

Pharmacotherapy of Cachexia

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Cachexia is a wasting syndrome that involves loss of muscle with or without loss of fat. (1) Hallmark of this syndrome is loss of appetite and weight resulting in extreme weakness. Cachexia is outcome of number of chronic diseases like malignancy AIDS, COPD, rheumatoid arthritis, tuberculosis, hepatic renal and cardiac failure.

The loss of weight results from skeletal muscle breakdown, abnormalities in carbohydrate and fat metabolism. There is negative nitrogen balance due to increased catabolism and decreased anabolism. (2) Anorexia, inflammation, insulin resistance, and increased muscle protein breakdown are frequently associated with cachexia.

Cachexia, is outcome of number of events like anorexia, decreased physical activity, decreased secretion of anabolic hormones, and abnormalities in protein, lipid, and carbohydrate metabolism. Basically, cachexia is result of cytokine-driven dysregulation of the peripheral signals (mainly leptin, ghrelin, and serotonin) (3), reaching the brain hypothalamic region, which plays a central role in balancing the orexigenic and anorexigenic signals, leading to decreased food intake and increased resting energy expenditure (REE).

The ideal management of cachexia is to cure the underlying disease but it is difficult in most of cases. Other choice is to counteract weight loss by increasing nutritional intake, however, nutrition modification may alone may not completely reverse cachexia in absence of protein synthesis.

Number of pharmacological agents are gaining place in management of cachexia and they either enhance anabolism or decrease catabolism. Since these two aspects are interlinked therefore alone anabolic therapy will not be effective. Thyroid hormones, growth hormone, insulin, melatonin and testosterone are known to affect anabolic process. Whereas glucagon, cortisol, proinflammatory cytokines, eicosanoids and tumor

glycoproteins cause increased catabolism. Malignancy is known to mimic body response to systemic inflammation involving proinflammatory cytokines like interleukin IL-6, TNF, Interferon gamma. TNF is well established to cause muscle wasting (4) as it causes insulin resistance. Insulin is known to have anabolic effect therefore TNF alpha leads to increase catabolism.

Eicosanoids are major inflammatory mediators also similarly result in cachexia (5). Drugs like NSAIDs, Cox-2 inhibitors, macrolides and thalidomide those block prostaglandins have role to treat cachexia.

Other useful agents in management of cachexia are clenbuterol, omega fatty acids aminoacids like cysteine, leucine, arginine, glutamine, ATP, creatine, ACEI, progestins, cannabinoids, ubiquitin (proteasome), statins, hydralazine, multivitamins.

Progestagens, like megestrol, medroxyprogesterone acetate are approved for treatment of cancer and AIDS related cachexia. (6) They increase appetite by releasing central neuropeptide Y and reverts weight loss. The weight gain is result of fat accumulation and not due to increase in muscle mass. Progestagens also downregulate synthesis of proinflammatory cytokines. In addition they increase body weight by water and fat mass accumulation.

Corticosteroids are appetite stimulants but on the other hand they may lead to muscle breakdown due to their catabolic actions. Therefore, their long-term use will have side effects like protein breakdown, insulin resistance, water retention, and adrenal suppression. (7)

Cannabinoids also act centrally to increase appetite but lack effect on muscle metabolism. (8)

ACE inhibitors: Angiotensin 2 increase production of proinflammatory cytokines influence muscle wasting. Therefore, ACEI improve muscle mass and function (9)

Statins have anti-inflammatory action independent of their action on cholesterol pathway. (10) Statins decrease CRP which is a nonspecific marker of inflammation and

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is persistently raised in cachexia and cancer patients.

Macrolide antibiotics possess anti-inflammatory properties and prokinetic properties. This anti-inflammatory action may have role in cachexia by decreasing TNF and interleukin 6.(11)

Creatine is an essential phosphate donor for synthesis of ATP which is main energy source for muscular activity. It also increases muscle mass in healthy individuals. (12) It is consumed as safe dietary supplement Carnitine is a cofactor required for transforming the free long-chain fatty acids into acyl-carnitine and for their subsequent transport into the mitochondrial matrix to produce acetyl-coenzyme A through the β oxidation pathway. The relation between coenzyme A and carnitine is pivotal for cell energy metabolism: Coenzyme A is required for β -oxidation, metabolism of several amino acids, pyruvate dehydrogenase synthesis, and thus for triggering the tricarboxylic acid cycle. Patients with cancer develop carnitine deficiency as antineoplastic drugs interfere with the absorption and synthesis of carnitine.

