

Catabolic Wasting

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Catabolic wasting or cachexia is a clinical wasting syndrome that is characterized by unintended and progressive weight loss, weakness, and low body fat and muscle. At least 5% of body weight is lost. Cachexia is not caused by poor appetite and nutritional intake, but rather by a metabolic state in which a "breaking down" rather than a "building up" occurs in bodily tissues no matter how much nutritional intake occurs. Additionally, whether a patient receives nutrition orally or intravenously makes no difference. The patient simply cannot gain weight, so eating more is not an answer.

It is estimated that half of all cancer patients experience catabolic wasting, with a higher occurrence seen in cases of malignancies of the lung, pancreas, and gastrointestinal tract. The syndrome is equally common in AIDS patients and can also be present in bacterial and parasitic diseases, rheumatoid arthritis, and chronic diseases of the bowel, liver, lungs, and heart. It is usually associated with anorexia and can manifest as a condition in aging or as a result of physical trauma. Catabolic wasting is a symptom that diminishes the quality of life, worsens the underlying condition, and is a major cause of death.

CACHEXIA AND CANCER

Researchers previously believed that cancer increased metabolic demand (stolen protein), produced toxins, and suppressed appetite, resulting in malnutrition. New research, however, shows that although cancer may raise resting metabolic rate, improved nutrition does not alleviate the symptoms of anorexia, chronic nausea, early satiety, and changes in taste that make even favorite foods unpalatable to some cancer patients. The view of clinicians is that bodily wasting is the result of a combined action of tumor products and host immune factors--in particular, cytokines--that lead to poor appetite, muscle wasting, and an altered metabolism. The cytokines interleukin-1 (IL-1), IL-6, interferon-gamma, tumor necrosis factor-alpha (TNF-alpha), and brain-derived neurotrophic factor appear to increase and play a role in the progression of cachexia in cancer, as well as in other diseases associated with bodily wasting.

Other metabolic alterations associated with the syndrome are hyperglyceridemia, lipolysis, and accelerated protein turnover, all leading to a loss of fat mass and body protein. The dysregulation of metabolic processes produces a negative energy balance.

Clinicians are currently treating cancer-related catabolic wasting with a variety of interventions, including nutritional supplementation, administration of cytokine inhibitors, steroids, hormones, cannabinoids, and thalidomide. Gemcitabine, a chemotherapeutic drug, has shown clinical benefits in treating cachexia. Newer nutritional intervention with megestrol acetate derivatives, gamma-receptor agonists, amino acid manipulations, myostatin inhibitors, and uncoupling protein modifiers is currently being explored. Further research must be done to investigate gender differences in relation to pathophysiology and therapy.

There is some evidence that the drug hydrazine sulfate may help cancer patients gain weight and improve the cachectic state. The drug is by prescription and should be given by a complementary physician familiar with its use, as it can be toxic. The dose is usually 60 mg a day. Narcotic painkillers or benzodiazepine anxiety-reducing agents cannot be given concomitantly.

CACHEXIA AND HIV

Bodily wasting is a common manifestation of HIV, occurring at any state of infection and indicative of disease progression.

Malnutrition, a result of appetite loss, is commonly due to nausea and vomiting. Weakness and diarrhea are often present as well. Persons with HIV may also experience malabsorption of nutrients due to enteric infections associated with the disease, even if they consume sufficient calories.

The effects of malnutrition are thought to contribute to increased immune suppression including a reduction in T-lymphocyte helper and suppressor cells, altered phagocytic functions, and decreased killer-cell activity, leading to opportunistic infections and cancers. Proinflammatory cytokines IL-1, IL-6, and TNF have been cited in many studies as potential causes of wasting. Most people with advanced HIV and AIDS have some degree of wasting.

To reverse weight loss, appetite stimulants, anabolic agents (such as growth hormone or testosterone), cytokine inhibitors, and hormones are often prescribed. Megestrol acetate and dronabinol (which contains the active ingredient in marijuana) are approved for the treatment of wasting. Thalidomide, which aids in the healing of aphthous ulcers of the mouth and esophagus, is now available.

DIAGNOSIS

Unfortunately, the cachectic state is all too apparent to any observer. In severe chronic disease with the development of multiple organ failure, some degree of malabsorption of nutrients probably contributes to the cachectic state. The entire picture is reflected in a continuing decline of the serum albumin as the illness progresses. Conversely, an increase in serum albumin suggests an improvement in the nutritional state. As long as a patient is maintained on nutrition by the normal route (by mouth), optimizing the state of digestive secretions is probably advisable, although there may not be clinical studies demonstrating this. The Heidelberg test reflects this environment and can be used to ascertain the need for either hydrochloric acid or pancreatic enzyme supplementation.

