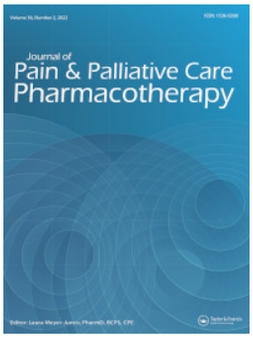

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REVIEW

Pharmacotherapy in Cachexia: A Review of Endocrine Abnormalities and Steroid Pharmacotherapy

Magdalena Celichowska*, Miłosz Miedziaszczyk*, and Katarzyna Lacka

ABSTRACT

Cachexia is a state of increased metabolism associated with high morbidity and mortality. Dysregulation of cytokines and hormone activity causes reduced protein synthesis and excessive protein breakdown. various treatments are available, depending on the primary disease and the patient's state. Besides pharmacological treatment, crucial is nutritional support as well as increasing physical activity. The main purpose of pharmacological treatment is to diminish inflammation, improve appetite and decrease muscle wasting. Therefore a lot of medications aim at proinflammatory cytokines such as Interferon-α or Tumor Necrosis Factor-β, but because of the complicated mechanism of cachexia, the range of targets is very wide. in cachexia treatment, use of corticosteroids is common, which improve appetite, diminish inflammation, inhibit prostaglandin metabolism, Interleukin-1 activity. They can also decrease protein synthesis and increase protein degradation, which can be prevented by resveratrol. Estrogen analogs, progesterone analogs, testosterone analogs, Selective Androgen Receptor Modulators (SARM), Angiotensin-Converting-Enzyme Inhibitors (ACEI), Nonsteroidal anti-inflammatory drugs (NSAIDs), thalidomide, melatonin, Growth Hormone Releasing Peptide-2 (GHRP-2) may play important role in wasting syndrome treatment as well. However, for the usage of some of them, evidence-based recommendations are not available. This review highlights current therapeutic options for cachexia with a specific focus on steroid therapy.

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Introduction

Cachexia, also known as wasting syndrome is a state of increased metabolism, which cannot be compensated by daily caloric intake in the setting of ongoing disease. It manifests with increased muscle mass loss (with or without loss of body fat) and usually fatigue, lack of appetite, apathy, weakness, sleep disturbances, depression, anemia, and early satiety. Furthermore noticed should be problems with food intake from xerostomia stomatitis or inflammatory condition in oral cavity, pain, nausea, emesis, diarrhea, and depression. Cachexia is very often underestimated as a potential cause of death and also is hard to treat. Proper management of patients with cachexia is crucial to achieve therapeutic success. With the increasing age of society as well as the increasing number of patients with cancer, the incidence of cachexia may also increase (1–4).

The aim of this review is to summarize current data about pathophysiology and treatment of cachexia, especially about the endocrinological aspect of that state and steroid therapy. This review will also highlight pharmacologic therapeutic strategies which could be helpful in managing wasting syndromes and also those which need further study. Although nutritional interventions are also important in the management of cachexia, these strategies are outside of the scope of this review.

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Pathophysiology of cachexia

There are various conditions, which lead to cachexia, but the most common ones are cancer, AIDS, chronic heart failure (CHF), rheumatoid arthritis, chronic obstructive pulmonary disease (COPD), chronic kidney disease, liver cirrhosis, cystic fibrosis, Crohn's disease, stroke, degenerative neurological disorders, sepsis, states after spinal cord injuries, malaria or tuberculosis (5). In cancer disease cachexia is caused probably by deficiency of testosterone, insulin-like growth factor I (IGF-1), myostatin, as well as glucocorticoids and cytokines excess. This hormonal imbalance also disturbs the physiological mechanisms of food intake by leptin-analogous cytokines. Tumor cells can mimic leptin and suppress orexigenic ghrelin and NPY signaling. Numerous cytokines play role in the cachectic process in cancer patients, but the most important appears to be interleukin-1 (IL-1), which may influence hypothalamic neuropeptide Y (NPY) concentration (4–6).

Cancer-related muscle wasting also involves tumor necrosis factor α (TNF-α), IL-1, interleukin 6 (IL-6), and interferon γ (IFN-γ). Additionally, TNFα causes upregulation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB), which also play role in proteolysis and breakdown of myofibrillar proteins (6,7). Another reason for cachexia is chronic kidney disease, where the hypercatabolic state is induced by uremia. In that state can also occur anorexia due to poor appetite and inflammation from systemic conditions (like diabetes), and autoimmune conditions that generally lead to end-stage renal disease (ESRD) (8).

The main reason for muscle wasting in cancer might be the down-regulation of mammalian target of rapamycin (mTOR) and mTOR complex 1 (mTORC1) and decreased protein synthesis. This pathway can be initiated by myostatin, which is a member of the transforming growth factor β (TGFβ) family secreted by muscle cells, which circulates in the blood and acts locally as a negative muscle mass regulator. Muscle protein breakdown is also stimulated by ubiquitin-proteasome pathway and caspases under control of the transcription factors forkhead O (Fox-O) and NF-κB (9,10).

