Pharmacological Treatment of Geriatric Cachexia: Evidence and Safety in Perspective

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Anticachexic or antisarcopenic medications are prescribed worldwide for geriatric patients with poor appetite and associated weight loss. They represent a valuable treatment option for managing cachexia. However, the well-publicized adverse reports about these medications in acquired immunodeficiency syndrome (AIDS) and in the cancer population has led to some concern and much subsequent discussion over the safety of these medications being used in geriatric population. This review looks at the evidence in relation to the benefits and risks of these medications and discusses what we know about their use in the geriatric population. **(J Am Med Dir Assoc 2007; 8: 363–377)**

Keywords: Cachexia; elderly; pharmacotherapy; safety

To establish the optimal means of treating patients with age-related cachexia, both the benefits and risks associated with these presently available and potentially useful medications will be evaluated here. This review assesses the efficacy, safety, and tolerability of medications that have been used in cancer and AIDS-associated cachexia and gives a practical overview on maximizing the risk:benefit ratio for the use of the particular class of drugs in the geriatric population.

Epidemiological evidence supporting the notion that significant weight loss is associated with high mortality comes from community studies and nursing home studies,[1–6] from AIDS studies,[7,8] and cancer study.[9] Further evidence in support of this notion comes from prospective longitudinal studies of free-living and institutionalized elderly, which assessed the relationship between weight loss and survival.[1,4]

The understanding of the pathophysiology of geriatric cachexia has increased with effective and safe nutritional measurements.

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PHYSIOLOGIC CAUSES OF WEIGHT LOSS IN THE ELDERLY

Food intake regulation changes with age. The mechanisms regulating food intake in the elderly are complex and multifactorial, making treatment more challenging. Mechanisms[10,11] involved in the process of weight loss and poor food intake are summarized in Table 1.

TREATMENT OPINIONS

Nutritional Supplementation

Rolls and colleagues[12] found that even healthy elderly men consumed significantly less baseline energy compared with younger men. Roberts and coworkers found that healthy elderly men had both a short-term (7 weeks), as well as long-term (6 months) impairment in adjusting their food intake after an episode of either overfeeding or underfeeding.[13–15,16–18] Encouraging the elderly to take extra food (with verbal prompts, physical assistance) at mealtime over a period of time, then allowing them to eat at their own volition, can promote weight gain. Because the elderly are not able to adjust their food intake after a period of overfeeding, they will continue exceeding their eating needs, and thus, increase their weight. Providing an energy-dense nutritional supplement at least 30 minutes before a meal can increase energy intake in elderly people. These elderly men did not decrease food intake even when they were given supplements before meals. They obtained 10% to 30% extra energy from the "preload" (supplements given 30 minutes before lunch) and still were able to take their usual amount of food at mealtime.[12] Wilson and colleagues[19] found that administration of dietary supplements between meals ($>$ 60 minutes

Table 1. *Etiology of Weight Loss in the Elderly**

Etiology	Examples
Normal aging	Reduced basal hunger, dysgeusia, decreased gastric emptying time, failure to adjust food intake after a period of overfeeding or underfeeding
Endocrine disorders	Hyperthyroidism, hyperparathyroidism, and hypoadrenalism
Medications	Theophylline, lithium, digoxin, chemotherapeutic agents, antibiotics and many other medications that distort normal smell and taste.
Psychiatric	Dementia, depression, anorexia nervosa, alcoholism, and paranoia (late-life)
Gastric intestinal disorders	Dysphagia, missing dentures, pain, malabsorption, diarrhea, and constipation
System diseases	Stroke, Parkinson's disease, achalasia, and scleroderma
Chronic disease	Chronic obstructive pulmonary disease, congestive heart failure, rheumatoid arthritis, AIDS, cancers.
Dysfunction	Inability to feed oneself, limited income, and poor eyesight
Infections	Acute and chronic diseases, AIDS, gastritis, and cholecystitis

* Modified from Morley and Kraenzle[10] and Robbins,[11] with permission.

before the next meal), instead of with meals, may be more effective in increasing energy consumption.

McCrory and coworkers[20] found that a wide variety of sweets, snacks, condiments, and high-carbohydrate entrees coupled with a low variety of vegetables promoted long-term increase in energy intake and body fat. Providing nutritional supplements with a wide variety of sweets and carbohydrates may be helpful as the second step for the treatment of weight loss. Medications and aging play a major role in taste loss and in distortions of taste.[21] Because loss of taste and smell are common in the elderly, use of flavor-enhanced food has been found to have a positive effect on food intake.[22,23]

Additionally, resistance to eating at meal times in patients with dementia is widely reported.[24] Behavior disturbances also play a role in low body weight and weight loss in demented patients.[24] Providing feeding assistance with the regular use of feeding assistants may promote intake in the demented population.[25]

Tube Feeding

Tube feeding has been the treatment of choice in those with neuromuscular diseases (impaired swallowing or gag reflex), postoperative patients, those who are not able to eat, or patients using ventilators. Numerous studies have tried to determine the benefits of tube feeding.[26–28] Mitchell et al[27] found that there is no evidence that tube feeding prolonged survival. They found that advanced age and malignancy were the most frequent reasons for having poorer survival with tube feeding. Tokuda and coworkers[29] investigated the influence of feeding tube placement on survival in hospitalized elderly patients. In the multivariate survival model, which included older age, hip fracture history, admitting diagnosis of pneumonia, and tube feeding placement, only feeding tube placement (hazard ratio, 2.29; 95% confidence interval, 1.22–4.33) was significantly associated with higher mortality. Feeding tube–associated side effects include aspiration, diarrhea, and vomiting.[28] Only a small subset of nursing home residents (stroke and head and neck cancer survivors) have been reported to benefit from tube feeding.[30]

