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Review

A new look at an old drug for the treatment of cancer cachexia: Megestrol acetate

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SUMMARY

Cachexia is a multiorganic syndrome associated with cancer, characterized by body weight loss, muscle and adipose tissue wasting and inflammation, being often associated with anorexia. The aim of the present review is to examine the impact of megestrol acetate in the treatment of cancer cachexia, both at the biochemical and physiological level taking into account new experimental data related to protein muscle metabolism. Based on experimental evidence, it is concluded that megestrol acetate is a good candidate for muscle wasting treatment and future studies addressed at the interaction between the drug and protein turnover in human skeletal muscle should be performed.

1. Introduction: wasting in cancer: the cachexia definition

Cachexia – from the Greek: "kakos" and "hexis", meaning "bad condition" – is a multiorganic syndrome associated with cancer, characterized by body weight loss (at least 5%), muscle and adipose tissue wasting and inflammation, being often associated with anorexia.[1] The abnormalities associated with cachexia include alterations in carbohydrate, lipid and protein metabolism.[2] Cachexia occurs in the majority of terminal cancer patients, and it is responsible for the deaths of 22% of cancer patients.[3] In addition, survival of patients affected by different types of neoplasias is clearly dependent on the presence of weight loss.[4] Therefore, cachexia represents an important factor in the treatment of a cancer patient, affecting not only survival, but also the efficacy of anticancer treatment, quality of life and, ultimately, sanitary costs. It is thus clear that there is both a medical and a social need for the treatment of cancer cachexia. According to an international consensus[1]: "cachexia, is a complex metabolic syndrome associated with underlying illness and characterized by loss of muscle with or without loss of fat mass. The prominent clinical feature of cachexia is weight loss in adults (corrected for fluid retention) or growth failure in children (excluding endocrine disorders). Anorexia, inflammation, insulin resistance and increased muscle protein breakdown are frequently associated with cachexia. Cachexia is distinct from starvation, age-related loss of muscle mass, primary depression, malabsorption and hyperthyroidism and is associated with increased morbidity".[1] Similar definitions have been recently published.[5,6] Fearon et al.[7] describe cancer cachexia as a "multifactorial syndrome defined by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment. Its pathophysiology is characterised by a negative protein and energy balance, driven by a variable combination of reduced food intake and abnormal metabolism". The diagnostic criterion for cachexia was: weight loss greater than 5%, or weight loss greater than 2% in individuals already showing depletion, according to current body weight and height (body mass index (BMI) <20 kg/m^2 or skeletal muscle mass (sarcopenia)). The same consensus group reached the conclusion that the cachexia syndrome develops progressively through various stages: pre-cachexia to cachexia to refractory cachexia (Table 1).[7]

In spite of the different definitions, the staging of cancer cachexia patients is not an easy task. Several malnutrition screening tools are available including the Patient-Generated Subjective Global Assessment (PG-SGA) developed by Ottery.[8] This tool has two sections – a medical history section that is completed by the patient, and a physical assessment section that is completed by nursing, medical, or dietetic staff. The medical history section includes additional questions regarding the presence of oncology nutrition impact symptoms. A simpler assessment tool is the

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Table 1
Characteristics of the main studies included in this review.

Study	Type of patient	Observed effects	References
Clinical Trial	Cancer (advanced)	Increased appetite/caloric intake Improved nutritional status	[20–23]
Clinical Trial	AIDS (wasting)	Increased appetite, weight gain Increased lean body mass	[27]
Clinical Trial	Cancer (advanced)	Improved sense of appetite Moderate weight gain	[25]
Clinical Trial	Cancer (advanced)	Weight gain Increased fat mass/oedema	[28]
Clinical Trial	Cancer (advanced)	Appetite stimulant	[30,31]
Clinical Trial	Cancer (advanced)	Increased appetite, weight gain Improved QoL	[33]
Clinical Trial	Cancer	Amelioration of cachexia/anorexia Symptoms. No effect on survival	[34,35]
Clinical Trial	Cancer	Improvement of appetite under radiation therapy	[36]
Pre-clinical	Healthy	Increased food and water intake Increased hypothalamic NPY	[26]
Pre-clinical	Cancer	Increased food intake and body weight Increased muscle mass and grip force Increased physical activity Decreased muscle proteolysis	[46]
Pre-clinical	Cancer	Increased food intake and body weight Increased muscle protein synthesis Increased muscle amino acid uptake	[47]