Given the current pandemic situation, it is worth mentioning, that SARS-Cov2 infection can also lead to cachexia and sarcopenia. The receptor for novel coronavirus-2, which is angiotensin-converting enzyme 2, is located in skeletal muscles among others. Hypoalbuminemia, elevated levels of C-reactive protein and inflammatory cytokines such a TNFα, IL-1, and IL-6 as well as anorexia due to anosmia, impaired taste, and inflammation are responsible for the wasting syndrome due to the coronavirus (11) (Figure 1).

Pharmacological treatment

Treatment

Non-steroid pharmacological treatment

The most important treatment in cachexia is to diminish inflammation and improve appetite (4). Increased inflammation, which appears in most patients with wasting syndrome, leads to enhanced metabolic process and to decreased muscle mass. Most patients also do not have an appetite and this contributes to further weight loss, making them potentially unable to achieve treatment goals. Those two mechanism are the most important in cachexia management. There are various medications used in cachexia to increase food intake, by increasing appetite. Appetite can be improved by cannabinoids (Dronabinol). Studies showed, that in cancer or AIDS-related cachexia, the use of dronabinol does not reverse weight loss, but may slow this process down (25). Cannabinoids have antiemetic properties as well, but to observe a positive influence on body mass, they should be applied in lower doses (initial dose – 2.1 mg/m^2 in oral solution). Dronabinol in anorexia associated weight loss in adult patients is used at the dose of 2.5 mg (26). Another cannabinoid, nabilone, could be also helpful in management of chemotherapy induced nausea and vomiting, however, according to European Society for Medical Oncology (ESMO) and American Society of Clinical Oncology (ASCO) Guidelines, there is no significant improvement in weight gain and quality of life improvement, so it is not recommended (27–29). Further research on cannabinoids in cachexia is needed as there is

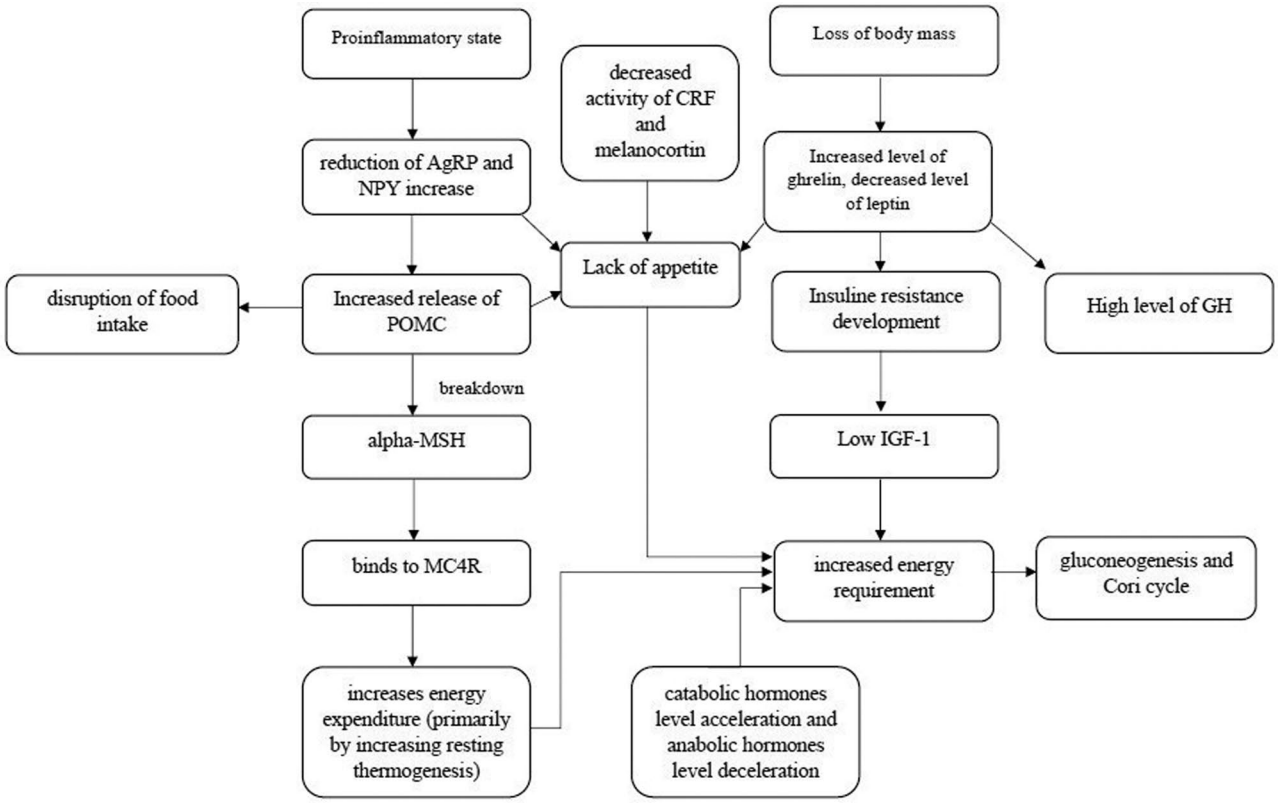

Figure 1. Endocrine changes in cachectic patients (4–6,12–17). AgRP - orexigenic peptide associated with agouti; NPY - neuropeptide Y; POMC - pro-opiomelanocortin peptide; alpha-MSH - melanocyte-stimulating hormone; MC4R - melanocortin 4 receptors; CRF - corticotropin-releasing factor; GH - growth hormone; IGF-1 - insulin growth hormone 1.