Parenteral Nutrition

Parenteral nutrition can be given to those elderly immediately after acute disease who are not capable of taking adequate calories or fluid.[31,32] Peripheral parenteral nutrition can only provide a limited amount of calories, and the infusion site has to be changed frequently or a central, indwelling catheter, with its risk of infection, may be placed. Marra and coworkers[33] reviewed 47 patients who received long-term total parenteral nutrition and found that the incidence of catheter-related infections was high, and that a significant proportion of catheter-related infections were polymicrobial and attributable to multidrug-resistant bacteria and fungi.

Thomas and colleagues[34] found a benefit in treating patients with parenteral nutrition for a longer period of time in a single-center, prospective, randomized, parallel group design clinical trial that evaluated long-term safety of peripheral parenteral nutrition in postacute patients receiving inadequate enteral nutrition in the nursing home. They found that the peripheral parenteral nutrition group demonstrated a trend toward improvement in nutritional and functional status, and that it could be safely administered with a low complication rate.[34]

Pharmacologic Interventions

The effects of nutritional support on the prevention and treatment of cancer and AIDS cachexia have been investigated extensively.[35–37] The review below looks at the evidence in relation to the benefits and risks of these medications and discusses proper use of these medications for geriatric safety.

PHARMALOGICAL AGENTS MOST COMMONLY USED FOR CACHEXIA

Megestrol Acetate

Megestrol acetate (MA) is a synthetic derivative of progesterone. The literature supports that MA may act as a progestational agent, an anti-inflammatory/glucocorticoid agent, and an intrinsic androgen agent.[38–46] It has been approved by the US Food and Drug Administration (FDA) as an appetite stimulant for HIV patients. Studies in both cancer patients and HIV patients have shown that megestrol acetate can improve appetite and help patients gain weight.[47–49]

MA is one of the more potent appetite stimulants available.[50,51] Jatoi[50] found that eicosapentaenoic acid (EPA) supplement, either alone or in combination with MA, does not improve weight or appetite better than MA alone. Jatoi and colleagues[51] also found that megestrol acetate provided superior anorexia palliation among advanced cancer patients compared to dronabinol alone, and combination therapy did not appear to add additional benefit.

Several studies have shown that treating cachexia in the elderly with MA improved quality of life and weight.[52–55]

One less widely known problem with megestrol acetate oral suspension (Megace OS, Bristol-Myers Squibb, Princeton, NJ) relates to its poor solubility and its poor absorption in the fasting state.[56] A newer megestrol acetate nanocrystal formulation (Megace ES) can be given at a lower dosage and possibly without meals.[56]

Potential Problems

Megestrol treatment can cause thromboembolism and adrenal suppression even within 12 weeks of treatment, but this has been much less commonly reported.[52,53,57,58] Long-term administration (>12 weeks) of MA has been associated with hyperglycemia, hypoglycemia, venous thromboembolism, secondary adrenal suppression, and adrenal insufficiency.[59–66] After 8 to 12 weeks of treatment with MA, study patients failed the low-dose adrenocorticotropic hormone (ACTH) stimulation test but responded normally once off of MA.[58] As MA has a long half-life, there is no need for tapering MA when stopping the drug.[39,67] During MA treatment, if the patient is scheduled for urgent surgery or has an infection, the patient should be given a stress dose of steroids. If the patient has clinical adrenal insufficiency, a short course of steroid replacement may be given; eg, prednisone 7.5 mg can be given for 3 to 4 days and then tapered off in 2 to 3 weeks. MA can be given again if needed after a of 3- to 6-month rest period.

Lambert and coworkers[68] reported that MA also has an antianabolic effect on muscle size even when combined with testosterone replacement, despite patients having significant weight gain. Combining MA with resistance exercise lessened this reduction in muscle mass. Sullivan and colleagues,[69] on the other hand, have recently reported that MA appears to blunt the beneficial effects of progressive resistance muscle strength training, resulting in less muscle strength and functional performance.

Potential Usage

MA may be used as an appetite stimulant for cancer, HIV, and geriatric cachexia for a short treatment period. MA oral suspension should be given 800 mg at a maximum dose, with meals.[49,56] Likewise Megace ES, which is "indicated for the treatment of anorexia (loss of appetite), cachexia (severe malnutrition), and/or an unexplained, significant weight loss in patients with acquired immunodeficiency syndrome (AIDS)" may be used. Its smaller volume (5 mL) and decreased viscosity may make it more palatable to geriatric patients. The maximum duration of either MA formulation should be no more than 8 to 12 weeks at a time.

There is now compelling evidence that progressive resistance training in the elderly can positively influence whole body energy expenditure, and significantly increase insulin sensitivity,[70] functional muscle strength, and fat-free mass in elderly persons.[70–75]

Megestrol improves appetite, weight gain, and body fat. Since megestrol is also a strong catabolic hormone (just like glucocorticoids), once patients stop the drug, it should not continue to exert this effect on the body. Sullivan and coworkers[69] found that MA could blunt the beneficial effects of progressive resistance exercise if given together (resulting in less muscle strength and functional performance gains). We hypothesize that progressive resistance training can improve functional muscle strength and fat-free mass in postmegestrol-treated patients. We need more studies to determine whether progressive resistance training can induce meaningful improvements in physical function and outcomes in postmegestrol-treated patients.

