International Journal of Nutrology
(Official Journal of the ABRAN - Brazilian Association of Nutrology)

REVIEW ARTICLE

DOI: 10.54448/ijn26108

Drug therapy in cancer cachexia: how to manage patient based on evidence

Patrícia Alves de Oliveira Ferreira Sbragi[1,*]

[1]USP - University of São Paulo. Cancer Institute of the State of São Paulo, Faculty of Medicine, São Paulo, Brazil.

***Corresponding author:** Patrícia Alves de Oliveira Ferreira Sbragi.
USP - University of São Paulo. Cancer Institute of the State of São Paulo, Faculty of Medicine, São Paulo, Brazil.
E-mail: paty_medd@hotmail.com
DOI: https://doi.org/10.54448/ijn26108
Received: 10-04-2025; Revised: 12-05-2025; Accepted: 01-27-2026; Published: 02-12-2026; IJN-id: 26108

Editor: Dr Eemaz Nathaniel, MBBS.

Abstract

Cancer cachexia is a multifactorial disorder characterized by malnutrition associated to chronic disease with loss of body weight with specific losses of skeletal muscle and adipose tissue. Patients presents with elevated energy expenditure, excess catabolism, lipolysis, proteolysis, insulin resistance, less glucose uptake and reduced appetite secondary metabolic changes and inflammation due to cytokines released by tumor cells Cachexia leads to progressive functional impairment, treatment related complications, poor quality of life and more mortality. It has been estimated that up to 10-20% cancer patients die due to consequences of malnutrition rather than for the tumor itself. Despite the severity of this condition, cancer cachexia remains underdiagnosed and undertreated, and most patients don't have a nutritional monitoring. Generally, they are forwarded to a professional nutrition specialist in more advanced stages of diseases or refractory cachexia. Unfortunately, at this moment the reversal of muscle waist and all symptoms related to cachexia are irreversible. Therefore, is fundamental to identify early and manage patients in stages as pre cachexia and cachexia with aim of avoid muscle loss, attenuate symptoms related to cachexia and therefore bring better quality of life and oncologic treatment results. In this review, we have the intention to outline the drug therapies for cancer cachexia based on evidence and what in fact can show better results in the management of this complex multifactorial syndrome.

Keywords: Cancer. Cachexia. Muscle loss. Anorexia. Appetite. Weight loss.

Introduction

Cachexia is a syndrome that present with complex metabolic abnormalities caused by underlying disease and characterized by loss of skeletal muscle mass with or without loss of fat mass and represents one end of a broad spectrum of nutritional abnormalities observed in the cancer patient **[1,2]**.

The term cachexia is derived from the Greek words kakos, meaning "bad" and hexis, meaning "condition" **[3]**. It is associated with reduced physical function **[1]** reduced tolerance to anticancer therapy **[4]** and reduced survival **[5]**. Weight loss in patients with cancer is rarely recognized, assessed, or managed actively **[6]**. The importance of gross cachexia as a major factor contributing to the morbidity and mortality of cancer patients is clearly established **[7]**.

In advanced cancer patients, cancer cachexia affects the life quality of 50 to 80% patients and is responsible for 20% of deaths **[7]**. However, recent data also point to an association between even minor weight loss and a shortened duration of survival **[7]**. The overall prevalence of low muscle mass is >50% in people with newly diagnosed cancer, which is considerably higher than the approximately 15% prevalence in healthy individuals of similar age (median 65 years old) **[6]**. Decreased skeletal muscle mass, muscle strength and function have been reported to have adverse effects on QOL and life expectancy **[7-8]**.

In this review, it was aimed to present the intention was to outline the pharmacological therapies for cancer cachexia-related symptoms, such as weight gain, increased appetite, better quality of life, and muscle gain ,based on evidence, in cancer patients with cachexia.

Definition of Cachexia

Since the 90's cachexia has been received several definitions. In late 2006, Evans et al. classified cachexia as a syndrome that present with complex metabolic abnormalities caused by underlying disease and is characterized by loss of skeletal muscle with or without loss of fat mass **[1]**. In 2011, Fearon et al. defined cachexia as weight loss of 5% or more within 6 months, weight loss of 2% or more in patients with a body mass index (BMI)< 20% **[9]**.

In 2017, the European Society of Clinical Nutrition and Metabolism (ESPEN) synonymous cachexia with "chronic disease-associated malnutrition with inflammation in its first guideline on nutrition in cancer patient **[10]**. In 2018, a new criterion for cachexia specific to advanced cancer has been proposed **[11]**. This criterion is called cachexia staging score (CSS) and includes weight loss in 6 months (0–3 points), SARC-F (a screening tool for sarcopenia, 0–3 points), ECOG-PS (0–2 points), appetite loss (0– 2 points), and abnormal biochemistry (0–2 points), and thus it consists of five items (total of 12 points) **[11]**. Patients were classified into the four groups according to CSS (noncachexia (0–2 points), pre-cachexia (3–4 points), cachexia (5–8 points), and refractory cachexia (9–12 points). Subjects with more advanced cachexia stages had lower skeletal muscle index, higher prevalence of sarcopenia, more severe symptom burden, poorer QOL, and shorter length of survival **[11]**.

In 2020, The American Society of Clinical Oncology (ASCO) published a guideline for management of cancer cachexia **[12]**. In 2021, the European Society of Medical Oncology (ESMO) issued clinical practice guidelines for patients with cancer cachexia **[13]**. In the same year, the European Society of Clinical Nutrition and Metabolism (ESPEN) published its second guideline on nutrition in cancer patient **[14]**. The evolution of cachexia classification and guidelines are represented in Figure 1.

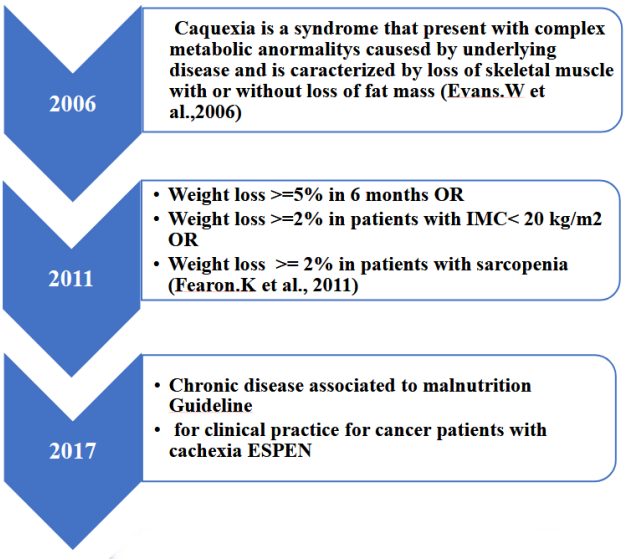

Figure 1. The evolution of cachexia classification and guidelines. Source: Own authorship.

