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Obesity, Cancer and Cachexia

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Abstract

Obesity is a modern times malady of globalized world and it is linked to various types cancer. The cachexia is a multifactorial paraneoplastic disease and it is also associated with obesity and cancer. The main features of cachexia are loss of muscle mass, fat mass, nausea, vomiting, fatigue, increased systemic inflammation and associated involuntary weight loss. This may be described as a result of destructive communication between tumor cells, adipose tissue, skeletal muscle characterized by an inflammatory response by the host against tumor cells and tissues. Due to all these cellular and molecular events, systemic inflammation is considered as a major feature in cachexia progression and maintenance. There are many other primary, secondary and tertiary molecular events and mechanisms are associated with these diseases. In this mini review, we briefly describe the inter relation between obesity, cancer development and cachexia and their therapeutic interventional approaches.

Key words: Obesity, Cachexia, adipose tissue, inflammation.

Introduction

Obesity is a major leading global health problem of 21st century (1). It is also a major causing factor for various diseases, very importantly it is associated with development and metastasis of almost all types of cancer (2). Cancer cells can easily access and get large amount of energy and nutrition from neighboring adipose tissue via blood vessels and small capillaries (3). Obese patients have high risk and more chances of tumor growth, development and metastasis (4). Dysregulated cancer cells release various cellular and molecular factors and these factors will stimulate adipocytes of adiposetissue (5). This will lead to release large amount of energy from stimulated adipocytes in the form of release of fatty acids and glycerol. Unregulated stimulation aids in further progression of tumor growth (3, 4, 5). This will also lead to migration of tumor cells from one organ to other distant organ via blood vessels and this process is called tumor angiogenesis (6). They start growing in newly lodged remote area of the body other than their site of origin. Again, they will start growing bigger and form bigger tumor in new place and this property of cancer cells is better known as tumor metastasis (7). In other words, due to increased tumor burdencancer cells requireeven larger amount energy and nutrition (8). Increased cellular communication between tumor cells and adipose tissuewill results in rapid and continuous lipolysis. Adipocytes willlose all the stored lipids, fats and energy (9). These starved adipose tissues will start losing various structural and functional proteins inside their cells (10). At this stage of the cancer, tumors cells will starts getting energy from other source especially from skeletal muscles of that cancer patient. Finally, even skeletal myocytes will also start undergoing proteolysis resulting in complete loss of both adipose tissue and skeletal muscle (11). This complete loss of adipose tissue

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and skeletal muscle in cancer patient is called cancer cachexia (10,11). Therefore, these cancer cells depend on adipose tissue and skeletal muscle for their growth and nutrition and utilization of complete energy from fat mass and muscle mass leads to cancer cachexia.

The causes and molecular mechanism of cancer cachexia : The exact cause and its molecular mechanism involved in cancer cachexia is still elusive. Available published data from various studies clearly shows that it is a multifactorial disease (12). Primary symptoms of this disease are loss of appetite, body weight, increased energy expenditure and metabolic activity, anorexia with anemia, finally leading to asthenia, characterizes the morbidity status of cancer cachexia (13). Due all these deleterious effects this will proceeds to respiratory failure and myocardial infarction (14).

Adipose tissue breakdown: Adipose tissue breakdown is one of the very important features of cachexia (15). In obesity accumulation of fats and lipids takes place in adipose tissue. In cachectic patients loss of adipose tissue has seen and is primarily due to an increase in lipolytic activity by different enzymes (16). Due to this increased lipolytic activity these cachectic patients immediately lose their adipose tissue mass and shows an increased turnover of glycerol and freefattyacids in blood streamin comparison with cancer patients with no weight loss or healthy subjects with normal weight (17). There are various molecules are involved in adipose tissue breakdown. One of the very important factors involved in cancer cachexia islipid mobilising factor (LMF), which is atumour-secretedcatabolic factor with molecular weight of 43 kDa glycoprotein and it acts directly on the adipose tissue and stimulates the release of free fatty acidsandglycerol (18).

Inflammation: Obesity, cancer, cachexia and inflammation are interdependent relative terms (19). Inflammation plays a major role in all these diseases. Human cachexia shows elevated levels of various inflammatory cytokines such as TNF-α, Interleukin-1, Interleukin-6, IFN-β etc (20). These inflammatory cytokines are produced by cancer cells, adipocytes and skeletal muscle. Therefore, cachectic patients may have deleterious effects from all these cells during the disease progression (21).

Muscle metabolism: Large amount of skeletal muscle loss is one of the very important symptoms of cachectic patients (22). There are numerous cellular signaling pathways plays a major role in activating muscle loss and catabolic activity, this will lead to an increase in whole body protein turnover and protein breakdown (23). Protein catabolic pathways are also associated with muscle loss[24]. Here, both proteasome mediated protein degradation and lysosome meditated protein degradation plays a major role (24). But, due the dysregulation in protein synthetic pathways, synthesis of new functional and structural proteins may not take place in these cachectic patients.