Dronabinol

The use of dronabinol, a cannabinoid derivative, has been reported anecdotally to lead to weight gain and appetite stimulation.[76,77] Reports in the literature indicate that cannabinoids may act both as an anti-inflammatory and a neuroprotective agent in the brain.[78] Volicer and coworkers[79] found that dronabinol treatment can increase body weight in Alzheimer's patients.

Morley[80] and his group have suggested that Dronabinol has a particularly good profile for persons with anorexia who are at the end of life. It has been used by HIV patients and is approved by the FDA as an appetite stimulant and antiemetic.[81–84]

Potential Problems

The main side effects are euphoria, somnolence, sedation, fatigue, and hallucinations.[79] Because of the sedation, dizziness, and hallucinations, dronabinol should be used with extreme caution in unsteady and confused elderly patients.

Potential Usage

It has been used by HIV and cancer patients and has been approved by the FDA as an appetite stimulant and antiemetic for HIV patients.[81–84] Morley[80] and his group have suggested that dronabinol has a good profile for persons with anorexia who are at the end of life. In our opinion, the case report evidence is encouraging, but not yet sufficient to be reasonably confident that dronabinol will not have more untoward adverse effects than benefits in the elderly. It may be particularly effective in patients whose anorexia is secondary to nausea.

Dronabinol should initially be given at a low dose (2.5 mg) in the evening. The dose should be increased to 5 mg per day if no improvement in appetite is seen after 2 to 4 weeks.[80]

Anabolic Agents

The use of anabolic drugs such as oxandrolone, and nandrolone has been explored in clinical trials with cachectic AIDS patients. The literature suggests that anabolic agents may induce hypertrophy of type I and II muscles.[85] Studies have found that nandrolone decanoate can decrease the weight loss in cancer and HIV patients.[86] Batterham and Garsia[86] studied nandrolone decanoate and megestrol acetate in HIV weight-loss patients and concluded that nandrolone decanoate and megestrol acetate both resulted in an increase in fat-free mass greater than seen with dietary counseling alone. Frisoli and colleagues[87] found that nandrolone may increase bone density and muscle mass in the elderly. Schols and colleagues[88] found that nutritional supplementation in combination with a short course of nandrolone may enhance the gain in lean muscle mass and respiratory muscle function in severe chronic obstructive pulmonary disease (COPD) patients without causing adverse side effects. Gaughan et al[89] also found that combination of low-dose erythropoietin and nandrolone decanoate is effective treatment for the anemia of end-stage renal failure.

Oxandrolone has been studied for treating weight loss in patients with HIV infection, cachectic COPD patients, and cancer patients with weight loss or delayed wound healing.[90–96] There also have been case reports such as those by Demling and DeSanti,[97] Spungen et al,[98] Mikulin,[99] Cioroiu and Hanan,[100] and Krasner and Belcher[101] reporting that oxandrolone increased wound closure.[97–104] Weight gain was primarily in the form of lean body mass.[91,95] Earthman and coworkers found that oxandrolone therapy in HIV infection improves weight, quality of life, and lean body mass.[96]

Potential Problems

The main side effects were masculinization in women, fluid retention, and hepatic toxicity (jaundice, cholestatic hepatitis, peliosis hepatitis, hyperplasias, and neoplasm).[94,105–107] Anabolic steroid abuse in athletes has been associated with a wide range of adverse conditions, including hepatotoxic effects, hypogonadism, testicular atrophy, impaired spermatogenesis, gynecomastia, and psychiatric disturbances.[108,109] Anabolic steroids can also cause prostatic hypertrophy, which is already a common problem in elderly men. Likewise, androgens could stimulate a focus of prostate cancer if present.

Concerns about long-term risks have restrained enthusiasm about their usage. We need more studies to determine whether anabolic steroids can induce meaningful improvements in physical function and patient-important outcomes in patients with physical dysfunction associated with chronic illness or aging.

Potential Usage

In our opinion, the case report evidence is encouraging but not yet sufficient to be reasonably confident that anabolic agents will improve nonhealing wounds in any particular patient group, despite Demling's finding that oxandrolone could increase wound closure.[102–104] At the same time, we believe it would not be unreasonable for a clinician to try these drugs in selected patients with nonhealing wounds (on a "trial basis") for a short duration.

Testosterone and Selective Androgen Receptor Modulators (SARM)

It is well reported that testosterone may induce hypertrophy of type I and II muscles.[85] Androgens increase muscle mass in part by acting on several cell types to regulate the differentiation of mesenchymal precursor cells in the skeletal muscle.[110] Testosterone has been used as a treatment for cachexia and weight loss in HIV patients, increasing weight and lean muscle mass but with unknown clinically meaningful changes in muscle function and disease outcome in HIV-infected men.[111] Older men are as responsive as young men to testosterone's anabolic effects.[112]

Dolan and coworkers[113] found that testosterone administration can increase muscle strength in low-weight HIV-infected women and suggested that it may be a useful adjunctive therapy to maintain muscle function in symptomatic HIV-infected women. Morley and others[114–116] were able to give testosterone safely to older men with hypogonadism and noted an increase in their muscle strength, decreased fat mass, and increased hemoglobin. A meta-analysis found that testosterone treatment is able to increase fat-free mass without change in body weight and with heterogeneous effects on muscle strength (a tendency toward improvement only for leg/knee extension and handgrip of the dominant arm) and bone density changes.[117]