Pharmacological Therapies for Cancer Cachexia

Omega-3 fatty acids

EPA (eicosapentenoic acid) and DHA (docosapentaenoic acid) are incorporated in the blood and tissues, and they mediate several biological effects. They are involved in membrane organization, elasticity, ion permeability (including receptors, transporters, signaling proteins and lipids mediators with less inflammatory and pro-resolving activity **[15-17]**.

This anti-inflammatory action has been evaluated for several studies and its impact in weight gain, appetite, quality of life and muscle gain in cancer patients with cachexia. One of the first studies, Bruera et al. **[18]**, randomized sixty patents to ômega-3 fatty acid versus placebo and evaluated appetite, fatigue, nutritional functional status and nausea. Patients were evaluated in day one and 14. The study was negative for all end points evaluated. Fearon et al. **[19]**, in the same year, in randomize double- blind trial enrolled 200 patients to receive 2.2 g EPA in the experimental group versus placebo. There were a significant association between supplementation and weight gain and increase in muscle mass in the experimental group in the correlation analysis.

Colomer et al. **[20]**, in a systematic review with eight studies evaluated weight gain, appetite and quality of life in patients with advanced cancer. Patients received EPA dosage greater than or equal to 1,5 grams/day in eight weeks. The systematic review was positive for all end points evaluated. However, the weight gain and quality of life had more studies to analyze these outcomes. Eight of eight studies included in the review evaluate weight gain and seven of eight evaluate quality of life. The others end points were

evaluated in a small number of studies in the systematic review.

Other systematic review with ten studies and 383 patients receiving chemotherapy and/or radiotherapy, Chua et al. **[21]** evaluated weight gain, inflammatory status, peripheral neuropathy, quality of life and others end points in patients that received EPA with or without DHA. Patients received EPA 600 mg a 3,6 g/day with or without DHA from one to 12 weeks. The incorporation of EPA and/or DHA resulted in weight maintenance or gain, modification in body composition with less muscle mass loss, reduction in inflammation, lower oxidative status and improve in quality of life.

Castro et al. **[22]**, in a systematic review and meta-analysis with six studies evaluated weight and inflammatory biomarkers and conclude that wasn't change in inflammatory biomarkers in the group of omega-3 fatty acid but there was a trend in terms of weight gain. A recent meta-analysis with advanced non-small cell lung cancer patients with six studies and 354 patients evaluated change in weight as first end point and muscle mass and quality of life as secondary end points demonstrating a weight gain, better quality of life. The study was negative for muscle gain. The summary of the results of studies can be seen in Table 1.

Table 1. Summary of the results of studies.

Authors/ Variables	Appetite	Weight gain	QOL	Muscle mass	Inflammatory biomarkers
Bruera et al. 2003 (RT)	No difference	No difference	No difference	Not evaluated	Not evaluated
Coloner et al. 2007 (RT)	positive*	positive	positive	Not evaluated	Positive
Silva et al. 2015 (review)	Heterogneous Results	Positive or stabilization	positive	Reuction in both groups (less for ômega-3)	Positive
Castro et al. 2022	Not evaluated	Tendency to gain **	Not evaluated	Not evaluated	Negative
Chua et al. 2024 (review)	Not evaluated	positive	positive	Negative	Not evaluated

*Just two studies of review evaluated appetite
**Just to studies of review evaluated weight gain
RT: randomized trial.

Beta-hydroxy-beta-methylbutyrate -HMB

Several pathways have been proposed to explain the effects of HMB on muscle health, which includes both an increase in muscle protein synthesis and a decrease in muscle protein breakdown. HMB stimulates muscle protein synthesis by activating the mechanistic target of the rapamycin(mTOR) system and the growth hormone/insulin like growth hormone factor axis **[23,24]**.

May et al. **[25]** evaluated HMB associated with arginine and glutamine in patients with colon cancer stage IV. Patients that received the supplementation presented muscle mass gain. In a phase III trial, 472 patients with lose weight between two and ten percent were randomized to receive HMB, glutamine and arginine versus placebo twice a day for eight weeks. These patients were evaluated to muscle mass as primary end point and quality of life and weight as secondary end point.

Berk et al. **[26]**, found no difference in the end points analyzed but author highlighted that study had great following up fail and others bias that may be influenced in the results. In 2019, Bear et al. **[27]**, accomplished a systematic review with meta-analysis with 15 studies with various pathologies that evaluated lean mass as primary end point and weight gain as secondary end point. The study showed a trend to weight gain and positive to lean mass increase but the size of gain was small. However, only two of 15 studies had cancer patients and only one study was included in the metanalysis. This study evaluated hand grip and found a positive correlation.

A multicenter, randomized controlled phase II trial evaluated muscle mass in 38 patients with advanced non-small cell cancer. The results of trial were negative with the controlled group presenting more muscle mass gain than experimental group **[28]**.

Prado et al. **[29]**, in a systematic review with 15 studies that included six randomized trial, and nine no randomized studies evaluated HMB supplement (HMB/Arg/Gln) or HMB-enriched ONS in cancer patients with cachexia. Supplementation time varied from 10 days to eight weeks. Four randomized trials and four no randomized trials evaluated muscle mass, and three randomized trials showed muscle mass gain. There was gain in muscle function in the follow up of no randomized trials and in one randomized trial . The force reduction was smaller in hand grip in the experimental group in randomized trial and in no randomized trials there was a increase in muscle function. The summary of the results of studies can be seen in Table 2.

Table 2. The summary of the results of studies.

