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Treatment of cachexia: An overview of recent developments ☆

Stephan von Haehling [a,b,*], Stefan D. Anker [a]

[a] Division of Innovative Clinical Trials, Department of Cardiology and Pneumology, University Medical Centre Göttingen, Göttingen, Germany
[b] Applied Cachexia Research, Department of Cardiology, Charité Medical School, Campus Virchow-Klinikum, Berlin, Germany

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ABSTRACT

Body wasting in the context of chronic illness is associated with reduced quality of life and impaired survival. Recent clinical trials have investigated different approaches to improve patients' skeletal muscle mass and strength, exercise capacity, and survival in the context of cachexia and body wasting, many of them in patients with cancer. The aim of this article is to summarise clinical trials published over the last two years. Therapeutic approaches discussed here include appetite stimulants like megestrol acetate, L-carnitine, or melatonin, anti-inflammatory drugs like thalidomide, pentoxyphylline, or a monoclonal antibody against interleukin-1α as well as ghrelin and the ghrelin agonist anamorelin, nutritional support, and anabolics like enobosarm and testosterone.

1. Introduction

Changes in body composition that occur with chronic diseases are usually considered unwanted and are associated with loss of skeletal muscle mass, fat mass, or both [1,2]. The loss of lean and fat tissue may in turn be associated with weight loss. Such involuntary weight loss has been termed *cachexia*. Much confusion exists with regard to the different terminologies [3]. A recent consensus definition suggests diagnosing cachexia when there is loss of more than 5% of body weight over 12 months or less in the presence of a chronic illness such as heart failure, chronic obstructive pulmonary disease (COPD), chronic kidney disease, or cancer [4], altogether providing the basis for an estimated 9 million subjects being affected by cachexia in industrialized countries alone [5]. The mere loss of skeletal muscle mass in the limbs that exceeds two standard deviations of the mean of a healthy young reference population has been termed *sarcopenia* [6–8]. Some researchers have suggested to restrict the use of the term sarcopenia to apparently healthy elderly subjects who lose muscle mass as a consequence of the ageing process. In the context of chronic illness, the terms muscle wasting, myopenia, or even muscle wasting disease have been used or proposed [7,9,10]. In contrast to cachexia, sarcopenia and muscle wasting are not usually associated with weight loss, but with reduced exercise capacity and reduced quality of life [11]. Whilst the development of cachexia is mostly associated with impaired survival, the development of sarcopenia can be associated with poor survival as well. The two conditions have seen much attention in recent years, first, with regard to their definition [4,6], second, with regard to their pathophysiology [12–14], and third, with regard to their treatment [15,16]. In fact, pathophysiological pathways of the two clinical entities can, but do not necessarily have to overlap. For clinicians actively involved in the care of patients at risk of cachexia or muscle wasting, *i.e.* surgeons, oncologists, nephrologists, cardiologists, and many more, the available terms often create more confusion than help, making the diagnosis of cachexia and muscle wasting a rarity [17]. This is unfortunate, in particular because both require medical attention, and treatment approaches are currently underway that will hopefully enable physicians to maintain their patients' muscle mass and body weight and therefore their ability to maintain activities of daily living for longer than is currently possible. The aim of this article is to highlight clinical intervention trials that have been published over the last 2 years with the primary purpose of treating cachexia. Studies that have shown beneficial results in animal experiments only using approaches such as myostatin blockade [18], use of green tea [19], ursodeoxycholic acid [20], or inhibition of nuclear factor-κB [21] are not discussed.

2. Appetite stimulants

Loss of appetite appears in many patients with cancer, which is not only frequent, but also associated with poor prognosis and reduced quality of life. The origin of appetite loss has been deemed multifactorial, and a recent study failed to show a genetic association of appetite loss in patients with cancer [22]. However, overexpression of pro-inflammatory cytokines like interleukin-1, interleukin-6, tumour necrosis factor, or interferon-γ as well as macrophage inhibitory cytokine-1/growth differentiation factor 15 (MIC-1/GDF-15) appears to be involved [23,24]. Activation of these factors has effects on peripheral (lipolysis, proteolysis, insulin resistance) as well as on central pathways

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* Corresponding author at: Division of Innovative Clinical Trials, Department of Cardiology and Pneumology, University Medicine Centre Göttingen, Robert-Koch-Str. 40, 37075 Göttingen, Germany.
E-mail address: stephan.von.haehling@web.de (S. von Haehling).

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Table 1
Cachexia intervention trials published between 2012 and 2014.

Reference	Study design	Disease	Number of patients[a]	Duration	Intervention groups	Main results
Appetite stimulation						
Wen et al. [27]	Single centre, randomised, controlled, open-label	Cancer with loss of 5% of body weight	102 (93)	8 weeks	(1) Megestrol acetate 160 mg twice daily p.o. plus thalidomide 50 mg twice daily p.o. (2) Megestrol acetate 160 mg twice daily p.o.	Increases in body weight, quality of life, appetite, and grip strength. Increases in body weight and appetite.
Greig et al. [28]	Single centre, non-randomised, uncontrolled, open-label	Cancer	13 (7)	8 weeks	Formoterol 80 μg/day p.o. plus megestrol acetate 480 mg/day p.o.	Six responders with an increase in quadriceps volume; trend for increases in quadriceps and handgrip strength.
Maddedu et al. [30]	Single centre, randomised, controlled, open-label	Cancer with weight loss 5%	60	4 months	(1) L-Carnitine 4 g/day p.o. plus celecoxib 300 mg/day p.o. (2) L-Carnitine 4 g/day p.o. plus celecoxib 300 mg/day p.o. plus megestrol acetate 320 mg/day p.o.	Increases in lean body mass and 6-minute walk distance. No significant difference between the two groups.
Kraft et al. [31]	Multi centre, randomised, placebo-controlled, double-blind	Advanced pancreatic cancer	72 (26)	12 weeks	(1) L-Carnitine 4 g/day p.o. (2) Placebo	Weight gain due to increases in body cell mass and body fat. No effect.
Cuvelier et al. [32]	Single centre, randomised, placebo-controlled, double-blind	Cancer with weight loss ≥5%	26 children	90 days	(1) Megestrol acetate suspension 7.5 mg/kg/day p.o. (2) Placebo	Increases in body weight, body mass index, and mid upper arm circumference. Weight loss.
Del Fabbro et al. [34]	Single centre, randomised, placebo-controlled, double-blind	Cancer with weight loss ≥5%	73 (48)	28 days	(1) Melatonin 20 mg at bedtime p.o. (2) Placebo	Terminated early for futility.
Inflammation						
Hong et al. [35]	Single centre, non-randomised, uncontrolled, open-label	Cancer	52 (42)	8 weeks	Monoclonal anti-interleukin-1α antibody (MABp1) 3.75 mg/kg IV	Decrease in serum interleukin-6, increase lean body mass, partial response in 1 of 34, stable disease in 10 of 34 patients.
Yennurajalingam et al. [38]	Single centre, randomised, placebo-controlled, double-blind	Cancer with weight loss ≥5%	31 (21)	14 days	(1) Thalidomide 100 mg/day p.o. (2) Placebo	Decrease and fat mass and fat-free mass. No effect.
Davis et al. [39]	Single centre, non-randomised,	Cancer	35	14 days	Thalidomide 50 mg po at bedtime, up-titrated to	Improvments in appetite, insomnia, and quality of

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