A selective androgen-receptor modulator (SARM) is also being developed to build lean muscle mass in elderly patients.[85] A phase II clinical trial revealed preliminary findings that an experimental SARM can improve bone, muscle, and sexual function.[118]

Potential Problems

Older men have lower testosterone clearance rates and a higher frequency of adverse effects.[112] The frequency of a higher hematocrit (>54%), leg edema, and prostate events (exacerbation of prostate cancer) were more significant in older men.[112] Although older men can gain substantial muscle mass and strength with supraphysiological testosterone doses, they also experience a high frequency of the above noted adverse effects.[112]

Selective androgen-receptor modulators that are preferentially anabolic and that spare the prostate hold promise as anabolic therapies.

Potential Usage

Testosterone may be given to hypogonadal or glucocorticoid-treated men[114]; it also may possibly be given as a lean muscle enhancer for geriatric sarcopenic patients for a limited period of time.[112]

Dr. Bhasin's group[112] suggested a low testosterone treatment dose (125 mg/week), in patients with low normal testosterone levels, and in combination with resistance training exercise, had a lower frequency of adverse events and significant gains in fat-free mass and muscle strength; it's use, however, was not recommended by ISSAM (International

Society for the Study of the Aging Male) report.[119] They suggest that the appropriate therapeutic level should be toward mid- to lower young adult male serum testosterone levels.[119] Because of insufficient evidence, particularly regarding psychological safety and efficacy, general testosterone replacement in elderly hypogonadal men (and to maintain the physiological circadian rhythm of serum testosterone levels) is not warranted.[85,119]

Growth Hormone and Insulin-like Growth Factor-1

Growth hormone (GH) and insulin-like growth factor –1 (IGF-1) stimulate both amino acid uptake and protein synthesis in muscle and improve myocyte proliferation and differentiation in one animal study.[120] Reports from HIV-associated weight-loss studies had mixed results.[121–123] The use of either agent alone or a combination of recombinant human growth hormone (rhGH) and recombinant human insulin-like growth factor 1 (rhIGF-1), according to results from the HIV-associated weight-loss study, improved lean muscle mass but did not improve functional ability.[124] The effects of GH may be mediated through IGF-1; however, the combination of GH and IGF-1 did not consistently improve quality of life.[124]

Reports from Kaiser et al[125] and others[126–128] have demonstrated that this expensive form of therapy (recombinant GH) led to nitrogen retention and weight gain in malnourished older patients. Low-dose growth hormone given to stable malnourished elderly subjects leads to a faster gain in total lean body mass when compared with dietary intervention alone.[129] Aging-related, symptom complex improvements were normally observed within 6 months.[129,130]

Potential Side Effects

Dose-dependent side-effects include glucose intolerance/insulin resistance, tissue edema (ie, peripheral edema), carpal tunnel syndrome, and gynecomastia in the geriatric population.[127,128] After trauma, the anticatabolic action of rhGH is associated with a potentially harmful decrease in muscle glutamine production and increased mortality.[131]

The safety of long-term usage of GH has been observed in pediatric growth hormone users who had more fluid retention-related adverse events such as headache, edema, and arthralgia.[132,133] There was a higher proportion of pituitary adenoma (relative to craniopharyngioma), decreased glucose metabolism, cardiovascular events, and neoplasms in the older age usage group.[134]

Potential Usage

To avoid adverse events, investigators have recommended that patients should be treated with a lower dose (<0.03 mg/kg of body weight, 3 times/week), with close follow-up and monitoring for the above possible side effects.[128] Low-dose growth hormone in combination with resistance exercise may be given to stable sarcopenic-obese patients over a short period of time to enhance the lean muscle development.[129,135–138] Overall, long-term treatment with growth hormone cannot be justified in view of side effects that occur beyond 6 months.

OTHER POTENTIAL AGENTS

Ghrelin

Ghrelin, an endogenous ligand for growth hormone secretagogue receptor, was identified in the rat stomach. Ghrelin, with a structural resemblance to motilin, exhibited gastroprokinetic activity and potent orexigenic activity through its action on the hypothalamic neuropeptide Y (NPY) and Y(1) receptors, which was lost after vagotomy.[139] Peripherally administered ghrelin blocked interleukin (IL)-1 beta-induced anorexia and a produced positive energy balance by promoting food intake and decreasing energy expenditure.[139] Ghrelin, which is negatively regulated by leptin and IL-1 beta, increases NPY expression, which in turn acts through Y(1) receptors to increase food intake and decrease energy expenditure. Ghrelin is a potent releaser of GH in normal individuals with a dose-response relationship.[140] Gastric peptide ghrelin may, thus, function as part of the orexigenic pathway downstream from leptin and is a potential therapeutic target not only for obesity, but also for anorexia and cachexia.[139] Neary and coworkers[141] found that ghrelin increases energy intake in cancer patients with impaired appetite. Repeated administration of ghrelin improves body composition, muscle wasting, functional capacity, and sympathetic augmentation in cachectic patients with heart failure or chronic obstructive pulmonary disease.[142,143] These results suggest that ghrelin has anticachectic effects.[144] Ghrelin treatment may represent a new therapeutic strategy for the treatment of cardiopulmonary-associated cachexia.[144–147]

Potential Side Effects

The safety of long-term usage of ghrelin has not been established. Since ghrelin is a potent releaser of GH in man, the side effects of ghrelin is possibly quite similar to that of growth hormone—glucose intolerance/insulin resistance and tissue edema.