Authors/ Variables	Weight gain	QOL	Muscle mass	Hand grip
May et al. 2002 (RT)	positive	No difference	positive	Not evaluated
Berk et al. 2008 (RT)	negative	negative	negative	Not evaluated
Bear et al. 2019 (review)	negative	Not evaluated	Positive*	positive
Pascoe et al. 2021 (RT)	Not evaluated	Negative	negative	negative
Prado et al. 2022 (review)	Heterogeneous results	Heterogeneous results	positive	positive

RT: randomized trial
*small gain size

Anamorelin

Anamorelin is a oral ghrelin mimetic and selective agonist that exert its action at the ghrelin receptor. In

December 2020, anamorelin 100 mg has been approved for CACS in Japan, largely based on its positive effect on patients' weight observed in phase II trials; however, anamorelin has not been approved in the United States or Europe, with the Committee for Medicinal Products for Human Use noting its limited effect on lean body mass and no proven impact on hand grip strength or quality of life; additionally, its safety data was inadequately recorded **[30]**. A multicentric phase III trial with non-small-cell lung cancer and cachexia (ROMANA 1 and ROMANA 2), patients were randomized to anamorelin 100 mg versus placebo. The primary end point evaluated lean mass and handgrip. The secondaries end points were weight and cachexia related symptoms. The study was positive for lean mass gain but not handgrip. The study too was positive for weight gain, cachexia related symptoms except for fatigue that didn't show significative difference between both groups. There was no difference in terms of collateral effects. The effect most common was hyperglycemia grade three and four **[31]**.

A systematic review with meta-analysis with seven studies which patients received 50 and 100 mg anamorelin showed weight gain with moderate evidence degree, tendency to lean mass gain and no benefit to hand grip and overall survive. The result to appetite was heterogenous with increased appetite for dose of 100 mg and negative for 50 mg **[32]**. The summary of the results of studies can be seen in Table 3.

Table 3. The summary of the results of studies.

Authors/ Variables	Appetite	Weight gain	QOL	Muscle mass	Hand grip
Temel et al. 2016 (RT) (ROMANA 1)	Not evaluated	Positive	Positive	Positive	Negative
Temel et al. 2016 (RT) (ROMANA 2)	Not evaluated	Positive	Positive	Positive	Negative
Taniguch et al. 2023 (review)	Heterogeneous results	Positive	positive	Positive	Negative

*RT: randomized trial

Megestrol Acetate

In 1993, megestrol had been approved in FDA to anorexia treatment and weight loss in HIV patients. The mechanism that promotes increased appetite is unknown **[33]**. Randomized study with 122 patients with sarcoma, lung cancer and head and neck cancer patients evaluated patients in two moments. In first analysis, patients received megestrol in dose of 160 mg and 320 mg for 30 days and there was increased appetite in both dosages with more increase in doses of 320 mg but without statistical significance and there was trend favoring higher dose for weight gain, not statistical significative. In second analysis, patients that didn't present weight gain or presented weight stabilization without increased appetite with initial dosages after three months were randomized to higher doses. There was more percentage of weight gain and increased appetite with higher dosages but without statistical significance.

In accordance with previous studies Feliu et al. **[34]**, Tchekmedyian et al. **[35]** and Loprinizi et al. **[36]** the most of patients will respond to dosage of 160 mg. A small portion of patients can respond to higher dosages. The study suggests that climbing dosages is the best way to administered efficacy and collaterals effects and doses above 480 mg may not be useful to the symptoms control **[33]**.

Pascual López et a al. **[37]** in a systematic review evaluate weight gain, appetite and quality of life in patients with HIV, cancer and other pathologies. Megestrol versus placebo was evaluated in 19 studies and showed a not statistical significance tendency in weight gain for higher doses of megestrol in oncologic patients. Appetite and quality of life too presented weight gain for patients that received megestrol.

Ruiz-García et al. **[38]** performed a systematic review with HIV, cancer patients and other pathologies in 2005, 2013 and 2018 with slight weight gain in megestrol group versus placebo. However, the weight gain was not clinically relevant. There wasn't difference in collateral effects between megestrol and placebo in the first two reviews, but the latest one showed more collateral effects in megestrol group.

In 2022, Lim Y et al. **[39]** found different results in a systematic review and metanalysis that included eight studies with only cancer patients and the analysis was divided between two groups: minor dose (for those that received until 320 mg) and higher dose (for those that received dose above 320 mg). The results for weight gain were negative. Patients who received high dose megestrol tended to have weight loss rather than weight gain.

These contradictory results may have been possible due to Garcia et al systematic review have been included other pathologies and not just oncologic patients and for not had included other studies published after like a Currow et al. **[40]**, a randomized study that compared mesgestrol versus placebo versus dexamethasone and was negative for weight gain. The same negative results for weight gain were seen in Telebi. et al. **[41]** review with 13 randomized trials. However, a linear dose–response meta-analysis indicated that each 200-mg/day increment in MA consumption had a significant increase in weight gain. This study showed a better quality of life with a low evidence level. This result for

quality of life was the opposite found by Lim et al., [39]. The summary of the results of studies can be seen in Table 4.

Table 4. The summary of the results of studies.

Authors/Variables	Weight gain	Appetite	QOL	Colateral effects	Higher versus low
Gebbia et al. 1996 (RTC)	Positive	Positive	Not evaluated	Similar high versus low doses	Positive
López et al. 2004 (review)	Positive	Positive	Positive	Similar high versus low doses	Positive **
Garcia et al. 2005 Garcia et al. 2013 Garcia et al. 2018 (review)	Positive	Positive	Negative	Versus placebo positive *	Not evaluated
Lim et al. 2022 (review)	Negative	Negative	Negative	Positive (more thromboembolic risk)	negative
Telebi et al. 2024 (review)	Negative	Negative	Positive	Not evaluated	Negative

* In first two review there wasn't difference between placebo and megestrol group in terms of collateral effects. In the latest review there was more collateral effects in megestrol group compared to placebo but there wasn't difference when megestrol was compared to other drugs or different dosages (higher versus low).
** Study included diseases other than cancer like HIV, nervous anorexia and degenerative diseases. RT: randomized trial.

Corticoesteroid

Bruera et al. [42] conducted a randomized study with 40 terminal cancer patients and evaluated methylprednisolone 32 mg versus placebo for 14 days and found increased appetite, better pain control and diary activity. Popiela et al. [43] evaluated methylprednisolone in 173 patients with terminal cancer for eight weeks and found significative improvement in quality of life in the experimental group versus placebo. There were more gastrointestinal and cardiovascular events in the corticoid group, but the severity of these events was similar in both groups.