Oxidative stress: Almost all cancer patients at very advanced stage of disease progression shows pathological symptoms such as loss of appetite, nausea and vomiting (25). Due to these symptom cancer patients may lack the supply of very essential nutrients such as glucose, proteins, lipids, vitamins and micro elements. This will lead to the malnutrition state and imbalance in the availability of free radicals and antioxidants (Vitamin A, Vitamin C,Vitamin E, beta-carotene, lycopene, lutein, selenium, manganese)in cachectic cancer patientsbody (26). This will increase the number of free radicalsor free oxygen-containing molecules with an uneven number of electrons in these patients and this will eventually be leading to the accumulation of Reactive oxygen species (ROS) (27). This will again make them easily react with chemicals in the body and cause large number of biochemical reactions and chain of harmful effects. Natural antioxidants which are ingested through the food molecules that can donate electron to a free radical without making themselves unstable (28).

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This will stabilize the free radical and makes them to become less reactive molecules. It is a fact that cachectic cancer patients lack these antioxidants and stabilizing mechanism, thereforeaccumulation of large number of free radicals creating more worsen scenario.

Different stages of Cachexia

Pre-cachexia: Pre-cachexia is an early stage condition of the diseaseand it starts with loss of appetite and thedysregulation is various metabolic activitiesand physical changes with substantial involuntary weight loss (d" 5%).

Cachexia: Cachexia is a middle stage. In this stage, patients have alreadyloss of >5% of their total body weight along with additional loss of 2% body weight and <20 kg/m2 loss of body mass index.

Refractory cachexia: Refractory cachexia is a final stage. In this stage it's very difficult to treat patients, they are not responsive to any treatment options. Symptoms are characterized by low performance status andtheir external appearance looks like almost a walking skeleton and they may have maximum expected survival time of less than 3 months (29).

Prevention and treatment options for cachexia

Nutrition: The role of proper diet and nutritional interventions is very much required, and it is an essential part of prevention and treatment option for cachexia (30).It is very difficult task to treat cachexia by single drug or therapy (31). It can be prevented and treated using a multimodal and multidimensional approach (32). Because, cachexia itself is a pathological condition in which lack of an adequate energy and nutrient supply is exist and malnutrition condition is primary triggering factor for muscle and fat mass loss.Therefore, in this condition muscle mass and fat mass cannot be reversed or increased or stabilized by sudden over or hyper nutrition. Cachexia patients shows symptoms of loss of appetite and reduction in food intake and this can be reversed slowly with beneficial nutrition (31).

Good nutritional supplements with all the essential micro, macro nutrients and carbohydrates, proteins, lipids, vitamins can be provided to cachexia patients and supplementation of these diet should be started very early stage of that patients rather than delayed until at end stage where there is an advanced degree of body weight loss (33,34).Sometime proper diet can become lifesaving elixir for these patients (35). In many cases, these efforts may fail because cachexia is not a simple malnutrition or starvation, it is also associated with tumor cell mediated inflammation and also skeletal muscle and adipose tissue may have lost their biosynthetic capacity along with their mass. Therefore, metabolic modulation of adipose tissue and skeletal muscle function is very much essential (36).

Along with just basic nutrition (carbohydrates, proteins, lipids and vitamins)the nutritional intervention using nutraceuticals, dietary compounds such as Withaferin A, Curcumin, Resveratrol, Quercetin is need of the time to counteract inflammation, proteolysis, apoptosis, necrosis, autophagyand other molecular mechanisms involved in the pathogenesis of cancer cachexia is required (37).

Pharmacologic modulators: Synthetic or natural pharmacological modulators have played a beneficial role in cancer cachectic patients wellness and recovery. These modulators of pharmacologic therapies for cancer cachexia have mainly focused onadipose tissue and skeletal muscle (38). They have been used to improve the appetite, modulating deleterious inflammatory effect and interfering with anabolic and catabolic metabolic pathways which are involved in adipogenesis, skeletal muscle activity (39).

Cachexia is a very complex disease with various mediators and regulators (40). It cannot be cured by a single pharmacological modulator or a method. There are many modulators are available in the market and many modulators are continuously emerging at pre-clinical and clinical experimental level. Therefore, various scientists

and clinicians are trying to include combinatorial integrated approach to treat this disease (38).

Therefore, these pharmacological agents or modulators for the treatment of cancer cachexia can be classified into 4 groups based on their mode of action. They are as follows :(1) Appetite stimulants, (2) Cytokine modulators, (3) Anabolic agents and (4) Combination therapies.

Appetite Stimulants: There are several classes of pharmacological modulators have been studied and used as stimulants of appetite. So that to make cachexia patients canshowmore desire for food and eat more food. The best-established appetite modulators include various hormones such progestogens, megestrol, medroxy progesterone acetate, corticosteroids, ghrelin, circadian rhythm associated melatonin, erythropoietin, metoclopramide, dronabinol, fish oil, interferon, non-steroidal anti-inflammatories, nandrolone, antidepressants such as mirtazepine, atypical antipsychotics such as olanzapine, Anamorelin, Cannabis Sativa, Nabilone and many more (41).