limited evidence on their safety and efficacy (22,25,30,31). In cardiac cachexia beneficial can be administrating angiotensin-converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers. These drugs have muscle-protective properties related to mitochondrial function, insulin sensitivity, and local inflammation (acting indirectly on molecules such as glucocorticoids, IL-6, TNF-α, and serum amyloid-A (SAA)), derived by angiotensin II (Ang II). Ang II may also play role in reducing appetite through orexigenic/anorexigenic neuropeptides (NPY and orexin) in the hypothalamus (4,21,25,32). ACEI decreases the risk of weight loss and improves cardiac remodeling and ventricular function (25). The beta-adrenergic receptor antagonists such as carvedilol, althought not used independently, can be used in cardiac cachexia treatment because of its ability to improve the hypermetabolic state seen in cachexia, what is also associated with increased level of Ang II. It is also important agent against increased sympathetic activity and energy expenditure in cachectic patients (4,21,33). Another important beta-blocker in cachexia treatment can be espindolol, undergoing clinical trials, which can significantly reversed weight loss, improved fat free mass, and maintained fat mass in advanced colorectal cancer and non-small cell lung cancer-related cachexia. It also reduces catabolism, through non-selective β receptor blockade, reduces fatigue and thermogenesis, through central 5-HT1a receptor antagonism and increases anabolism, through partial β2 receptor agonism (34). Methylxanthine analogs, such as pentoxifylline, stimulate vascular endothelial production of noninflammatory prostaglandins through inhibition of TNF-α production, muscle atrophy prevention, ubiquitin expression suppression. V. Mehrzad, R. Afshar and M. Akbari's study showed that in short-term (1 month) treatment, quality of life was improved in cachectic patients (34). However pentoxifylline use is limited due to its side effects (22,34–36) (Tables 1 and 2).

Another agent, which is associated with influence on TNF-α serum levels is thalidomide. That

Table 1. Cachexia underlying conditions and their pathophysiologic elements (5–9,18–24).

Disease	Pathophysiology
Cancer	• cytokine excess • deficiency of testosterone and insulin-like growth factor I (IGF-1) • myostatin and glucocorticoids excess • disorders of the physiological mechanisms of food intake by leptin-analogous cytokines • tumor cells can mimic leptin and suppress orexigenic ghrelin and NPY signaling • interleukin-1 (IL-1) may influence hypothalamic neuropeptide Y (NPY) concentration • related are tumor necrosis factor α (TNF-α), IL-1, interleukin 6 (IL-6), and interferon γ (IFN-γ) • TNFα causes upregulation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB), which also play role in proteolysis and breakdown of myofibrillar proteins
Chronic kidney disease	• hypercatabolic state induced by uremia • anorexia due to poor appetite • inflammation from systemic conditions (like diabetes), and autoimmune conditions that generally lead to end-stage renal disease (ESRD)
SARS-Cov2	• hypoalbuminemia, elevated levels of C-reactive protein as well as inflammatory cytokines such a TNFα, IL-1, and IL-6 • anorexia due to anosmia, impaired taste, and inflammation
Malaria	• glycosylphosphatidylinositol (GPI) produced by Plasmodium falciparum is a parasite toxin inducing the production of TNF and IL-1 by host macrophages • continuous large supply of nitric oxide in tissues and cause cerebral symptoms, immune suppression, and weight loss
AIDS	• reduced nutrient intake • malabsorption • a hypermetabolic state: an increase in resting energy expenditure (REE) and disturbances in the metabolism of protein (muscle proteolysis) and fat (hypertriacyglycerolemia) • elevated TNF and IL-α • TNF and IL-1 can promote HIV-1 • IL-1 reduces f lipoprotein lipase (LPL) activity and produces lipolysis
Chronic heart failure	• increased angiotensin II production, which altered insulin-like growth factor-1 (IGF-1) signaling • increased apoptosis, • enhanced muscle protein degradation breakdown by overactivation of the ubiquitin proteasome system (UPS), • reduced appetite • myostatin (MYO) gene expression is increased
Rheumatoid arthritis	• excess INFα and TNFβ
Stroke	• increased C-reactive protein plasma level
Crohn's disease	• E3 ubiquitin ligases atrogin-1/MAFbx and MuRF1 are upregulated during and target MyoD, calcineurin, eIF3f and myofibrillar proteins for proteolysis. • increased production of TNF, which ligates receptors on myocytes to activate NF-κB, inducing death of muscle cells and inhibition of IGF-1-induced anabolism. • activated NF-κB reduces muscle formation through MyoD transcription, and increases muscle proteolysis.
Liver cirrhosis	• elevation of the pro-inflammatory cytokines including TNF-α and IL-1, −6, which in turn stimulate muscle autophagy. • the ubiquitin-proteasome system can be linked to muscle atrophy through activation of muscle atrophy-related genes. • hyperammonemia elevate muscle myostatin expression via TLR-independent nuclear factor kappa beta activation • the decrease in serum free testosterone levels, b ranched-chain amino acids and INF-1 levels result in elevated myostatin levels • myostatin suppresses muscle satellite cell proliferation and differentiation.
Cystic fibrosis	• increased level of proinflammatory cytokines such as IL-1, INF-α
Injuries	• increased level of proinflammatory cytokines such as IL-1, INF-α
Tuberculosis	• increased level of proinflammatory cytokines such as IL-1, INF-α