Testosterone is well known to induce muscle growth and has been misused by the sportspersons. However, they are associated with adverse effects like hepatotoxicity, hirsutism and lipid profile abnormalities. Testosterone levels are usually lower in patients of advanced severe diseases. Testosterone analogues like nandrolone, oxandrolone, danazol are established to stimulate muscle synthesis. (13)

Amino acids like N acetyl cysteine increase plasma albumin and body cell mass in cancer patients. beta hydroxyl beta methyl butyrate which is a leucine metabolite is also known to promote lean body mass.(14)

Omega fatty acids EPA and DHA found in fish oil inhibit proteolysis. Fatty acid alter cell permeability and transport properties resulting in beneficial effects. They reduce proinflammatory prostaglandins, inflammatory cytokines, CRP and block proteolytic enzymes. Omega-3 fatty acid result in net gain of weight, lean tissue, and improved quality of life. (15)

Bortezomib, an NF- κ B and ubiquitin-proteasome inhibitor have been tested in experimental models of cachexia, with some positive results. This specifically and reversibly inhibit the threonine residue of 26 S proteasome enzyme complex and plays role in regulating protein degradation.(16)

Thalidomide has been in use for treatment of cachexia associated with acquired immunodeficiency syndrome, tuberculosis, and cancer due to its immunomodulatory and antiinflammatory properties; It inhibits TNF- α and IL-6 production. (17)

Ghrelin is a 28 amino acid peptide produced by the P/D1 cells of the stomach. (18) Ghrelin stimulate GH secretion and promotes food intake (via the orexigenic NPY system) and decreases sympathetic nerve activity (19). Ghrelin has been shown to decrease muscle wasting and functional capacity in cachexia .

Insulin is known to be associated with increase in weight and it attenuates the progression of cancer cachexia . Insulin treatment stimulate carbohydrate intake, decrease serum-free fatty acids and increase whole body fat.(20)

Branched-chain amino acids are neutral amino acids have beneficial metabolic actions. They interfere with brain serotonergic activity and inhibit the overexpression of critical muscular proteolytic pathways. They stimulate food intake and counteract muscle wasting (21) .

Olanzapine, an atypical neuroleptic cause significant weight gain with positive metabolic effects. Its lower doses very well tolerated with promising clinical activity on weight, nutrition, and function in advanced cancer patients with cachexia. (22)

Formoterol, a β 2-adrenergic agonist, is a very efficient agent preventing muscle weight loss . (23)

Hydrazine Sulfate interrupts the ability of the liver to convert lactic acid from tumours into glucose result in starvation of tumour cells . Gluconeogenesis requires a great deal of energy and excessive gluconeogenesis is thought to be a significant factor that contributes to cancer cachexia (24).

Currently progestagens and corticosteroids remains only approved drugs for cancer Cachexia and even they are partially effective; Newer drugs include anti-IL-6 and IL15. Anti IL6 a humanized monoclonal antibody inhibits cachexia; (25) IL-15, a cytokine in skeletal muscle, suppress the increased DNA fragmentation associated with muscle wasting (26) and also to have muscle anabolic.

Selective androgen receptor modulators (SARMs) modulate myoblasts proliferation, promotes sexual dimorphic muscle development and alters muscle fiber type. SARMs like Ostarine with predominantly anabolic activity in muscle and bone with minimal androgenic

effects in most other tissues. Ostarine improve LBM and physical performance in healthy older men and women (27).

Myostatin has been implicated in several forms of muscle wasting, including cancer cachexia. Anti-myostatin strategies may prove beneficial in cachectic patients.(28)

Blockade of melanocortin signaling using antagonists to the melanocortin MC4 receptor is shown to attenuate disease-associated anorexia and wasting.(29)

Conclusion

Since the chronic ailments are showing upward trend ,cachexia has assumed a major challenge to the treating physician . Though the ideal management is to treat the root cause of cachexia which mostly is not possible especially in the situations like advanced cancers. Therefore , there is more scope for the pharmacological interventions but at present the ideal therapy still eludes us .

