

TREATMENT OF CACHEXIA IN CHRONIC DISEASE.
The importance of **Optimal Nutrition**.

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Introduction:

The human body is composed of 3 main components: protein, glucose and fat. With loss of body weight a diminution of all these components is possible; however in the following discussion the importance of the loss of the macronutrient: protein will be emphasized.

Protein mass in a healthy adult is about 6-10 kg, carbohydrate stock is 600-800 grams and lipid stock is variable. One difference between the last two and the first one is that carbohydrate and fat exist in the body as a real stock. This is not true for protein. Every protein in the body has a function, by example enzyme, contractile protein etc. There are no inert protein stores. Loss of protein is therefore always a loss of organ function. Loss of organ function below a certain critical mass is an independent parameter for morbidity and mortality.

A hunger striker, who will drink a sufficient amount of fluid, will die after about 70 days as shown by the Irish and Turkish hunger strikers (1). In this period about 40% bodyweight has been lost and also 40% of the protein mass (= 40% of organ mass)(2). About 5% of the fat mass is left at that moment; the carbohydrate stores are disappeared. In normal functioning organs a close relation has been found between weight and function; a loss of about 40% in weight means also a loss of 40% in function. This continuing loss in protein mass is found despite a major adaptation of the body to starvation. During short-term starvation about 300 grams of protein are synthesized and a little bit more broken down, resulting in a net protein loss of about 60 grams per day. After about 3 days of starvation the adaptation process for protein metabolism starts slowly. After 3 weeks the healthy body is maximally adapted to starvation with still a net loss of 25 grams of protein per day in a 70 kg man. It can be calculated that without this adaptation the hunger strikers would have died after 28 in stead of 70 days. This adaptive response gives the opportunity to the starving man for another 42 days to find food.

Not only in healthy subjects protein loss is a major determinant for morbidity and mortality. In many diseases, like HIV-infection, chronic obstructive lung disease, congestive heart failure and chronic renal failure wasting has been shown to be an independent predictor of morbidity and mortality (3-8). There are indications that the relation between loss of organ mass and time of death is the same in health and disease. Although systematic research is lacking observations in groups of patients suggest that patients will also die when 40% of organ mass is lost.. This relation has been shown in patients with HIV infection and in surgical patients (3,4). All these data support the idea that death is imminent at a certain body weight associated with the loss of a certain quantity of protein. The logical consequence is to try to stop loss of protein. There are 2 ways to accomplish this: causal treatment of the underlying disease or institution of specific measures to maintain or increase protein mass. The first option is by far the most effective one, but due to the chronic nature of many diseases often not possible. The second option will be discussed in following paragraphs.

Measures to maintain or increase protein mass.

The size of the protein mass is the resultant of the combined effects of protein synthesis and protein breakdown. In the preceding paragraph is explained that loss of protein mass is sometimes due to diminished protein synthesis and sometimes to increased breakdown. The first pattern (diminished synthesis) is seen when the subject is starving; the latter is related to the severity of disease state (9). It is important to realize this difference, as it is rather easy to stimulate protein synthesis, while it has been proven extremely difficult to inhibit protein breakdown significantly.

A) Measures to stimulate protein synthesis.

Starvation has a major influence on the rate of synthesis. After a fast of 3 days this rate is decreased by 20%. After 10 days of starvation the synthesis rate has dropped by another 20%. The most important determinant of this drop is lack of substrate (= lack of aminoacids). In healthy humans a direct relationship has been found between the amount of protein in the diet and the degree of stimulation of protein synthesis, measured with stable isotopes. This relationship is not infinite. Maximal stimulation has been found with 1.5-1.7 gr. protein/kg/day (9). This relationship and the upper limit of stimulation are the same in health and disease. Measurements in septic patients have shown maximal stimulation with 1.5 gr. protein/kg/day (10). There is one important difference between health and disease. In health anabolism is induced, while in severe disease anabolism is never induced. In disease catabolism is diminished with this maximal stimulation, prolonging the period before the patient dies due to loss of lean body mass below the level necessary for survival. An anabolic response is also not always found in less acutely catabolic diseases like chronic obstructive lung disease and HIV infection. These data indicate the necessity of a two-way approach: **at first maximal stimulation of protein synthesis by supply of enough protein** (usually via enteral nutrition) and **secondly** (when the patient is still catabolic) **pharmacological interventions** aimed at reducing protein breakdown rate.

b) Pharmacological interventions aimed at stimulating protein synthesis and/or reducing protein breakdown rate.