Willox et al. [44] evaluated prednisolone for two weeks in a randomized study with 41 cancer patients. There was increased appetite in patients that received corticoid but no weight gain. Della Cuna et al. [45], found better quality of life, in a randomized trial with terminal cancer patient, who received methylprednisolone for eight weeks. In systematic review with 55 randomized studies Yavuzsen et al. [46], evaluated several drugs in cancer patients and found two drugs that presented evidence for the anorexia treatment: corticosteroid and progestines. Corticoesteroid increased well-being, appetite and less chemotherapy collateral effect.

A randomized double-blind study with 84 patients with advanced cancer that received dexamethasone 4 mg for two weeks, there was improvement of fatigue, better quality of life, less anorexia. The frequency of adverse effects was similar in both groups [47]. The summary of the results of studies can be seen in Table 5.

Table5: The summary of the results of studies.

Authors/Variables	Apettite	Weight gain	QOL	Colateral effects
Popiela et al. 1989 (RT)	Not evaluated	Not evaluated	Positive	More for corticoid group
Willox et al. 1984 (RT)	Positive	Similar	Tendency to better	Not evaluated
Bruera et al. 1985 (RT)	Positive	Not evaluated	Positive	No severe toxicity
Della Cuna et al. 1989 (RT)	Not evaluated	Not evaluated	Positive	Not evaluated
Yavuzsen et al. 2005 (RT)	Positive	Positive NES*	Positive	Not evaluated
Yennurajalingam et al. 2013 (RT)	Positive	Positive	Positive	Similar

RT:randomized trial
*NES: Not statistic significative

Megestrol versus Corticosteroid

Two randomized studies evaluated the direct comparison between megestrol and corticosteroid. Loprinizi et al. [48] evaluated dexamethasone 0,75 mg versus megestrol 800 mg versus fluoxymesterone 10mg twice a day in cancer patients with cachexia. The primary end point was weight gain and toxicity. The secondary end point was appetite. Megestrol and dexamethasone had similar increased appetite with a non-statistical trend favor to megestrol. Fluoxymesterone was inferior. In terms of toxicity, dexamethasone presented more discontinuity treatment rate and megestrol more thromboembolic events rate.

Currow et al. [49] evaluated, in a randomized trial, megestrol acetate 480 mg versus dexamethasone 4 mg/day for treatment of symptomatic anorexia in people with advanced cancer and there was little difference in appetite, weight gain and quality of life. The study couldn't define one standard medication to treat anorexia in advanced cancer. The summary of the results of studies can be seen in Table 6.

Table 6. The summary of the results of studies.

Authors/Variables	Appetite	Weight gain	QOL	Collateral effects
Currow et al. 2021 (RT)	Similar	Similar	Similar	Similar
Loprinizi et al. 1999 (RT)	Similar (1)	Similar	Note evaluated	More thromboembolic events to megestrol and more rate of descontinuity to dexamethasone

(1) Trend favoring megestrol.
RT: randomized trial.

Esteroids

As far as we know we didn't find many studies the evaluate steroids for treatment of cachexia in cancer. One randomized trial evaluated nandrolone decanoate and other enobosarm in this context. A randomized trial evaluates non-small lung cancer patients that received 200 mg nandrolone decanoate once per week for four weeks versus placebo. There was a tendency to a weight loss less severe to nandrolone group. However, a half patient in this group lose weight [50].

Dobs et al. [51] evaluated enobosarm for muscle loss and physical function. Patients were randomized to receive enobosarm 1 mg versus 3 mg versus placebo for 113 days. The primary end point was muscle mass and secondaries end points were weight gain, appetite, quality of life and physical function. This was the first trial to evaluate the efficacy of one selective androgen receptor modulator. The study showed significative lean mass gain and better physical function that was evaluated in a stair climbing test. However, there wasn't alteration in hand grip test. The author highlighted that the study presented some limitations as heterogeneous group of tumors, patients in different time of treatment and small sample. The summary of the results of studies can be seen in Table 7.

Table 7. The summary of the results of studies.

Authors/Variables	Appetite	Weight gain	Hand grip	Muscle mass	Collateral effects
Chlebowski et al. 1986 (review)	Not evaluated	Tendency towards Less severe weight loss	Not evaluated	Not evaluated	Not evaluated
Dobis et al. 2013 (review)	negative	negative	Negative	Positive**	similar

*More than half of patients lost weight in both groups.
**Lean mass gain wasnt accompanied by handgrip improvement.

Mirtazapine

Mirtazapine is a noradrenergic and specific serotonergic antidepressant that has been used in the management of several symptoms in cancer patients [52]. As an antidepressant, mirtazapine use is associated with more appetite stimulation and weight gain when compared to other antidepressants [53]. Phase II study evaluated mirtazapine 15-30 mg/day for eight weeks in 17 advanced cancer patients with cachexia. 24% of patients had weight gain and increased appetite and one maintained weight. The study concluded that mirtazapine is a promised drug for treatment of cachexia [54]. Hunter et al., evaluated, in a randomized study with 120 patients, mirtazapine 15 mg once day for eight weeks versus placebo and there wasn't difference in appetite between groups. Patients that received mirtazapine presented more drowsiness e less depression been considered one option for patients that present depression and insomnia in oncologic treatment [55]. The summary of the results of studies can be seen in Table 8.

Table 8. The summary of the results of studies.

Authors/Variables	Appetite	Weight gain	QOL	Colateral effects
Riechelmann et al. 2009 (RT)	positive	positive	Not evaluated	Not evaluated
Hunter et al. 2021 (RT)	Not evaluated	Similar	Not evaluated	Inrcreased drowsiness and less depression

RT: randomized trial.

Olanzapine

Olanzapine is a antipsychotic that blockade various neurotransmitters as dopamine, serotonin, catecholamines, acetylcholine and histamine. Phase II study evaluated weight gain, appetite and quality of life in 80 patients with advanced cancer to receive megestrol 800 mg/day versus olanzapine 5mg/day plus megestrol for eight weeks. The association of megestrol and olanzapine showed more weight gain and increased appetite than megestrol alone, been a reasonable association for cachexia treatment. The improvement in nausea and vomiting and quality of life was bigger for combination [56].

In 2020, the same author evaluated 30 patients to receive olanzapine 5 mg versus placebo for seven days and the group that received olanzapine presented with less nausea and vomiting and increased appetite and well-being [57]. Naing et al. [58] evaluated weight gain, in randomized trial, with 39 patients that received olanzapine in doses that varied from 2,5 mg to 20 mg. Treatment results in modes effect on weight gain, not statistical significative.