Potential Usage

Following the results from ongoing clinical trials and monitoring the unexpected side effects, we believe the evidence so far to be encouraging, but not yet sufficient to be reasonably confident that ghrelin can potentially be given for a short duration to sarcopenic-obese patients as a lean muscle enhancer. Because of insufficient evidence, particularly regarding safety and efficacy, administration of ghrelin cannot be recommended in geriatric weight loss at this time.

Amino Acids (Arginine, Glutamine, Leucine), Creatine, and Protein Supplement

Despite progress in our understanding of the weight loss and protein energy malnutrition in the elderly, poor protein intake remains a frequent and serious problem in both acute and long-term care facilities.[6,148–150] Campbell and colleagues[151] found that the intake of protein at the recommended daily allowance (RDA) (0.8 g/kg/day) is not sufficient to maintain muscle in the elderly. Brodsky and colleagues[152] found that myosin content was 51% less in young adults who consumed protein at a rate of 0.6 g/kg/day compared with those who consumed 1.5 g/kg/day. Evans[153] suggested that optimal dietary protein intake of 1.6 g protein/kg/day would enhance building lean muscle mass when coupled with resistance exercise in the elderly. It has also been demonstrated that a protein-calorie supplement in the elderly is associated with greater strength and muscle-mass gains.[153]

Additional protein supplementation for the elderly with wounds can improve wound healing.[95,154] Potter and colleagues[155] found that oral protein energy supplement during hospitalization reduced mortality and improved function. Arginine has been shown to stimulate the immune system during infections, to enhance wound healing, and to decrease the rate of tumor growth.[154,156]

Glutamine supplementation has been shown to attenuate cytokine release from lipopolysaccharide (LPS)-stimulated human peripheral blood mononuclear cells; this anti-inflammatory effect was reported to be associated with attenuation of mortality in heatstroke,[157,158] sepsis,[159] and post abdominal surgery[160]; and augments phagocytosis and improves neutrophil action postoperatively.[161] High cytokine levels may be a potential mediator of the alterations in gut glutamine metabolism during acute infection, which makes glutamine unavailable for protein synthesis.[162] Glutamine supplementation can also prevent down-regulation of myosin heavy-chain synthesis and muscle atrophy from glucocorticoids.[163]Collagen synthesis and improvement in mood or memory is significantly enhanced in the elderly with intake of a mixture of arginine, and glutamine.[164,165] Rathmacher et al[166] performed a meta-analysis of several prospective, randomized, double-blind studies in cancer and HIV patients and found positive weight gain after supplementing the diet with glutamine and arginine. May and colleages[167] found reversal of cancer-related wasting using oral supplementation with a combination of beta-hydroxy-beta-methylbutyrate, arginine, and glutamine. The efficacy of glutamine/arginine in treating geriatric cachexia is unknown.

Leucine and creatine supplementation has been shown to improve muscle protein synthesis in the elderly.[168–171]

Potential Side Effects

Excess protein or amino acid supplementation in elderly people with hyperuricemia or metabolic syndrome increases gout attacks and related complications.[172–177] Furthermore, glutamine is an essential nutrient for cell growth; exogenous supplementation of this substance might be used by rapidly growing tumor cells in patients with cancer.

Potential Usage

Most elderly Americans tend not to have adequate protein intake. The side effects of these supplements are minimal with modest supplementation, short duration, and close monitoring. Therefore, it would not be unreasonable for a clinician to use amino acid supplementation in malnourished patients with chronic diseases on a "trial basis."

Polyunsaturated Fatty Acids, Eicosapentaenoic Acid (EFA), N-3 Fatty Acids and Fish Oil

Dietary polyunsaturated fatty acids (PUFAs) are potent inhibitors of hepatic glycolysis and lipogenesis. Polyunsaturated fatty acids coordinately regulate the expression of several enzymes involved in carbohydrate and lipid metabolism.[178] Recently, carbohydrate-responsive element-binding protein (ChREBP) was implicated in the regulation of glucose metabolism.[179] Dentin et al[180] suggested that the PUFA suppresses glycolytic and lipogenic genes via ChREBP and thus decrease catabolism. Mishra et al[181] also suggested that the anti-inflammatory effects of polyunsaturated fatty acids (fish oil) may result from the inhibitory effects of oxidized omega-3 fatty acids on NF-kappaB activation and thus decrease muscle catabolism. Indirect evidence in the community-based sampling study conducted by Ferrucci and colleagues[182] found that the plasma concentration of PUFAs, and especially total N-3 fatty acids, were independently associated with lower levels of proinflammatory markers (IL-6, IL-1ra, tumor necrosis factor alpha [TNF-α], C-reactive protein) and higher levels of anti-inflammatory markers (soluble IL-6r, IL-10, TGF-beta) independent of confounders.