IGF-1 – insulin growth hormone 1.
TNF-α – tumor necrosis factor α.
IL-1 – interleukin 1.
IL-6 – interleukin 6.
IFN-γ – interferon γ.
INF-1 – interferon 1.
INF-α – interferon α.
IGF-1 – insulin-like growth factor I.
GPI – glycosylphosphatidylinositol.
LPL – lipoprotein lipase.
NF-kB – nuclear factor kappa-light-chain-enhancer of activated B cells.
NPY – hypothalamic neuropeptide Y.
MYO – myostatin.
UPS – ubiquitin proteasome system.

medication, used to treat AIDS, leprosy, tuberculosis, and cancers, has been shown to possess anti-inflammatory, immunomodulatory, anti-angiogenic, sedative, and anti-emetic effects. Its application leads to inhibition of TNF-α production and weight gaining. Even though thalidomide is a promising drug, its treatment was associated with constipation, peripheral neuropathy, and rash (36). According to the American Society of Clinical Oncology (ASCO) Guidelines of Management of Cancer Cachexia, there is no sufficient evidences to refute or support the use of thalidomide for the management of cachexia in advanced cancer patients (28). Further

Table 2. Stages of wasting syndrome (3,4,6).

Stage	Weight loss of body mass	Additional factors
Precachexia	≤5%	Anorexia, metabolic disturbances
Cachexia	>5% >2%* * when BMI is lower than 20 kg/m2 or sarcopenia occurs	Decreased food intake, general inflammatory state
Cachexia resistant to treatment	>5% > 2%* * when BMI is lower than 20 kg/m2 or sarcopenia occurs	Neoplastic disease that does not respond to treatment, low level of functional efficiency (ECOG* scale) *Eastern Cooperative Oncology Group

randomized studies should be carried out (22,33,37). Currently, research is ongoing concerning the role of anti-cytokines such as anti-IL-1, anti-IL-6, anti-IL-10, anti-IL-15, and anti-TNF-α antibodies in cachexia treatment, which might have a positive impact on muscle wasting and weight gaining, as well as reduction of inflammation (22,34,37). Non-steroidal anti-inflammatory drugs (NSAIDs) also may play important role in managing cachexia, because of their ability to inhibit prostaglandin synthesis. Celecoxib in combination with fish oil as well as ibuprofen can decrease C-reactive protein (CRP) level, whereas indomethacin may reduce fever and granulocytosis. In addition, studies indicate that NSAIDs improve the well-being of patients in cancer patients (3,22,38). According to ASCO and ESMO Guidelines, the evidences are insufficient for a clear conclusion regarding the efficacy of NSAIDS for cachexia treatment (28,29). Melatonin has anti-inflammatory properties, due to its ability to decrease the level of circulating TNF in advanced cancer and reduced chemotherapy-induced malaise, asthenia, and thrombocytopenia (22,35,36). It also may have a positive impact on the patient's appetite and probably on body mass (38,39) and a positive side effect as sleep regulation (35). Ghrelin-receptor agonist GHRP-2 (growth hormone-releasing peptide-2), such as Anamorelin, is another drug able to enhance food intake and body weight (~2-3 kg). Probably by increasing fat (~1 kg), bone masses, and lean mass (~1-2 kg). It may act through the decreasing activity of hypothalamic NPY neurons as well as through stimulation of IGF-1 and GH production (13,22,25,39,40). Anamorelin might also act by improving the balance between orexigenic and anorexigenic pathways (40). Ghrelin mimetics have been proved as agents significantly associated with mean differences in total body mass compared to placebo (41). Anamorelin is not included in the current ASCO Guidelines recommendations (28). Furthermore cyproheptadine is a first-generation H1-antihistamine drug and it is another orexigenic medication, which can be used to increase appetite (42). Same properties has olanzapine, an atypical antipsychotic. Furthermore case reports suggest that olanzapine has antiemetic activity in patients with advanced cancer and usefulness as prophylaxis against chemotherapy-related nausea and vomiting, what is also very important in cachexia management (43). ESMO Guidelines indicates, that there are only moderate evidences to suggest the use of olanzapine to treat appetite and nausea in patients with advanced cancer (29). For cyproheptadine, melatonin and TNF inhibitors, ASCO Guidelines underlines the lack of sufficient evidences and because of that, do not recommend that medications in cachexia management (28). Worth noting is also metoclopramide, a prokinetic agent and dopamine receptor agonist. Metoclopramide can help treat autonomic dysfunction related to advanced cancer and impaired gastric emptying due to opioids, additionally the use of metoclopramide can result in the improvement of nausea, vomiting, and bloating in patients with chronic nausea and dyspepsia from advanced cancer (39). According to ESMO Guidelines, the evidences are insufficient to recommend the use of metoclopramide alone to treat cancer cachexia (29). Because the main focus of this article are endocrine based therapies, this is a brief overview on the non-steroid pharmacological treatment.