A review with seven studies investigated the effect and tolerability of olanzapine in doses of 2.5, 5, and 7.5 mg in 14 patients with advanced cancer. Overall, improvements were observed in functional status including sleep, appetite, and well-being. One limitation of this pilot study was a lack of control group and small sample size, but this study provided a positive result for further investigation on the use of olanzapine for this indication. Low dose olanzapine (2.5-5 mg once daily) may be useful in the treatment of cachexia for increasing appetite, reducing nausea and vomiting, and promoting weight gain. Further large-scale multi-center randomized placebo-controlled studies will be necessary to investigate the impact of olanzapine on weight change in patients with cachexia [59]. The summary of the results of studies can be seen in Table 9.

Table 9. The summary of the results of studies.

Authors/Variables	Appetite	Weight gain	QOL	Collateral effects
Navari et al. 2010 (RT)	Positive to olanzapin plus megestrol	Positive to olanzapin plus megestrol	Positive to olanzapin plus megestrol	Less nausea and vomiting to olanzapine and megestrol
Naing et al. 2015 (RT)	Not evaluated	Postive*	Not evaluated	Not evaluated
Navari et al. 2020 (RT)	Positive	Not evaluated	Not evaluated	Less nausea and vomiting
Poon et al. 2024 (review)	Positive	Positive	Not evaluated	Not evaluated

*Modest gain not statistically significative. RT: Randomized trial.

Cannabis

A randomized phase III study with 164 patients evaluated cannabis plus THC (tetrahydrocannabinol)

versus THC versus placebo and didn't find difference between groups for appetite, quality of life and toxicity **[60]**. Other randomized study evaluated dronabinol versus megestrol versus association of megestrol and dronabinol in patients with cachexia. The megestrol group presented more increased appetite and weight gain compared to group that received combination or dronabinol alone **[61]**.

Brisbois et al. **[62]** evaluated chemossensorial perception of food in patients that received THC 2,5 mg per twice a day versus placebo for 18 days. In the group of THC, there was more intake of proteins and better quality of sleep. Simon et al., evaluated increased appetite, weight gain, quality of life in patients that received cannabinoid in a systematic review and meta-analysis with ten studies. There wasn't weight gain, increased appetite or better quality of life in cannabinoid group **[63]**. The summary of the results of studies can be seen in Table 10.

Table 10. The summary of the results of studies.

Authors/Variables	Appetite	Weight gain	QOL	Collateral effects
Strasser et al. 2006 (review)	similar	Not evaluated	similar	similar
Jatoi et al. 2002 (review)	negative	negative	Not evaluated	Not evaluated
Brisbois et al. 2011 (review)	Positive*	Not evaluated	similar	similar
Simon et al. 2021 (review)	Negative	Negative	Negative	Not evaluated

* Chemosensory perception and food tasted better was superior for the cannabinoid group.

Discussion

There are many studies that evaluate weight loss, appetite, quality of life, collateral effects but many of these studies don't evaluate muscle mass loss and its function or the number of patients in the trials is small, being necessary studies with a bigger sample. The importance of muscle mass for better outcomes and less toxicity in oncologic treatment is already well known and overall survival is prolonged for patients that have muscle mass loss attenuated during treatment **[12-16]**.

Omega 3 fatty acid seems to be an option for patients, in terms of, maintaining or gain weight and quality of life with a tendency to muscle mass gain that need to be better evaluated in prospective studies. Corticosteroids promotes better quality of life and appetite improvement, being an option for patients with prejudice of this. Not all studies evaluated weight gain but there is a tendency to gain and positive results in some studies. Megestrol can be an option for weight gain, increased appetite and quality of life **[15-17, 33-36, 42,43]** .

The gain of weight is due to gain of fat mass and not muscle mass. And increased dose of megestrol can be an option for patients that don't respond to low dose being necessary to climb dose to find better results, despite, the most of patients will respond to smaller doses. Doses above 480 mg don't seem to bring better results. HMB seems to be associated to muscle mass gain but prospective studies with bigger size is needed to evaluate better its function in oncologic patients. It can be an option for selected patients **[23-25]**.

Olanzapine can be an option to increased appetite and with positive results or tendency to positive results to weight gain and can reduce nauseas and vomiting. It's association with megestrol can be an option too **[56-58]**. Mirtazapine showed positive results in increased appetite and weight gain with collateral effects as drowsiness and less depression. It can be an option for patients with insomnia and depression **[52-54]**. Cannabis didn't show positive results in most studies it terms of weight gain, increased appetite and better quality of life and don't must be used routinely in this context **[60,61]**.

Anamorelin showed versus placebo better quality of life, weight gain and muscle mass gain but without positive result in handgrip. Can be an option to patients but it is just available in Japan. The more evidence of positive outcomes in terms of weight gain, increased appetite and better quality of life with more representativity in controlled trial with largest samples seems to be for corticosteroids and megestrol. Some studies showed more collateral events for these drugs in comparison to placebo but not associated with more deaths **[30,31]**.

Conclusion

It was concluded that knowing how to manage patients with cachexia is fundamental for better results in oncologic patients. Estimates show that 20% of these patients don't die because of diseases and, in fact, because they didn't receive adequate nutrition support and didn't have health support and wright follow up the pre-cachexia and cachexia phase. More drugs need to be studied in this context, mainly by evaluating muscle mass gain and its function.

CRediT

Author contributions: Conceptualization, data curation, formal analysis, investigation, methodology, project administration, supervision, writing - original draft, and writing-review & editing- Patrícia Alves de Oliveira Ferreira Sbragi.

Acknowledgment

Not applicable.

Ethical Approval

Not applicable.

Informed Consent

Not applicable.

Funding

Not applicable.

Data Sharing Statement

No additional data are available

Conflict of Interest

The authors declare no conflict of interest.

Similarity Check

It was applied by Ithenticate®.

Application of Artificial Intelligence (AI)

Not applicable.

Peer Review Process

It was performed.