Tisdale et al[183] found that using omega-3 (N-3) fatty acids can stop the weight loss in an experimental cachexia model. Fearon and colleagues' cachectic cancer patients study also suggested that if given sufficient N-3 fatty acid supplementation, these patients had weight gain, lean tissue gain, and improved quality of life.[184] Their role in the treatment of cancer cachexia remains unclear[185]; however, their use is promising.[50,184]

Potential Side Effects

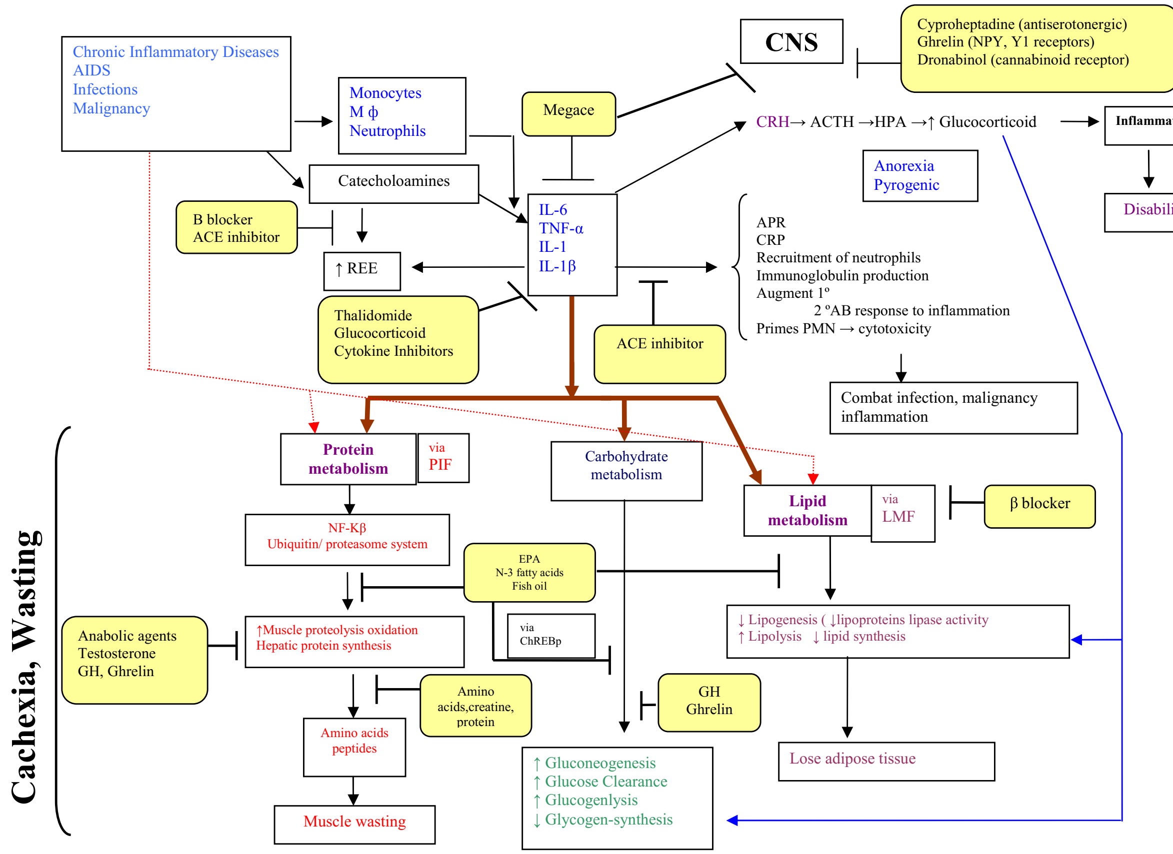
Excess supplementation can cause gastrointestinal side effects[186] and increase the potential adverse effects of polyunsaturated acids on lipid peroxidation in patients with chronic renal failure.[187] Long-term dietary supplementation with high doses of N-3 fatty acids can significantly modify red blood cell (RBC) structure and function, which might lead to harmful side effects especially in predialysis patients.[188]

Potential Usage

Safety is always an important issue. Long-term or high-dose supplementation with specific polyunsaturated fatty acids, N-3 fatty acids formulations creates a risk of inadvertently creating imbalance in metabolic pathways, for example, in relation to the w3:w6 ratio and to prostaglandin effects (eg, on bleeding time). At the same time, it must be said that a number of prominent researchers[50,183,184] have generally stated that they felt this form of supplementation to be a safe treatment, although more long-term data are necessary. The evidence from Tisdale et al,[183] Fearon et al,[184] and Jatoi[50] is encouraging but not yet sufficient to be reasonably confident that these supplements will improve cachexia and its related pathology in the geriatric group.

Cyproheptadine

Cyproheptadine is an antihistamine and antiserotonergic reagent. Cyproheptadine was reported to be effective in treat-



ChRZBp= carbohydrate-responsive element-binding protein, GH =growth hormone, NPY = hypothalamic neuropeptide Y, EPA = Eicosapentaenoic acid, LMF = Lipid Mobilising Factor, PiF = Proteolysis-inducing Factor, NF-Kβ = nuclear factor kappaB , PMN = polymorphonuclear cells, APR = acute phase response, CRP = C-reactive protein , CRH = corticotropin-releasing hormone, ACTH = adrenocorticotropin, HPA =hypothalamic-pituitary-adrenal axis, REE = resting energy expenditure, M ϕ = macrophage, IL-6 = interleukin-6, TNF-α = Tumor necrosis factor alpha, IL-1 = interleukin-1, IL-1β = interleukin-1beta, → = increase, ┤= inhibition

Fig 1. *How Drugs May Affect Complex Pathophysiology of Cachexia.*

ing selected groups of children with anorexia and reportedly affects central appetite centers. However, the results of clinical trials in cancer patients have been disappointing.[189]

Potential Side Effects

The side effects of sedation, dizziness, urinary retention, and even possible extrapyramidal symptoms[189,190] make it less likely to be a good drug to use in the geriatric population. Its efficacy in the geriatric population is unproven despite its surprising widespread usage in this group of patients.

