, Hirai K, Nakata S, *et al.* Anemia-inducing substance from plasma of patients with advanced malignant neoplasms. Cancer Res 1995;55:3623-8.
- Ishiko O, Hirai K, Nishimura S, Sumi T, Honda K, Deguchi M, et al. Elimination of anemia-inducing substance by cyclic plasma perfusion of tumor-bearing rabbits. Clin Cancer Res 1999;5:2660-5.

- 30. Ishiko O, Yasui T, Hirai K, Honda K, Sumi T, Nishimura S, *et al.* Lipolytic activity of anemia-inducing substance from tumor-bearing rabbits. Nutr Cancer 1999;33:201-5.
- Mehanna H, Nankivell PC, Moledina J, Travis J. Refeeding syndrome
 –awareness, prevention and management. Head Neck Oncol 2009;1:4.
- 32. Coss CC, Bohl CE, Dalton JT. Cancer cachexia therapy: A key weapon in the fight against cancer. Curr Opin Clin Nutr Metab Care 2011;14:268-73.
- 33. Richey LM, George JR, Couch ME, Kanapkey BK, Yin X, Cannon T, *et al.* Defining cancer cachexia in head and neck squamous cell carcinoma. Clin Cancer Res 2007;13:6561-7.

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