About The License©

References

1. Evans WJ, Morley JE, Argilés J, Bales C, Baracos V, Guttridge D, Jatoi A, Kalantar-Zadeh K, Lochs H, Mantovani G, Marks D, Mitch WE, Muscaritoli M, Najand A, Ponikowski P, Rossi Fanelli F, Schambelan M, Schols A, Schuster M, Thomas D, Wolfe R, Anker SD. Cachexia: a new definition. Clin Nutr. 2008 Dec;27(6):793-9.
2. Moses AWG, Slater C, Preston T, Barber MD, Fearon KCH. Reduced total energy expenditure and physical activity in cachectic patients with pancreatic cancer can be modulated by an energy and protein dense oral supplement enriched with n-3 fatty acids. Br J Cancer 2004; 90: 996–1002.
3. Muscaritoli M, Anker SD, Argilés J, Aversa Z, Bauer JM, Biolo G, Boirie Y, Bosaeus I, Cederholm T, Costelli P et al. Consensus definition of sarcopenia, cachexia and pre-cachexia: Joint document elaborated by Special Interest Groups (SIG) "cachexia-anorexia in chronic wasting diseases" and "nutrition in geriatrics". Clin. Nutr. 2010, 29, 154–159.
4. Bachmann J, Heiligensetzer M, Krakowski-Roosen H, Büchler MW, Friess H, Martignoni ME. Cachexia worsens prognosis in patients with resectable pancreatic cancer. J Gastrointest Surg 2008; 12: 1193–201.
5. Dewys WD, Begg C, Lavin PT, et al. Prognostic effect of weight loss prior to chemotherapy in cancer patients. Eastern Cooperative Oncology Group. Am J Med 1980; 69: 491–97.
6. Fearon KCH, Voss AC, Hustead DS, on behalf of the Cancer Cachexia Study Group. Defi nition of cancer cachexia: eff ect of weight loss, reduced food intake and systemic inflammation on functional status and prognosis. Am J Clin Nutr 2006; 83: 1345–50.
7. Warren S. The immediate causes of death in cancer. Am J Med Sci 1932; 184:610616.
8. Inagaki J, Rodriguez V, Bodey GP. Causes of death in cancer patients. Cancer 1974; 33:568-573.
9. Bazzan AJ, Newberg AB, Cho WC, Monti DA. Diet and nutrition in cancer survivorship and palliative care. Evid Based Complement Alternat Med. 2013;2013:917647.
10. von Haehling S, Morley JE, Anker SD. An overview of sarcopenia: facts and numbers on prevalence and clinical impact. J Cachexia Sarcopenia Muscle 2010;1: 129–133.
11. Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, Jatoi A, Loprinzi C, MacDonald N, Mantovani G et al. Definition and classification of cancer cachexia: An international consensus. Lancet Oncol. 2011, 12, 489–495.
12. Cederholm T, Barazzoni R, Austin P, Ballmer P, Biolo G, Bischoff S, Compher C, Correia I, Higashiguchi T, Holst M et al. ESPEN guidelines on definitions and terminology of clinical nutrition. Clin. Nutr. 2017, 36, 49–64.
13. Zhou T, Wang B, Liu H, Yang K, Thapa S, Zhang H, Li L, Yu S. Development and validation of a clinically applicable score to classify cachexia stages in advanced cancer patients. J. Cachex-Sarcopenia Muscle 2018, 9, 306–314.
14. Roeland EJ, Bohlke K, Baracos VE, Bruera E, Del Fabbro E, Dixon S, Fallon M, Herrstedt J, Lau H, Platek M, Rugo HS, Schnipper HH, Smith TJ, Tan W, Loprinzi CL. Management of Cancer Cachexia: ASCO Guideline. J Clin Oncol. 2020 Jul 20;38(21):2438-2453.
15. Arends J, Strasser F, Gonella S, Solheim TS, Madeddu C, Ravasco P, Buonaccorso L, de van der Schueren MAE, Baldwin C, Chasen M, Ripamonti CI; ESMO Guidelines Committee.

Electronic address: clinicalguidelines@esmo.org. Cancer cachexia in adult patients: ESMO Clinical Practice Guidelines☆. ESMO Open. 2021 Jun;6(3):100092. doi: 10.1016/j.esmoop.2021.100092.