FISH OIL STUDIES

Depletion of muscle and adipose tissue in cancer cachexia appears to arise not only from decreased food intake, but also from the production of catabolic factors secreted by certain tumors such as tumor necrosis factor and other autoimmune cytokines. Experiments with a cachexia-inducing tumor in mice showed that when part of the carbohydrate calories in their diet was replaced by fish oil, host body weight loss was inhibited. The catabolic-inhibiting effect occurred without an alteration of either the total calorie consumption or nitrogen intake (Tisdale et al. 1990).

Fish oil concentrate was found to inhibit tumor-induced lipolysis directly (Beck et al. 1991). The catabolic fat loss-preventing effect of fish oil arose from an inhibition of the elevation of cyclic AMP (adenosine monophosphate, a nucleotide involved in energy metabolism) in fat cells. The increased protein degradation in the skeletal muscle of catabolic animals was also inhibited by fish oil; this effect was due to the inhibition by fish oil of muscle prostaglandin E2 production in response to a tumor-produced proteolytic factor. Thus, reversal of cachexia by fish oil in this mouse model results from its capacity to interfere with tumor-produced catabolic factors (Tisdale 1996). Similar factors have been detected in human cancer cachexia.

Studies show that the DHA fraction of fish oil is the best documented supplement to suppress the inflammatory cytokines involved in the catabolic process such as TNF- α , IL-6, IL-1(b), and prostaglandin E2 (Khalfoun et al. 1997; De Caterina et al. 1998, 1999; Jeyarajah et al. 1999; Kelley et al. 1999; James et al. 2000; Kremer 2000; Watanabe et al. 2000; Yano et al. 2000; Das 2001; Tepaske et al. 2001). Catabolic wasting patients should consider taking 8 capsules a day of Super GLA/DHA, a combination of gamma-linolenic acid and primarily the DHA fraction of fish oil. Both GLA and DHA significantly suppress inflammatory cytokines (Purasiri et al. 1994; Mancuso et al. 1997; Dirks et al. 1998; DeLuca et al. 1999; James et al. 2000).

BENEFICIAL EFFECTS OF GLUTAMINE

Glutamine has been one of the most intensively studied nutrients in the field of nutrition support in recent years. Animal studies show that glutamine is effective against catabolic stress (Millward et al. 1989; Castell et al. 1994; Ziegler et al. 1996). Glutamine supplementation was shown to improve organ function, survival, or both in most published studies. These studies also have supported the concept that glutamine is a critical nutrient for the gut mucosa and immune cells (Furst et al. 1989; Castell et al. 1994; Campos et al. 1996; Ziegler et al. 1996).

Molecular and protein chemistry studies define the basic mechanism involved in glutamine action in the gut, liver, and other cells and organs (Ziegler et al. 1996). Double-blind prospective clinical investigations suggest that glutamine-enriched diets are generally safe and effective in catabolic patients (Griffiths 1997). Intravenous glutamine has been shown to increase plasma glutamine levels; exert protein anabolic effects; improve gut structure and function; and reduce important indices of disease, including infection rates and length of hospital stay in selected patient subgroups (Sacks 1999).

Glutamine is the most abundant free amino acid in the human body. In catabolic stress situations, such as after surgical operations or trauma and during sepsis, glutamine is rapidly transported to organs and to blood cells. This results in an intracellular depletion of glutamine in the muscles and the ensuing catabolic wasting effect (Balzola et al. 1996). Increasing evidence suggests that glutamine is a crucial substrate for immunocompetent cells. Glutamine depletion decreases the proliferation of lymphocytes, possibly by arresting a critical phase of the growth cycle of the cells (Roth et al. 1996).

Glutamine is a precursor for the synthesis of glutathione and stimulates the formation of heat-shock proteins (Zhou et al. 1997). Moreover, there are suggestions that glutamine plays a crucial role in the stimulation of intracellular protein synthesis (Hankard et al. 1996). Experimental studies revealed that glutamine deficiency causes a necrotizing enterocolitis--an inflammation of the small intestine and colon, leading to cell death--and increases the mortality of animals subjected to bacterial stress (Becker et al. 2000).

A clinical human study involving bone-marrow transplant patients demonstrated, after supplementation with glutamine, a decrease in the incidence of infections and a shortening of hospital stay. In critically ill patients, parenteral glutamine reduced nitrogen loss and caused a reduction of the mortality rate (Roth et al. 1996). In surgical patients, glutamine invoked an improvement of several immunological parameters (Slotwinski et al. 2000). Moreover, glutamine exerted a nutritional (tropic) effect on the intestinal mucosa, decreased the intestinal permeability, and thus may prevent the translocation of bacteria.

In conclusion, glutamine is an important metabolic substrate of rapidly proliferating cells. It influences the cellular hydration (molecular water content) state and has multiple effects on the immune system, intestinal function, and protein metabolism (Sacks 1999). In several disease states, glutamine may become an indispensable nutrient supplement. Catabolic wasting patients should consider supplementing with 2000 mg of glutamine a day.