Cytokine modulators: The cytokines are a broad category of small proteins with molecular weight ranges from ~5-20 kDa that are important in cell-cell communications and cell signaling. These small proteins play a very critical role in orchestrating and perpetuating inflammation in many diseases including obesity, cancer and cachexia. The specific cytokine and chemokine modulators are now used in the treatment of obesity, cancer and cachexia. These cytokine modulators include Etanercept, Infliximab, Pentoxifylline and Thalidomide.These cytokine modulators are known to increase the patients body weight and muscle mass (42).

Anabolic agents: Anabolic modulators include various chemicals, very importantly steroids. These steroids mimics human androgens. They also known more properly asanabolic-androgenic steroids (AAS). They include natural androgens (testosterone)and synthetic androgens (17á-alkylated androgens, 1-methyl androgens, and nandrolone and its derivatives). These synthetic anabolic agents are structurally related and have similar effects ofnatural testosterone. Other non-steroidal anabolic agents include peptide hormone Insulin. Insulin also increases muscle mass and body weight (43).

Combination treatments : Here combination of various agents was used to treat cancer cachexia, so that overall quality and lifestylewill be modified for betterment of these patients. Example thalidomide + cinobufagin, Megestrol Acetate + Thalidomide etc (44).

Physical exercise : Physical exercise improves overall health of normal people as well as cancer associated cachexia patients. Therefore, it is very important to include physical exercise along with dietary and nutritional interventions approaches in the treatment option, increased physical activity and exercise with lifestyle modification has been proposed as another crucial component of the multidimensional approach to treat cancer cachexiapatients (45,46).

Physical exercises have lot of beneficial effects and it plays very important role in converting white adipose tissue (WAT) to brown adipose tissue (BAT) and they improve the overall health by suppressing adipose tissue inflammation and other associated factors in cachexia patients (47). Exercise also decreases overall adipose tissue mass but aids in sustaining and building new skeletal muscle mass by increasing adiponectin and other adipokines (48). Exercise also prevents damage of cells from oxidative stress (49). Therefore, cancer cachexia patients also get these benefits from regular exercise. Physical activity is also very effective in improving cachexia and cancer survivors overall health.

Conclusion

Cachexia is a very serious health condition which disturbs these patients in many ways including physically, emotionally and mentally and it is also a severe, life threatening and limiting

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complication (50). Passive loss of stored fat and muscle mass due to rapid growth of tumor and its metastasis is a major culprit (51). Along with this the secondary effect of these tumor burden include loss of appetite, nausea, vomiting may also play a big role in this complication (52). Therefore, this disease is a complex multifactorial disorder with numerous drivers involved in the development and progression. The complex associationof obesity, cancer and cachexia and related events are illustrated in the Fig. 1. These metabolic events includeunrestrained lipolysis, increased energy expenditure due to WAT to beige and BAT expansion and activation (48,49). It is very clear that all these molecular events are caused by rapid division of tumor cells and demonic growth of these tumor cells.Tumor cells eternal desire for energy and nutrition and their requirement of large quantity of biomolecules makes cancer cachectic patients to lose adipose tissue and muscle mass (53). To better understand the cross talk between obesity, cancer and cachexia there is an urgent need of more and more advanced research with the identification of unknown factors which plays major role in these diseases (54). Therefore, new studies will in turn aidin development of therapeutic interventions and to improve the quality of life from this deadly health condition. Overall, the hard-gained knowledge of pathophysiology of obesity and cancer associated cachexiamay provide novel therapeutic targets and optionsto ameliorate from obesity, cancer and cachexia and their metabolic complications.

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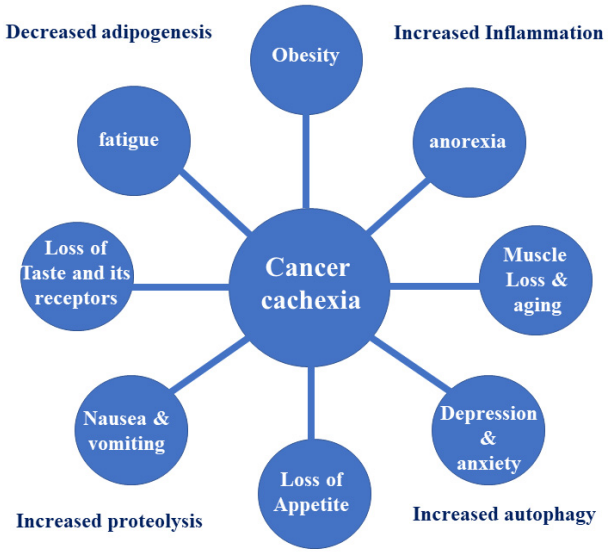

Figure 1: The complex symptoms and mechanisms of cancer cachexia

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