Steroid therapy

Adrenocortical corticosteroids. To treat cachexia crucial is managing inflammation. Therefore

Table 3. Division of adrenocortical corticosteroids depending on their biological activity.

Subgroup	Biological activity
Glucocorticoids	Metabolism and immunity (receptor complexed with heat stroke protein (hsp))
Mineralocorticoids	Salt retention in the body
Estrogens and androgens	Regulation of transcription of target genes (nuclear receptor)
Progesterone analogs	Effect on protein metabolism, decrease in Na + reabsorption, increase urinary nitrogen excretion, alveolobular development of the secretory apparatus in the breast (nuclear receptor)

basic treatment includes steroids. Adrenocortical hormones are steroids produced and released by the adrenal cortex under corticotropin (ACTH) control. That group is divided into a few subgroups depending on their biological activity (Table 3) (44).

Corticosteroids, such as dexamethasone (2-4 mg/day), prednisolone (15-30 mg/day), or methylprednisolone (8-24 mg/day), are used to treat cachexia (3,4). Their main mechanism of action is increasing appetite and diminishing inflammation (4,36). Additionally, they inhibit prostaglandin metabolism and IL-1 activity (22). With higher steroid doses, the probability of important adverse effects increases, particularly when dexamethasone dose is above 3 mg (in mice studies) or when serum levels increase in stressful situations. Corticosteroids can decrease protein synthesis and increase protein degradation, due to activation of the ubiquitin-proteasome system and muscle ring finger 1 (MuRF1) inhibition, reducing muscle strength (10,45). Because of corticosteroids' side effect profile, they are indicated only for short-term treatment – less than 4 weeks. That side effects include: osteoporosis, steroid-induced myopathy, osteonecrosis, suppression of the hypothalamic-pituitary-adrenal (HPA) axis, diabetes, cushingoid features, infections, fluid retention, edema, weight gain, hypertension, and arrhythmias by increasing renal excretion of potassium, calcium, and phosphate, cataract, open-angle glaucoma, skin thinning and atrophy (46). ESMO Guidelines indicate, that corticosteroids may be used to increase appetite for a short period of up to 2-3 weeks, and after that time effects on appetite usually disappear (29). Furthermore corticosteroids are associated with a regulatory network formed by NPY, AgRP and CRH, which leads to increasing appetite (47). Methylprednisolone is a corticosteroid applied in various inflammatory diseases. A randomized, placebo-controlled, double-blind trial showed that it may improve fatigue, appetite loss, and patient satisfaction (48). According to the ASCO and ESMO Guidelines, the choice of corticosteroid in cancer cachexia management should be taken individually for every patient and depends on duration of treatment, goals as well as on assessment of risk versus benefit. There are limited data available to recommend one corticosteroid over another (28,29).

Resveratrol is a medication, which can prevent corticosteroids-induced muscle atrophy, through SIRT1 (NAD+-dependent deacetylase Sirtuin 1; a key regulator of muscle metabolism) activation and increasing mitochondrial biogenesis in skeletal muscle (10). Resveratrol can also be used to protect against angiogenesis and inflammation (49,50). There is still no guideline-based recommendations for using resveratrol in combination with corticosteroids.

There are reports, that cardiac cachexia induce increase of aldosterone and neutrophil gelatinase-associated lipocalin (NGAL), which is an aldosterone-responsive gene increased in heart failure, which leads to worsening cardiac damage in cancer cachexia-induced cardiomyopathy. High plasma level of aldosterone can appear in patients suffering from either non-small cell lung or colorectal cancer, with or without cachexia or in experimental model of cancer cachexia-induced cardiomyopathy. Spironolactone treatment may attenuate cardiac dysfunction and lean mass atrophy associated with cancer cachexia (51). ESMO and ASCO Guidelines does not refer to spironolactone (28,29).

Progesterone analogs. Progesterone, another steroid hormone, is a natural progestin synthetized by ovary, testis, adrenal cortex from circulating cholesterol, also by the placenta during pregnancy (44). In wasting syndrome treatment we use synthetic progestin, which increases appetite and reduce inflammation –

Megestrol Acetate, Medroxyprogesterone Acetate and Fluoxymesterone.