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Catabolic Wasting

WHEY PROTEIN

Scientists have examined the impact of whey protein concentrate on preventing or treating catabolic wasting, immune dysfunction, and cancer. A study involving HIV-positive men fed whey protein concentrate found dramatic increases in glutathione levels, with most men reaching their ideal body weight (Bounous et al. 1993). In another study, when different groups of rats were given a powerful carcinogen, those fed whey protein concentrate showed fewer tumors and reduced tumor masses (McIntosh et al. 1995). Whey appears to inhibit the growth of breast cancer cells at low concentrations. In one clinical study, when cancer patients were fed whey protein concentrate at 30 grams a day, some patients' tumors showed a regression (Kennedy et al. 1995).

The research using whey protein concentrate has led researchers to a discovery regarding the relationships between cancerous cells, whey protein concentrate, and glutathione. Glutathione is an antioxidant that protects the body against harmful compounds. It was found that whey protein concentrate selectively depletes cancer cells of their glutathione, thus making them more susceptible to cancer treatments, such as radiation and chemotherapy (Kennedy et al. 1995; Baruchel et al. 1996). It has been found that cancer cells and normal cells will respond differently to nutrients and drugs that affect glutathione status.

The concentration of glutathione in tumor cells is higher than that in the normal cells that surround the tumor. This difference in glutathione status between normal cells and cancer cells is believed to be an important factor in the resistance of cancer cells to chemotherapy. Research has shown that cancer cells subjected to whey proteins were depleted of their glutathione and their growth was inhibited, although normal cells had an increase in glutathione and increased cellular growth. These effects were not seen with other proteins.

Not surprisingly, these researchers concluded, "Selective depletion of tumor glutathione may, in fact, render cancer cells more vulnerable to the action of chemotherapy and eventually protect normal tissue against the deleterious effects of chemotherapy."

Whey protein also appears to play a direct role in bone growth. Researchers found that rats fed whey protein concentrate showed increases in bone strength, as well as bone protein, such as collagen. Whey protein was found to stimulate total protein synthesis, DNA content, and increased hydroxyproline content of bone cells in a dose-dependent manner.

It should be noted that not all whey protein concentrates are created equal. Processing whey protein to remove the lactose and fats, but without losing its biological activity, takes special care by the manufacturer. The protein must be processed under low-temperature and low-acid conditions so as not to denature it. Maintaining the natural state of the protein is essential to its biological activity.

Whey protein has the highest biological value rating of any protein. When the biological value is high, that means protein is absorbed, used, and retained better in the body. High biological values also are associated with tissue sparing. Thus, whey protein concentrate can be beneficial for people with wasting catabolic diseases.

OTHER NUTRITIONAL SUPPLEMENTATION

Conjugated linoleic acid (CLA), a fatty acid, has anticatabolic properties. This has been demonstrated in laboratory mice injected with endotoxin to produce catabolic response. By 72 hours after feeding with linoleic acid, the mice presented body weights similar to controls. The researchers concluded that conjugated linoleic acid prevented anorexia in endotoxin-injected test subjects (Miller et al. 1994). The suggested dose of CLA for a person in a catabolic state is 2 1000-mg capsules taken 2 times a day.

The amino acid arginine can help to generate anabolic cell replacement throughout the body and can suppress excess levels of ammonia in the body, a common problem associated with catabolic breakdown (Vanaja et al. 2001; Kosenko et al. 1995; Kennedy et al. 1994; De Bandt et al. 1998). The suggested dose for arginine to counteract catabolism is 5-20 grams a day. Additional amino acid supplementation should include 2400 mg of L-carnitine and 4 capsules a day of a branched-chain amino acid complex which includes at least 1200 mg of leucine, isoleucine, and valine.

Warning: Some nutritionists are concerned about the use of high doses of glutamine or arginine in cancer patients. Glutamine and arginine promote cellular growth, and the concern is that these amino acids could cause cancer cells to grow faster. Scientific studies, however, show that glutamine and arginine provide beneficial effects to cancer patients. Only one study on breast cancer patients hinted at a risk for arginine supplementation.

RESISTANCE TRAINING

Resistance or strength training is defined by resisting, lifting, and lowering weights. Resistance exercise training for a period of 8-12 weeks results in significant increases in muscle mass, muscle strength, and muscle function. Even in cases where dietary intake of protein falls below recommended daily allowances, the anabolic effect of resistance training appears to improve energy intake and protein use, allowing nitrogen retention (Castaneda et al. 1998). The benefits of resistance training have been shown to improve muscle strength and functioning in people with disease-causing muscle wasting and in healthy but frail elderly people (Fielding 1995). Resistance exercise training should be considered as an adjunct treatment modality that is cost-effective, noninvasive, and a means to improve the quality of life.