In this section the theoretical possibilities for this option will be discussed. The appetite stimulating agents, like megestrol acetate, will not be discussed, although they are effective in increasing food intake, as these agents will never guarantee **optimal** nutritional intake as discussed before (11- 13). The agents used for pharmacological manipulation of protein metabolism in sick humans are growth hormone, insulin and anabolic steroids.

b-1) Growth hormone

Growth hormone stimulates protein synthesis in muscle and elsewhere in the body and is therefore theoretically the best manipulator of metabolism in patients (14). Many studies have been published on an effect of short-term treatment with growth hormone on certain metabolic parameters. In general these studies show the expected effects on protein metabolism. Longer lasting studies aimed to show a possible effect of growth hormone on morbidity, mortality and well-being have only been done in ICU patients and AIDS patients. The results in the ICU patients

were alarming. In 2 major studies with altogether 500 patients mortality was twice as high in the growth hormone treated group compared to the control group; mortality was mainly due to multiple organ failure. There was no obvious explanation for these results (15). In 178 AIDS patients with wasting an increase in lean body mass and exercise tolerance was found after 2 weeks of treatment with growth hormone (16). Other studies did not find this effect on exercise tolerance (17). Studies on the effect of growth hormone treatment on morbidity and mortality in Aids have never been published. It is quite doubtful that they will be found, as the anabolic effect of growth hormone diminishes with progression of the disease (18).

In conclusion: Based on the scarce available data it is quite doubtful that growth hormone will have a place in the treatment of cachexia in chronic diseases.

b-2) Insulin.

Insulin inhibits proteolysis and stimulates protein synthesis when enough amino acids are available (19, 20). It inhibits proteolysis in muscle and elsewhere in the body, although the effect on muscle is about twice as powerful as elsewhere in the body (21). Insulin can be a valuable agent to influence the rate of loss of body cell mass in cachexia, because the same positive effects have been found in severely ill patients (22,23). However studies on the effect of insulin on morbidity and mortality in cachectic patients have not been published.

b-3) Anabolic steroids.

Studies on clinical relevant effects of anabolic steroids are scarce. However one excellent study has been published (24). In a group of 233 patients with chronic obstructive lung disease the effect was tested of a high caloric food supplement plus an anabolic steroid (nandrolone decanoate) versus the same food supplement plus placebo. The chosen parameters were bodyweight, body composition and respiratory muscle strength (via measurement of maximal inspiratory mouth pressure). About 50% of the patients were malnourished, defined as a bodyweight less than 90% of the desired one or a lean body mass less than 65% of ideal weight. The results showed that in both groups bodyweight increased significantly after 8 weeks of treatment, in the placebo group mainly due to fat and in the other group mainly due to protein mass. In the malnourished group this increase in protein mass was accompanied by an increase in respiratory muscle strength., In conclusion: the **combination** of nutritional support plus an anabolic steroid in wasted patients with chronic obstructive lung disease has potential valuable effects. Studies on the possible effect of this combination on morbidity and mortality have not been published.

In conclusion:

Treatment of cachexia due to incurable disease is problematic. All data in literature suggest that **optimal nutrition** (1.5 gr. protein/kg/day and 35 kcal/kg/day) is a **necessity**. This conclusion is supported by a study in patients with mucoviscidosis. Patients with mucoviscidosis in Toronto and Boston were treated in the same way concerning all aspects of medical treatment with one exception: the Canadian doctors put a lot of emphasis on food intake, while the American doctors did not pay attention to this part of the treatment. The average life expectancy for the Canadian patients was 30 years and for the American 21 years. A difference of 9 years!!!! (25).

The value of **manipulation** of metabolism by **medicaments** is **doubtful**.

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