Megestrol Acetate is often used in the treatment of patients with metastatic breast cancer patients as well as in anorexia. Its mechanism may involve IL-1α and β, IL-2, IL-6, and TNF-α serum levels reduction. Megestrol acetate causes weight gain, but mainly fat tissue, not muscle (22,52,53). The dose range is 400-800 mg/day (higher doses do not bring benefit and increase the risk of adverse effects, mainly thromboembolic events and adrenal cortex suppression). Maximal weight gain is normally achieved within 8 weeks (54). In 2019 was published Cochran Database Systemic Review, which included 35 trials comprising 3963 patients for effectiveness and 3180 for safety. Meta-analysis showed a benefit of megestrol acetate (MA) compared with placebo, especially regarding appetite improvement and weight gain in cancer, AIDS, and other underlying conditions. According to this review, MA does not improve quality of life, and in patients treated with MA side effects are more frequent. The most common adverse effect is increased risk of blood clots, therefore swelling, pain or redness of one extremity and not the other, severe headache, sudden dyspnea or vision changes, as well as fluid retention, which can lead to swelling of the feet or hands, and death (55). According to Loprinzi et al clinical trial, there is no significant distinction between dexamethasone and megestrol acetate effectiveness on appetite stimulation as well as their influence on nonfluid weight status. However there were differences in their side effects – dexamethasone caused corticosteroid-type toxicity and a higher rate of drug discontinuation because of toxicity or patients refusal, megestrol acetate had a higher rate of deep venous thrombosis. In a randomized, double blind, placebo-controlled trial of megestrol acetate or dexamethasone in treating symptomatic anorexia in people with advanced cancer also showed, that there are no significant differences between treatment effect including weight, performance status (AKPS) and appetite score of megestrol acetate 480 mg or dexamethasone 4 mg compared to placebo daily. However the study lasted only 4 weeks (56). Other analogue, which is fluoxymesterone (testosterone analog), according to Loprinzi et al studies, is definitely less effective in appetite enhancement then dexamethasone or MA (57).

Medroxyprogesterone (MPA) acetate is synthetic progestin, which reduces the production of IL-6 (an important cytokine in cancer-induced cachexia, probably secreted by tumor cells) and serotonin involved in cachexia in cancer patients. Similarly to MA it might increase appetite and lead to weight gaining. Furthermore, according to Simon et al and Aaronson et al research, there also is a possibility that MA reduces nausea and vomiting. In a dosage of 500 mg twice a day MPA should be safe, however, there can appear edema or deep vein thrombosis (22,55,58–62). According to meta-analysis, which gathered 80 randomized clinical trials, MPA and MA are significantly associated with increased total body mass compared to placebo (41). ASCO Guidelines recommend short term use of progesterone analogs to patient suffering on weight loss and lack of appetite (28). ESMO Guidelines indicate, that clinical use of progestins is limited due to the significant risk of potentially serious side-effects, although they have significant effect on appetite improvement and having anti-inflammatory properties (29).

Testosterone analogs. Testosterone is an anabolic steroid synthesized primarily by interstitial or Leydig cells in testes in men, in women they are synthesized in adrenal glands and ovaries but in a much lower concentration. Luteinizing hormone (LH) stimulates the production of testosterone through increasing cAMP production. Its active forms, dihydrotestosterone, arise in target tissues from testosterone via reduction by 5α-reductase (44). In skeletal muscles, testosterone indicates IGF-1 initiate synthesis, therefore leads to muscle growth (63).

In cachexia treatment usage has testosterone analog, such as Oxandrolone, which is approved in the United States as an oral anabolic agent for a patient with weight loss after injuries, surgeries, infections, and other catabolic states. This drug has a minimal androgenic effect and an excellent safety profile. Oxandrolone significantly increases total body mass, appetite and improves the ability to physical exercises in HIV-related wasting (63). In cachectic patients, who underwent surgeries, it is also useful to improve wound healing (64).

Oxandrolone is less hepatotoxic and has a less virilizing effect, so is better tolerated in women. The side effects include elevated transaminase concentrations, decreased high-density lipoprotein concentrations, as well as hypogonadism due to decreased testosterone serum level, also fluid retention should be considered. Oxandrolone has interactions with oral hypoglycemics drugs and adrenal steroids, that is why is required to modify a dosage of that agents. It is worth noting, that Oxandrolone has drug-drug interaction with oral anticoagulants (increased risk of bleeding), since those are very common medication used in elderly population (53). Additionally, there is evidence that oral testosterone replacement can increase cardiovascular risk (65). Oxandrolone in a dosage of 5 mg/day to 15 mg/day in patients with AIDS-related wasting, is having positive impact on their wellbeing and body mass (66).

Another testosterone analog, nandrolone decanoate (ND), approved in the United States, in addition to MA may lead to significant weight gain and increase the fat-free mass in HIV-infected patients (63,67). There are still no guideline-based recommendations, but according to experimental studies on mice, nandrolone can be used in dosage of 2.5 mg/20 g intraperitoneally every second day for 11 days (68). That medication, while administered to cancer patients, do not enhance tumor growth (68).