APPETITE STIMULANTS

Appetite stimulants have been used in both HIV and cancer patients who have wasting syndrome.

Marinol (dronabinol) is a synthetic version of the active ingredient in marijuana, 9-tetrahydro-cannabinol (THC). Marinol can be prescribed by a physician and taken orally. Results have been mixed as a treatment for nausea and vomiting due to chemotherapy. However as an appetite stimulant, results are more encouraging. In a study of 139 people with HIV, Marinol significantly improved appetite, body weight, and mood and decreased nausea and vomiting compared to those on placebo (Beal et al. 1995). Side effects from Marinol may include heightened awareness, a sense of well-being, and elation. Dizziness, drowsiness, muddled thinking, and anxiety are also possible side effects.

Megace is a synthetic progesterone used to stimulate appetite in people with wasting syndrome caused by HIV or advanced stages of cancer. It is also used as a therapy in women with breast cancer by interfering with the action of estrogen on cancer cell receptor sites. Although an increase or stabilization of weight may be seen after 6 weeks at the therapeutic dose of 800 mg a day, most of the gain will be in fat. A lower therapeutic dose along with resistance training will help to promote more muscle mass. Megace has a low incidence of adverse side effects when taken as directed.

TESTOSTERONE

Testosterone is a natural anabolic steroid and can help place patients in a positive nitrogen balance. Dosages of 100-200 mg a week can be given to most men and women. Consideration can be given to DHEA (see the DHEA Replacement Therapy protocol) and pregnenolone as well. The intravenous administration of vitamins--in particular, vitamin C, 25-50 grams, 2-3 times a week--may be helpful.

Testosterone supplementation in male HIV patients with wasting syndrome has been shown to increase lean body mass at doses of 200 mg daily administered intramuscularly. The most significant results were seen in combination with resistance weight training. In a study conducted at Massachusetts General Hospital, 54 men were given testosterone or placebo and placed on a 12-week exercise training program or no training at all. Lean body mass and muscle increased in those undergoing training and testosterone therapy. Levels of beneficial HDL cholesterol increased in those training, but fell in those supplementing with testosterone. Viral load fell in those taking the hormone (Fairfield et al. 2001).

Consideration should be given to "adrenal support." Patients with catabolic wasting should be assumed to have some degree of adrenal fatigue from the stress of chronic disease (see the Adrenal Disease protocol).

Warning: The possibilities discussed above have not been thoroughly studied with respect to potentially worsening cancer (if cancer is the source of the cachectic state). It is suggested that you discuss any potential treatment with a physician practicing complementary medicine prior to initiating therapy.

SUMMARY

Catabolic wasting can be counteracted by proper nutrient supplementation. A daily dose of 2000 mg of glutamine is suggested to prevent glutamine depletion in the tissues and the ensuing catabolic effect. Fish and borage oil supplementation, in the dose of 1300 mg of DHA, 500 mg of EPA, and 1200 mg of GLA a day, should be considered to suppress inflammatory cytokines and prostaglandins that can destroy tissue. Two 1000-mg CLA capsules should be taken 2 times a day to facilitate the transport of glucose into muscle cells. The intake of 30 grams a day of biologically active whey protein concentrate, 10-20 grams of arginine, 2400 mg of L-carnitine, and a branched-chain amino acid complex may produce a dramatic anticatabolic tissue-sparing effect and regulate immune system cytokines that are thought to cause cachexia.

The multinutrient Life Extension Mix formula should be given to all people with catabolic breakdown to provide the basic building

blocks the body needs to start rebuilding.

A person at risk for developing catabolic wasting syndrome or who is already suffering from cachexia (tissue wasting) should consider the following supplements:

1. Glutamine, 2000 mg a day, available in capsule or powder form.
2. Super GLA/DHA oil, 8 capsules a day (provides optimal potencies of GLA from borage oil and DHA/EPA from fish oil concentrate).
3. Conjugated linoleic acid (CLA), (76%) 2000 mg 2 times a day.
4. Biologically active whey protein concentrate, 30-60 grams a day.
5. Arginine, 10-20 grams a day in divided doses.
6. L-carnitine, 2400 mg a day in divided doses.
7. Life Extension Mix, 9 tablets, 14 capsules, or 3 scoops of powder daily in divided doses.
8. Consider growth hormone, DHEA, and/or testosterone replacement therapy.
9. Branched Chain Amino Acid Formula, 1200-2400 mg a day.

PRODUCT AVAILABILITY

Glutamine, enhanced whey protein, arginine, Life Extension Mix, Super GLA/DHA, CLA, Mega EPA, L-carnitine, DHEA, and the Branched Chain Amino Acid Formula can be ordered by calling (800) 544-4440 or by ordering online. Growth hormone and testosterone are prescription drugs.



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