Potential Usage

The side effects of cyproheptadine can be minimal with lower dosage, short duration, and under close monitoring. However, its benefit is questionable. It is unlikely that this drug will have a major effect on appetite.

Beta Blockers

Wasting in cancer patients is multifactorial, but at least in part is associated with an increased beta (1) and beta (2)-adrenoceptor activity, as well as elevated basal metabolic rate and altered host metabolism.[191] Weight gain in response to beta blocker therapy in the hypertensive population may be attributable to decreased resting energy expenditure, inhibition of lipolysis, and decreased insulin sensitivity.[192] Beta blocker therapy has also shown to reverse excess protein catabolism after severe burns and may increase skeletal muscle mass.[193] Hryniewicz and coworkers[194] were able to partially reverse cachexia through beta-adrenergic receptor blocker therapy in patients with chronic heart failure.

Potential Side Effects

There is a higher percentage of elderly patients with sick sinus disease, orthostatic hypotension, and bradycardia after beta blocker therapy.[195] The intrinsic property of beta blockers alone or in combination with other cardiac medications taken by the elderly population can exacerbate their risk for sick sinus syndrome, cause bradycardia, hypotension, syncope, and even sinus arrest.[196]

Potential Usage

Beta blocker treatment could possibly be used for cachectic cancer patients.[191,197] Cautious use of beta blocker treatment can potentially prevent further weight loss in cachectic geriatric patients, particularly those with cardiac problems that benefit from this form of treatment.

Table 2. *Summary of Possible Pharmacological Treatment Agents*

Medications	Potential Usage	Potential Problems	Recommended Regimens
Megestrol acetate	Appetite stimulant for AIDS-related cachexia and possible use in cancer and geriatric-related cachexia.	Edema, hypertension, deep vein thrombosis, adrenal suppression	400–800 mg/day
Dronabinol	Appetite stimulant for HIV, cancer, and geriatric (dementia)-related cachexia, and patients with symptoms of pain and agitation.	Sedation, fatigue, and hallucinations	2.5 mg initially in the evening. Increase to 5 mg per day after 2 to 4 weeks
Anabolic agents	Cancer, HIV, and chronic renal failure–related cachexia	Masculinization, fluid retention, hepatic toxicity	Oxandrolone-2.5 mg 2–4 times/day
Testosterone	Hypogonadal or glucocorticoid-treated cachexia and possible use in sarcopenic cachexia	Hemo-concentration, leg edema, prostate events	Not recommended in geriatric patients
Growth Hormone, Insulin-like Factor-1 and Ghrelin	HIV-related cachexia and possible use in sarcopenic cachexia	Dose-dependent side effects—glucose intolerance/insulin resistance, edema, carpal tunnel syndrome	Not recommended in geriatric patients
Amino acids, creatine, and protein supplement	Malnourished (HIV, cancer, elderly) or in patients with nonhealing wounds	Gout and hyperuricemia-related complications	1.6 g protein/kg/day
Antioxidant- polyunsaturated fatty acids, N-3 fatty acid and Fish oil	Possible use in cancer-related cachexia	Gastrointestinal side effects, interference with red blood cells' structure and function	Undetermined
Cyproheptadine	Depression-related cachexia	Sedation, dizziness, urinary retention	Not recommended
Cardiac-neuro inhibitors (Beta blockers, Angiotensin-converting enzyme inhibitors)	Cardiac-related cachexia	Cardiac bradycardia, hypotension	Pending cardiac assessment
Cytokine production inhibitors or antibodies	Inflammation-related cachexia (rheumatoid arthritis, HIV, cancer)	Gastrointestinal disturbances, neuropathy, teratogenicity, infections, and malignancies	Undetermined

Angiotensin-Converting Enzyme Inhibitors

Elderly cachectic patients often have some form of cardiovascular disease. When comparing the features of cachectic and noncachectic congestive heart failure patients to those of healthy subjects, cachectic patients are more likely to have raised plasma levels of catecholamines, cortisol, aldosterone, TNF-α, and the highest plasma renin activity.[198] Angiotensin-converting enzyme (ACE) inhibitors inhibit angiotensin-converting enzyme and have been shown to be effective in many cardiovascular diseases and may even be helpful for those with cardiac cachexia.[199–201] ACE inhibitor treatment potentially can possibly prevent further weight loss in cardiac-related cachexia, even in geriatric patients.[202,203]

Maggio and coworkers[203] in their Chianti study also found that those elderly patients treated with ACE inhibitors had significantly higher levels of insulin-like growth factor 1 (IGF-1) and greater muscle strength and better physical performance. They suspect that ACE inhibitors might slow the decline in muscle strength and physical function that are often observed in older subjects. From above studies, we believe that often both cardiac conditions and other independent effects on cachexia may be at play in the elderly.

Potential Side Effects

The renin-angiotensin-aldosterone system plays a key role in the regulation of fluid and electrolyte balance. There are a number of side effects associated with angiotensin-converting enzyme inhibitors such as cough, hypotension, allergic dermatitis, headache, vertigo, paresthesia, and renal failure in renal stenosis patients.[204,205] The intrinsic side effects of these drugs alone or in combination with other cardiac medications taken by the elderly population can also exacerbate the risk for fall and syncope and should be monitored closely.