16. Muscaritoli M, Arends J, Bachmann P, Baracos V, Barthelemy N, Bertz H, Bozzetti F, Hütterer E, Isenring E, Kaasa S, Krznaric Z, Laird B, Larsson M, Laviano A, Mühlebach S, Oldervoll L, Ravasco P, Solheim TS, Strasser F, de van der Schueren M, Preiser JC, Bischoff SC. ESPEN practical guideline: Clinical Nutrition in cancer. Clin Nutr. 2021 May;40(5):2898-2913.
17. Calder PC, Deckelbaum RJ. Omega-3 fatty acids: time to get the messages right! Curr Opin Clin Nutr Metab Care. 2008 Mar;11(2):91-3.
18. Bruera E, Strasser F, Palmer JL, Willey J, Calder K, Amyotte G, Baracos V. Effect of fish oil on appetite and other symptoms in patients with advanced cancer and anorexia/cachexia: a double-blind, placebo-controlled study. J Clin Oncol. 2003 Jan 1;21(1):129-34.
19. Fearon KC, Von Meyenfeldt MF, Moses AG, Van Geenen R, Roy A, Gouma DJ, Giacosa A, Van Gossum A, Bauer J, Barber MD, Aaronson NK, Voss AC, Tisdale MJ. Effect of a protein and energy dense N-3 fatty acid enriched oral supplement on loss of weight and lean tissue in cancer cachexia: a randomised double-blind trial. Gut. 2003 Oct;52(10):1479-86.
20. Colomer R, Moreno-Nogueira JM, García-Luna PP, García-Peris P, García-de-Lorenzo A, Zarazaga A, Quecedo L, del Llano J, Usán L, Casimiro C. N-3 fatty acids, cancer and cachexia: a systematic review of the literature. Br J Nutr. 2007 May;97(5):823-31.
21. Chua AV Jr, Hernandez ARB, Mendoza MJL, San Juan MD. Omega-3 Fatty Acids Increase Weight and Quality of Life Scores in Patients With Advanced Non-Small Cell Lung Cancer and Cancer Cachexia: A Meta-Analysis. Integr Cancer Ther. 2024 Jan-Dec;23:15347354241275052.
22. de Castro GS, Andrade MF, Pinto FCS, Faiad JZ, Seelaender M. Omega-3 Fatty Acid Supplementation and Its Impact on Systemic Inflammation and Body Weight in Patients With Cancer Cachexia-A Systematic Review and Meta-Analysis. Front Nutr. 2022 Jan 31;8:797513.
23. Wilkinson DJ, Hossain T, Hill DS, Phillips BE, Crossland H, Williams J, et al. Effects of leucine and its metabolite β-hydroxyβ-methylbutyrate on human skeletal muscle protein metabolism. J Physiol 2013; 591:2911–2923.
24. Eley HL, Russell ST, Baxter JH, Mukerji P, Tisdale MJ. Signaling pathways initiated by β-hydroxy-β-methylbutyrate to attenuate the depression of protein synthesis in skeletal muscle in response to cachectic stimuli. Am J Physiol Endocrinol Metab 2007;293:923–931.
25. May PE, Barber A, D'Olimpio JT, Hourihane A, Abumrad NN. Reversal of cancer-related wasting using oral supplementation with a combination of beta-hydroxy-beta-methylbutyrate, arginine, and glutamine. Am J Surg. 2002 Apr;183(4):471-9.
26. Berk L, James J, Schwartz A, Hug E, Mahadevan A, Samuels M, Kachnic L; RTOG. A randomized, double-blind, placebo-controlled trial of a beta-hydroxyl beta-methyl butyrate, glutamine, and arginine mixture for the treatment of cancer cachexia (RTOG 0122). Support Care Cancer. 2008 Oct;16(10):1179-88.
27. Bear DE, Langan A, Dimidi E, Wandrag L, Harridge SDR, Hart N, Connolly B, Whelan K. β-Hydroxy-β-methylbutyrate and its impact on skeletal muscle mass and physical function in clinical practice: a systematic review and meta-analysis. Am J Clin Nutr. 2019 Apr 1;109(4):1119-1132.
28. Pascoe J, Jackson A, Gaskell C, Gaunt C, Thompson J, Billingham L, Steven N. Beta-hydroxy beta methylbutyrate/ arginine/ glutamine (HMB/Arg/Gln) supplementation to improve the management of cachexia in patients with advanced lung cancer: an open-label, multicentre, randomised, controlled phase II trial (NOURISH). BMC Cancer. 2021 Jul 12;21(1):800.
29. Prado CM, Orsso CE, Pereira SL, Atherton PJ, Deutz NEP. Effects of β-hydroxy β-methylbutyrate (HMB) supplementation on muscle mass, function, and other outcomes in patients with cancer: a systematic review. J Cachexia Sarcopenia Muscle. 2022 Jun;13(3):1623-1641.
30. Wakabayashi H, Arai H, Inui A. The regulatory approval of anamorelin for treatment of cachexia in patients with non-small cell lung cancer, gastric cancer, pancreatic cancer, and colorectal cancer in Japan: facts and numbers. J Cachexia Sarcopenia Muscle. 2021 Feb;12(1):14-16. doi: 10.1002/jcsm.12675.
31. Temel JS, Abernethy AP, Currow DC, Friend J, Duus EM, Yan Y, Fearon KC. Anamorelin in patients with non-small-cell lung cancer and cachexia (ROMANA 1 and ROMANA 2): results from two randomised, double-blind, phase 3 trials. Lancet Oncol. 2016 Apr;17(4):519-531.

32. Taniguchi J, Mikura S, da Silva Lopes K. The efficacy and safety of anamorelin for patients with cancer-related anorexia/cachexia syndrome: a systematic review and meta-analysis. Sci Rep. 2023 Sep 14;13(1):15257.
33. Gebbia V, Testa A, Gebbia N. Prospective randomised trial of two dose levels of megestrol acetate in the management of anorexia-cachexia syndrome in patients with metastatic cancer. Br J Cancer. 1996 Jun;73(12):1576-80
34. Feliu J, Gonzales-Baron M, Berrocal A, Artal A, Ordonez A, Garrido P, Zamora P, Garcia De Paredes ML AND Montero JM. (1992). Usefulness of megestrol acetate in cancer cachexia and anorexia.
35. Tchekmedyian NS, Hickman M, Siau J, Greco FA, Keller J, Browder H. AND Aisner J. (1992a). Megestrol acetate in cancer anorexia and weight loss. Cancer, 69, 1269- 1274.
36. Loprinzi CL, Ellison NM, Schaid DJ, Krook DJ, Athmann LM, Dose AM. Mailliard JA, Johnson TS, Ebbert LP and Geeraerts LH. (1990). Controlled trial of megestrol acetate for the treatment of cancer anorexia and cachexia. J. Natl Cancer Inst., 82, 1127-1132.
37. Pascual López A, Roqué i Figuls M, Urrútia Cuchi G, Berenstein EG, Almenar Pasies B, Balcells Alegre M, Herdman M. Systematic review of megestrol acetate in the treatment of anorexia-cachexia syndrome. J Pain Symptom Manage. 2004 Apr;27(4):360-9.
38. Ruiz-García V, López-Briz E, Carbonell-Sanchis R, Bort-Martí S, GonzálvezPerales JL. Megestrol acetate for cachexia-anorexia syndrome. A systematic review. J Cachexia Sarcopenia Muscle. 2018 Jun;9(3):444-452.
39. Lim YL, Teoh SE, Yaow CYL, Lin DJ, Masuda Y, Han MX, Yeo WS, Ng QX. A Systematic Review and Meta-Analysis of the Clinical Use of Megestrol Acetate for Cancer-Related Anorexia/Cachexia. J Clin Med. 2022 Jun 28;11(13):3756.
40. Currow DC, Glare P, Louw S, Martin P, Clark K, Fazekas B, Agar MR. A randomised, double blind, placebo-controlled trial of megestrol acetate or dexamethasone in treating symptomatic anorexia in people with advanced cancer. Sci Rep. 2021 Jan 28;11(1):2421.
41. Talebi S, Zeraattalab-Motlagh S, Barkhordar M, Vaezi M, Ghoreishy SM, Ghavami A, Hosseini Y, Travica N, Mohammadi H. Dose-dependent effect of megestrol acetate supplementation in cancer patients with anorexia-cachexia syndrome: A meta-analysis. J Cachexia Sarcopenia Muscle. 2024 Aug;15(4):1254-1263.
42. Bruera E, Roca E, Cedaro L, Carraro S, Chacon R. Action of oral methylprednisolone in terminal cancer patients: a prospective randomized double-blind study. Cancer Treat Rep. 1985 Jul-Aug;69(7-8):751-4. PMID: 2410117.
43. Popiela T, Lucchi R, Giongo F. Methylprednisolone as palliative therapy for female terminal cancer patients. The Methylprednisolone Female Preterminal Cancer Study Group. Eur J Cancer Clin Oncol. 1989 Dec;25(12):1823-9.
44. Willox JC, Corr J, Shaw J, Richardson M, Calman KC, Drennan M. Prednisolone as an appetite stimulant in patients with cancer. Br Med J (Clin Res Ed). 1984 Jan 7;288(6410):27.
45. Della Cuna GR, Pellegrini A, Piazzi M. Effect of methylprednisolone sodium succinate on quality of life in preterminal cancer patients: a placebo-controlled, multicenter study. The Methylprednisolone Preterminal Cancer Study Group. Eur J Cancer Clin Oncol. 1989 Dec;25(12):1817-21.
46. Yavuzsen T, Davis MP, Walsh D, LeGrand S, Lagman R. Systematic review of the treatment of cancer-associated anorexia and weight loss. J Clin Oncol. 2005 Nov 20;23(33):8500-11.
47. Yennurajalingam S, Frisbee-Hume S, Palmer JL, Delgado-Guay MO, Bull J, Phan AT, Tannir NM, Litton JK, Reddy A, Hui D, Dalal S, Massie L, Reddy SK, Bruera E. Reduction of cancer-related fatigue with dexamethasone: a double-blind, randomized, placebo-controlled trial in patients with advanced cancer. J Clin Oncol. 2013 Sep 1;31(25):3076-82.
48. Loprinzi CL, Kugler JW, Sloan JA, Mailliard JA, Krook JE, Wilwerding MB, Rowland KM Jr, Camoriano JK, Novotny PJ, Christensen BJ. Randomized comparison of megestrol acetate versus dexamethasone versus fluoxymesterone for the treatment of cancer anorexia/cachexia. J Clin Oncol. 1999 Oct;17(10):3299-306.
49. Currow DC, Glare P, Louw S, Martin P, Clark K, Fazekas B, Agar MR. A randomised, double blind, placebo-controlled trial of megestrol acetate or dexamethasone in treating symptomatic anorexia in people with advanced cancer. Sci Rep. 2021 Jan 28;11(1):2421.
50. Chlebowski RT, Herrold J, Ali I, Oktay E, Chlebowski JS, Ponce AT, Heber D, Block JB. Influence of nandrolone decanoate on weight loss in advanced non-small cell lung cancer. Cancer. 1986 Jul 1;58(1):183-6.
51. Dobs AS, Boccia RV, Croot CC, Gabrail NY,