It is important to mention, that testosterone analogues should be avoided in patients with prostate cancer, male breast cancer, uncontrolled or poorly controlled congestive heart failure, untreated lower urinary obstructive symptoms, erythrocytosis and severe untreated obstructive sleep apnea (69). It is also very important to control the level of high-density lipoprotein (HDL) (70).The side effects of testosterone use must be specifically considered in women, because of the risk of hypogonadism, cardiovascular events or androgenization (71). ESMO Guidelines indicates, that in randomized clinical trials of lung cancer patients, the analogue nandrolone did not improve body weight compared with placebo, additionally a three-armed in another randomized clinical trials fluoxymesterone 10 mg was significantly inferior to MA 800 mg/day in terms of appetite improvement (29).

Estrogens analogs. Estrogens are steroid hormones produced in ovaries and smaller amounts in the liver or peripheral tissues via the androstenedione and other androgens conversion. Just as testosterone, estrogen receptors are located in the nucleus bound to heatstroke protein (hsp) (48). Estrogens promote the apoptosis of osteoclasts and antagonize the osteoclastogenic and pro-osteoclastic effects of parathyroid hormone and interleukin-6, therefore decrease bone resorption. Furthermore, estrogens increase leptin production in adipose tissue. They lead to increased circulating levels of thyroxine, testosterone, iron, and copper through increasing circulating levels of proteins such as transcortin (corticosteroid-binding globulin; CBG), thyroxine-binding globulin (TBG), renin substrate, SHBG, transferrin, and fibrinogen. Their metabolic effects include increases in the high-density lipoproteins (HDL) and plasma triglyceride levels, a reduction in the low-density lipoproteins (LDL) and total plasma cholesterol levels, as well as decreasing hepatic oxidation of adipose tissue lipid to ketones (44,72). Furthermore according to Mela et al estradiol and leptin physiologically antagonize the function of cannabinoid 1 receptor (CB1) and opioid receptor-like 1 (ORL1) receptors, which are orexigenic, Gi/o-coupled receptors. Therefore estrogens might be anorexigenic hormones and suppress appetite (73).

Based on research conducted by Counts et al on female $Apc^{Min}/+$ mice, there are presumptions that 17β-estradiol can be useful in cachexia treatment, because of its ability to decrease weight loss and bones degradation. 17β-estradiol regulates mTOR1 signalization, the ubiquitin-proteasome system, autophagy, and AMPK signaling, which are dysfunctional in cachectic patient's muscles. Estrogens also prevent mitochondrial dysfunction, therefore might be cachectic processes inhibiting agents (74). Another important function of estrogens is their ability to stimulate serotonin production via tryptophan hydroxylase (TPH) protein modulation. When their level is high, significant pain reduction through the 5-HT2A receptor has been noted. Its blockage by a 5-HT2A antagonist may decrease estrogen-induced pain relief. Because pain and depression in wasting syndrome are common, estrogens might be helpful in their management. It is also important to remember, that some

women should not receive estrogen therapy, among others women with estrogen hormone receptor sensitive malignancies including breast cancer, ovarian cancer, and endometrial cancers, patients with coronary arterial disease, with history of thromboembolism or thrombophlebitis, hypercoagulable disease or of ischemic stroke (75). However, there is no strong evidence, that estrogens can be significant agents to treat those states in cachexia, furthermore there are no humane studies using estrogens (72,76). Neither the ASCO nor ESMO Recommendations mention the use of estrogen to treat cachexia (28,29).

SARM: Selective androgen receptor modulators (SARM), such as enobosarm or espindolol, are tissue-specific non-steroidal androgenic agents. Currently, due to their potential toxicity, they are not recommended in a treatment of cachexia, even though numerous publications indicate their positive role in wasting syndrome (77). They may have an impact on muscle atrophy inhibition via blocking dephosphorylation and thus cascade inactivation of proteins in the phosphatidylinositol 3-kinase/protein kinase B (PI3/AKT) (11,77). Therefore they increase muscle mass and improve physical function (78). A randomized, double-blind, placebo-controlled phase 2 trial showed the effectiveness of enobosarm in improving lean body mass, without toxic effects related to androgens and progestogens (79). Another randomized, double-blind, parallel-group, placebo-controlled, phase II multicentre trial demonstrated, that espindolol 10 mg administered twice daily, significantly reversed weight loss. The administration of the drug improved fat-free mass, and maintained fat mass in advanced colorectal cancer and non-small cell lung cancer-related cachexia (80). While using SARM we have to consider possible side effects, such as erythrocytosis, prostate hypertrophy, hepatotoxicity, aromatization to estrogen and testicular atrophy (81).

Non-pharmacological therapy

Non-pharmacological treatment is a basis for cachexia management, which cover patients and their family education, which includes dietary advice and cooperation with a dietitian. This process cannot be inhibited just by providing caloric intake, after all energetic imbalance can lead to clinical deterioration. Hence nutritional supplementation is recommended as the first step of nutritional support when dietary counseling and standard preventive measures are not sufficient to achieve the planned nutritional requirements (3,77). Tube feeding may be necessary if oral supplementation is not tolerated (82).