Malnutrition Screening Tool (MST).[9] However, none of these tools include any biochemical, inflammatory or immunological measurements. Very recently, the so-called Cachexia Score (CASCO) has been introduced.[10] The aim of the score is to overcome the problem of patient staging. This score considers five main different factors: body weight and lean body mass loss, anorexia, inflammatory, immunological and metabolic disturbances, physical performance and quality of life. The score's scale goes from 0 to 100: mild cachexia (less than 25), moderate (more than 26 and less than 50), severe (more than 51 and less than 75) and terminal phase (more than 76 and up to 100). The score also takes into consideration the condition known as precachexia.

2. Pathophysiological mechanisms

In clinical terms, anorexia means decreased appetite resulting in decreased food intake, fatigue, changes in body image and weight loss. In addition to anorexia, cachexia includes asthenia, anaemia and loss of fat tissue and skeletal muscle, associated with abnormalities in protein, lipid and carbohydrate metabolism.[11]

Although a recent study involving 1853 cancer patients,[12] did not find common genetic causes in appetite loss in cancer patients, cytokines, neuroendocrine changes and tumour mediators are the main signals involved in appetite depression in cachexia.[13] Additional factors contributing to the anorectic state are: altered taste perception, therapy-induced side effects, depressed motor activity, possible mechanical interference on the gastrointestinal tract and, of course, psychological factors. Indeed, patients with cachexia often experience psychological distress as a result of the uncertainties of the disease, its diagnosis, its treatment, and its anticipated and final outcome. This psychological state, which often involves depression, is bound to affect food intake. Although anorexia represents a very important factor in the development of cachexia, it has to be pointed out that in many cases the use of total parenteral nutrition does not stop the loss of body weight.[13] It seems, therefore, quite evident that metabolic disturbances present in the patient (increased energy inefficiency, insulin resistance and abnormal carbohydrate metabolism, adipose tissue dissolution and hypertriglyceridemia, and muscle wasting) have a definitive role in the development of cachexia.[2] Different mediators are involved in the metabolic disturbances, cytokines playing a major role.[14]

Although cancer cachexia is a multiorganic syndrome involving many organs and tissue including liver, heart and fat, skeletal muscle tissue is perhaps the most significant cachexia target since this tissue alone represents over 40% of total body weight. At the level of skeletal muscle, data from our laboratory have clearly shown that during muscle wasting three main processes are activated: (a) DNA fragmentation or apoptosis, (b) myofibrillar protein degradation (activation of the ubiquitin–proteasome-dependent proteolytic pathway), and (c) increased uncoupling protein (UCPs) production.[15] Indeed, different pathological conditions are associated with increases in muscle UCP2 and UCP3. In the particular case of UCP3, this protein has been related with both energetic inefficiency and protection against oxidative damage.[16] The three events are not only interrelated but also coordinated. Lack of muscle regeneration is also involved in muscle wasting during cancer.[17]

3. Cancer cachexia treatment

Although a plethora of treatments for the cachectic syndrome have been proposed, unfortunately, not a single one is completely satisfactory in reversing weight loss. Bearing in mind the fact that both anorexia and metabolic disturbances are involved in the pathophysiology of the cachectic syndrome, the development of different therapeutic strategies has focused on these two factors. Several pharmacological and nutritional approaches have been used. The ideal candidate for an anticachectic drug would be a compound able to increase food intake and also improve muscle weight, which is the main component of the cachectic syndrome.

Unfortunately, nutritional strategies are not sufficient to reverse the cachectic syndrome. Indeed, patients on total parenteral nutrition are still subject to significant wasting, therefore emphasizing the role of the metabolic abnormalities in cachexia. It is perhaps for this reason that any therapeutic approach based on increasing food intake has to be combined with a pharmacological strategy to counteract metabolic changes. Another important problem associated with the design of the ideal therapeutic approach is that no definite mediators of cachexia have been yet identified. Both tumoural and humoural (mainly cytokines) factors seem to be involved and, therefore, it is doubtful that a simple drug may block the complex syndrome. In addition, some of the