Dalton JT, Hancock ML, Johnston MA, Steiner MS. Effects of enobosarm on muscle wasting and physical function in patients with cancer: a double-blind, randomised controlled phase 2 trial. Lancet Oncol. 2013 Apr;14(4):335-45.

52. Economos G, Lovell N, Johnston A, Higginson IJ. What is the evidence for mirtazapine in treating cancer-related symptomatology? A systematic review. Support Care Cancer. 2020 Apr;28(4):1597-1606.
53. Watanabe N, Omori IM, Nakagawa A, Cipriani A, Barbui C, Churchill R, Furukawa TA. Mirtazapine versus other antidepressive agents for depression. Cochrane Database Syst Rev. 2011 Dec 7;(12):CD006528.
54. Riechelmann RP, Burman D, Tannock IF, Rodin G, Zimmermann C. Phase II trial of mirtazapine for cancer-related cachexia and anorexia. Am J Hosp Palliat Care. 2010 Mar;27(2):106-10
55. Hunter CN, Abdel-Aal HH, Elsherief WA, Farag DE, Riad NM, Alsirafy SA. Mirtazapine in Cancer-Associated Anorexia and Cachexia: A Double-Blind Placebo-Controlled Randomized Trial. J Pain Symptom Manage. 2021 Dec;62(6):1207-1215.
56. Navari RM, Brenner MC. Treatment of cancer-related anorexia with olanzapine and megestrol acetate: a randomized trial. Support Care Cancer. 2010 Aug;18(8):951-6.
57. Navari RM, Pywell CM, Le-Rademacher JG, White P, Dodge AB, Albany C, Loprinzi CL. Olanzapine for the Treatment of Advanced Cancer-Related Chronic Nausea and/or Vomiting: A Randomized Pilot Trial. JAMA Oncol. 2020 Jun 1;6(6):895-899.
58. Naing A, Dalal S, Abdelrahim M, Wheler J, Hess K, Fu S, Hong DS, Janku F, Falchook GS, Ilustre A, Ouyang F, Kurzrock R. Olanzapine for cachexia in patients with advanced cancer: an exploratory study of effects on weight and metabolic cytokines. Support Care Cancer. 2015 Sep;23(9):2649-54.
59. Poon IO, Ajewole V, Braun UK. A Review of Olanzapine in the Treatment of Cancer Anorexia-Cachexia Syndrome. Pharmacy (Basel). 2024 Feb 17;12(1):34.
60. Cannabis-In-Cachexia-Study-Group; Strasser F, Luftner D, Possinger K, Ernst G, Ruhstaller T, Meissner W, Ko YD, Schnelle M, Reif M, Cerny T. Comparison of orally administered cannabis extract and delta-9-tetrahydrocannabinol in treating patients with cancer-related anorexia-cachexia syndrome: a multicenter, phase III, randomized, double-blind, placebo-controlled clinical trial from the Cannabis-InCachexia-Study-Group. J Clin Oncol. 2006 Jul 20;24(21):3394-400.
61. Jatoi A, Windschitl HE, Loprinzi CL, Sloan JA, Dakhil SR, Mailliard JA, Pundaleeka S, Kardinal CG, Fitch TR, Krook JE, Novotny PJ, Christensen B. Dronabinol versus megestrol acetate versus combination therapy for cancer-associated anorexia: a North Central Cancer Treatment Group study. J Clin Oncol. 2002 Jan 15;20(2):567-73.
62. Brisbois TD, de Kock IH, Watanabe SM, Mirhosseini M, Lamoureux DC, Chasen M, MacDonald N, Baracos VE, Wismer WV. Delta-9-tetrahydrocannabinol may palliate altered chemosensory perception in cancer patients: results of a randomized, double-blind, placebo-controlled pilot trial. Ann Oncol. 2011 Sep;22(9):2086-2093.
63. Simon L, Baldwin C, Kalea AZ, Slee A. Cannabinoid interventions for improving cachexia outcomes in cancer: a systematic review and meta-analysis. J Cachexia Sarcopenia Muscle. 2022 Feb;13(1):23-41.