According to the European Society for Clinical Nutrition and Metabolism (ESPN) guidelines food product is "any food that is suitable for human consumption which provides energy-containing macronutrients (e.g. carbohydrates, protein, fats), and/or micronutrients (e.g. vitamins, minerals), and/or other substances which may contribute to fulfill the nutritional requirements of the patient" (83). In weight-losing patients with cancer cachexia daily caloric deficit amount to 250-400 kcal/day (7). Nutrition therapy should include food modification depending on the patient's clinical condition and disorders, fortified foods, food supplements, functional food, texture modified food, and thickened fluids (83). Though average 1 calorie/mL supplementation in patients chemotherapy cannot improve patients nutritional status, it can lead to weight stabilization (6,7). It is recommended to eat small portions of food frequently, also foods that are high in energy in a small volume can be added to meals. It should be known that oral liquid supplements are also a therapeutic option. Specialists indicate, that very important is to provide omega3-polyunsaturated fatty acids (PUFA), which have been proposed as very active in reducing either tumor growth or muscle wasting. Docosahexaenoic acid (DHA), which belongs to that family, may decrease systemic inflammation, oxidative stress and may have anti-inflammatory effects, including reducing acute-phase response mediated by IL-6. Furthermore, PUFA has a great impact on improving weight gaining in cachectic patients (77,84,85). Food reach in antioxidants, like vitamin C, E, β-carotene, or selenium can have an impact on various cancer cells by inhibiting tumor angiogenesis, whereas glutamine play important role in protecting the patient's gut microflora during radiotherapy. However, important is to remember, that antioxidants can interfere with treatment with alkylating chemotherapy.

Table 4. The methods of cachexia treatment (project prepared by authors).

Non-pharmacological treatment
Patient and their family education, which include dietary advice and cooperation with a dietitian
Oral nutrition - small portions of food (foods that are high in energy in a small volume or oral liquid supplements can be added to meals)
Nutritional fistula - gastrostomy or jejunostomy (industrial diet)
Pharmacological treatment
Megestrol (400-800 mg/day) - increases appetite, weight gain
Corticosteroids: dexamethasone (2-4 mg/day), prednisolone (15-30 mg/day) or methylprednisolone (8-24 mg/day) - increase appetite, reduce inflammation
Medroxyprogesterone (500 mg/day) - increases appetite, weight gain, reduces nausea and vomiting
Testosterone - muscles growth
Oxandrolone, nandrolone - increase appetite, weight gain
NSAIDs

Additionally, because most of patients with cachexia have disturbed gut microflora, administration of probiotics and prebiotics can be necessary to push patient's physiological immunity (77,86).

A multicenter, open-label, pilot randomized phase II study investigating a 6-week multimodal intervention for cachexia. This included implementation of oral nutritional supplements (ONS) containing n – 3 PUFAs, exercise, and NSAIDs, compared to standard cancer care. The study showed that multimodal intervention leads to body weight stabilization, while patients in treated in a standard way lost weight. In the study following parameters have been measured: Karnofsky performance score, body mass index (BMI), body composition measures, physical function, baseline samples, CRP, plasma levels of adiponectin, zink-α2 glycoprotein (ZAG), IGF-1, n – 3 PUFA, and 25-Hydroxyvitamin D, and pre-inclusion weight loss. As a result, a significant improvement has been detected in patients BMI, body composition, especially in the case of muscle mass, the plasma level of eicosapentaenoic acid (EPA), DHA, docosapentaenoic acid (DPA), 25-OH vitamin D. There was no significant change in patients physical function, CRP, adiponectin, ZAG, IGF-1, glycerol, or lipolysis plasma level (87). When a patient is not able to ingest orally, there is another option to consider, which is enteral tube feeding such as gastrostomy or jejunostomy. We can use a tube, which can be inserted through a nose (i.e. naso-gastric tube feeding), or a stoma, which is inserted into a stomach or the jejunum. Tube enteral feeding can be total (when all nutrients need to be provided via a feeding tube) or supplemental (when oral nutrition is not able to provide all nutrients, but a patient can be fed that way) (83). Additionally, studies show, that physical exercises can improve patients quality of life, because of ability to increases insulin sensitivity, protein synthesis rate, anti-oxidative enzyme activity. They can also also suppress the inflammatory response and enhance immune functions (2,6,41,84). Last but not least, McKeaveney C et al in the review from 2021 collected data from the literature published between 2008 and 2019 focused on cachexia interventions in COPD, CKD, and cancer. In this review importance of multimodal interventions, which combine physical exercises, oral nutrition support, and pharmacological treatment, is being discussed. According to it, a single therapy can not lead to stabilization or reversing cachexia and multimodal intervention is essential (88).

Conclusion

The range of drugs used in the treatment of cachexia has grown significantly in recent years. The knowledge of the treatment of cachexia is essential for the therapy of patients, which should be selected individually. Dexamethasone and megestrol acetate are the most commonly used steroids for wasting syndromes, and current guidelines support their use in patients with cancer cachexia. Other steroid and non-steroid medications may be used in appropriate patients; however, further studies are need to recommend their use in cancer cachexia (Table 4).

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