Potential Usage

ACE inhibitors can be considered for the treatment of those with underlying cardiac conditions such as hypertension or heart failure patients with cachexia.[199–201,203]

Cytokine Inhibitors (TNF-α, Production Inhibitor-Pentoxifylline, Thalidomide and Anti-TNF Antibody-Infliximab and Adalimumab)

Aging is associated with increased production of catabolic cytokines, reduced circulating levels of IGF-1, and acceleration of sarcopenia.[206,207–214] Cachexia, a significant loss of lean body mass, arises from such conditions as cancer or HIV results in wasting of skeletal muscle. Unlike starvation, the weight loss seen in chronic illnesses arises equally from loss of muscle and of fat. It is actually a highly complex metabolic disorder involving anorexia, anemia, gluconeogenesis, glucogenlysis, lipolysis, ubiquitine metabolism, Nuclear factor kappa B (NF-kappaB) activation, proteasome destruction of myosin, myostatin overexpression, and insulin resistance.[212,215–217]

Available data indicate that a higher serum cytokine level is associated with a greater likelihood of disability and a higher mortality in older persons.[206,218–221] Cytokines play a significant role in the progression of catabolism, cachexia, and mortality. Interactions among various inflammatory cytokines and anabolic factors have been observed, with the balance skewed in favor of catabolism.[222–231] Inflammatory factors are likely to play an important role in the increased activity of gluconeogenesis, glucogenlysis, lipolysis, ubiquitine proteasome activity, NF-kappaB activation, myostatin overexpression, and insulin resistance.[212,215–217,228,229,232]

The complex pathophysiology of cachexia is simplified in Figure 1.

IL-1, IGF-1, IL-6, and TNF-a all have been implicated.[218–221,231,233–241] The interaction of these cytokines is simplified in Figure 1.

TNF-a is elevated in patients with advanced HIV, cancer, or those with opportunistic infections and has a correlation with the development of wasting.[242,243] Anti-tumor necrosis factor antibody has a great potential as a treatment for cachexia.[222,244–247] Pharmacologic manipulation of TNF-a regulation has been studied as a means of stabilizing or reversing the wasting process.[222,244–248]

TNF-a production inhibitors such as pentoxifylline, thalidomide, and anti-TNF antibody or TNF receptor blockers, infliximab and adalimumab, are commercially available now. Infliximab and adalimumab have been found to be useful as a treatment for chronic inflammatory conditions such as rheumatoid arthritis, but their use as single agents for the treatment of cachexia has not been successful.[249–252] There have been studies using pentoxifylline to treat cancer- and HIV-associated cachexia but the modest improvement in appetite, weight, and sense of well-being has been disappointing.[253,254]

Potential Side Effects

Gastrointestinal disturbances were among the major adverse effects from pentoxifylline.[255] Rash, peripheral neuropathy, somnolence, constipation, and teratogenicity were the major side effects from thalidomide.[256,257]

TNF also plays an important role in host defense and tumor growth control.[225] Sathe et al[258,259] found that pentoxifylline treatment increased the mycobacterial load in macrophages of AIDS patients with disseminated *Mycobacterium avium*-intracellulare complex infection. Bongartz and others found that using anti-TNF antibody therapy in rheumatoid arthritis patients increased the risk of serious infections and malignancies.[249–252]

Potential Usage

Cytokine inhibitors treatment can possibly be used for elderly patients with severe rheumatic arthritis. The exact role of cytokine inhibitors in the treatment of cachexia in the elderly otherwise remains to be elucidated.

CONCLUSION

Weight loss is associated with increased mortality and is a major problem in the geriatric population. It is understood that when the elderly stop eating, their death is imminent. The first step in management of elderly weight loss is to attempt to identify and treat any specific underlying treatable or contributing condition. Providing an energy-dense nutritional supplement 30 minutes to 90 minutes before a meal and in combination with resistance exercise can increase energy intake and improve function in the elderly. Use of flavor-enhanced food has a positive effect on food intake. Progressive resistance exercise coupled with optimal dietary protein intake (supplementation) would also enhance preserving muscle mass in the elderly. Providing feeding assistance and using feeding assistants may promote food intake in demented patients.

More than a half dozen agents have now been studied to improve appetite, weight gain, and sarcopenia in elderly patients with cachexia. Crypoheptadine, oxandrolone, dronabinol, megestrol acetate, and growth hormone all were tried in geriatric cachexia. These were all small studies and results were interesting (either with potential side effects or unimpressive results). We need more studies to determine whether these drugs can induce meaningful improvements in physical function in patients with physical dysfunction associated with chronic illness or aging.

In our opinion, small study evidence is interesting but not yet sufficient to be reasonably confident to endorse most of these drugs. Further research will be needed to fully evaluate the safety and efficacy of above drug interventions, as well as the value of newer agents to determine what their effects are in the treatment of geriatric cachexia. In rare selected cases, clinicians have tried on a "trial basis" some of these drugs for a short duration with close monitoring of the patients. A clear understanding of the risk/benefit ratio will guide the clinician in the use of these agents.

The potential usage and problems of these medications are summarized in Table 2. The interaction of these cytokines and how these medications affect complex pathophysiology of cachexia is simplified in Figure 1.

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