References

1. Evans WJ, Morley JE, Argiles, *et al.* Cachexia :a new definition. *Clinical Nutrition* 2008; 27(6):793-99
2. WL, Alaka KJ, Murphy MH, *et al.* Impact of the nutritional regimen on protein catabolism and nitrogen balance in patients with renal failure.*Macias J Parental Nutr*1996 ;20(1):56-62
3. Nandi J, Meguid MM, Inui A, *et al.* Central mechanisms involved with catabolism. *Curr opin Clin Nutr Metab Care* 2002 ;5(4):407-18
4. Paolo B , Marco S. Cellular and molecular mechanisms of muscle atrophy. *Dis Model Mech* 2013; 6(1):25-39
5. Ross JA, Fearon KC. Eicosanoid dependent cancer cachexia and wasting.*Curr Opin Clin Nutr Metab Care* 2002 ;5(3):241-8
6. Clelia M,Maccio A,Mantovani G.Multitargeted treatment of cancer cachexia.*Critical Review In Oncogenesis* 2012;17(3):305-314
7. Loprinzi CL,Kugler JW,Sloan JA,*et al.*Randomised comparison of megestrol acetate versus dexamethasone versus fluoxymestron for the treatment of cancer cachexia. *J Clin Oncol*1999;17:3299-306
8. Kirkham TC.Cannabinoids and appetite:food craving and food pleasure. *Int Rev Psychiatr* 2009;21(2):163-71
9. Schanze N, Springer J. Evidence for an affect of ACE inhibitors on cancer cachexia. *J Cachexia Sarcopenia Muscle* 2012;3(2):139
10. Antonopoulos AS, Margaritis M, LeeR, Channon K, Antoniadis C. Statins and cachexia. *Curr Pharm Des* 2012;18(11):1519-30
11. Sassa K, Mizushima Y, Kobayashi M. Differential modulatory effects of clarithromycin on the production of cytokines by a tumour. *Antimicrob Agents Chemother* 1999;43(11):2787-2789
12. Rawson ES, Volek JS. Effects of creatine supplementation and resistance training on muscle strength and weight lifting performance. *J strength Cond Res* 2003 ;17(4):822-31
13. Kadi F.Cellular and molecular mechanisms responsible for the action of testosterone on human skeletal muscle.A basis for illegal performance enhancement. *Br J Pharmacol* 2008;154(3):522-528
14. Madeddu C, Antonio Maccio A, Filomena Panzone, F, *et al.*Medroxyprogesterone acetate in the treatment of cancer cachexia. *Expert Opinion On Pharmacotherapy* 2009;10(8):1359-66
15. Yeh KY, Wang HM, Chang JW, *et al.* Omega-3 fatty acid-micronutrient- and probiotic- enriched nutrition helps body weight stabilization in head and neck cancer cachexia .*Oral Surg Oral Med Oral Pathol Oral Radiol* 2013;116(1):41-8
16. Adams J.The proteasome :a suitable antineoplastic target. *Nat Rev Cancer* 2004;4:349-60
17. Gordon JN,Trebbles TM, Ellis RD, Duncan HD, Johns T, Goggin PM.Thalidomide in the treatment of cancer cachexia:A randomised placebo control trial. *Gut* 2005;54:540-5
18. Kojiina M, Hosada H, Date Y. Ghrelin is a growth hormone releasing acylated peptide from stomach. *Nature* 1999;402:656-660.
19. Lely AJ, Tschop M, Heiman ML, Ghigo E.Biological, physiological,pathophysiological and pharmacological aspects of ghrelin. *Endocr Rev* 2004;25:426-457
20. Trobec K,Haehling S,Anker SD,Lainscak M.Growth hormone,insulin like growth factor-1 and insulin signaling-a pharmacological target in body wasting and cachexia. *J Cachexia Sarcopenia Muscle* 2011;2:191-200
21. Argilles J, Costelli P, Carbo N, *et al.* Bruera and R.Kurzrock. Branched chain amino acid metabolism and cancer cachexia. *Oncol Rep* 1996 ;3(4):687-90
22. Braiteh F, Dalal S, Khuwaja A, *et al.* Phase 1 pilot study of the safety and tolerability of olanzapine(OZA) for the treatment of cachexia in patients with advanced cancer. *J Clin Oncol* 2008; 26(15S):20529
23. Toledo M, Springer J, Busquets S, *et al.* Formetrol in the treatment of cancer cachexia:effects on heart functions. *J Cachexia Sarcopenia Muscle* 2014 ;5(4):315-20
24. Ray PD,Hanson RL,Lardy HA. Inhibition by hydrazine of gluconeogenesis in rat. *J Biol Chem* 1970;245:690-6
25. Andok, Takahashi F, Motojima S, *et al.* Possible role of tocilizumab,an anti IL-6 receptor antibody in treatment of cachexia. *J Clin Oncol* 2013 20;31(6):69-72
26. Figueras M, Busquets S, Carbo N, *et al.* Interleukin-15 is able to suppress the increased DNA fragmentation associated with muscle wasting in tumour bearing rats. *FEBS Lett* 2004;569:201-6
27. Evans W, Smith M, Morley J,*et al.* Ostarine increases lean body mass and improves physical performance in healthy elderly subjects:Implications for cancer cachexia patients. *J Oncol* 2007;25:4536-41
28. Lokireddy S, WiiesomalW, Bonala S, *et al.* Myostatin is a novel tumoral factor that induces cancer cachexia. *Biochem J* 2012 15;446(1):23-26
29. Foster AC, Chen C,Markinson S,Marks DL. MC-4 receptor antagonists: A potential treatment for cachexia. *Drugs* 2005 8(4):314-9