HIV-RELATED CACHEXIA-
POTENTIAL BIECHANISMS AND TREATMEN T

Jamie VonRoenn, M.D.
Ellen L. Roth R.N.,M.S.N.
Department of Medicine
Northwestern University
Chicago, Illinois

ABSTRACT
Involuntary weight loss or wasting indicative of severe protein energy malnuuition is a frequent complication of the acquired immunodeficiency syndrome (AIDS). Malnutn’tion, with its associated adverse effects on immunocompetence, may contn’bute to the progression of AIDS itself. Since death from wasting is ultimately related to the magnitude of tissue depletion, restoration of body cell mass may enhance survival. The mechanism of weight loss in AIDS has not been clearly elucidated. The etiology is likely to be multifactorial, the result of interactions between decreased caloric intake, malabsorption and alterations in energy expenditure secondary to a hormonal and or metabolic abnormalities. Although weight loss is occasionally reversible with treatment of underlying infections and/or easily identifiable and reversible causes, the majority of patients are not this fortunate. Enteral and parenteral nutrition, which are expensive, cumbersome and potentially morbid, have been suggested by some as therapeutic options. Megestrol acetate, a synthetic orally active progestational agent, has been reported to stimulate appetite and weight gain. Data regarding the use of megestrol acetate for the treatment of HIV-related cachexia demonstrate convincingly its effectiveness for the treatment of HIV-related anorexia and cachexia.

AIDS CACHEXIA- POTENTIAL NIECHANISMS AND TREATMENT

Involuntary weight loss or wasting indicative of severe protein energy malnutntion is a frequent complication of the acquired immunodeficiency syndrome (AIDS) and ultimately affects a majority of patients. 13 The severity and progression of weight loss in patients with AIDS varies with the course of the disease. Typically, weight loss occurs e arly in the course of HIV infection and increases in severity with progression of the disease. Significant weight loss, commonly associated with anorexia and weakness, has serious physical and psychological consequences which may influence overall morbidity. Moreover, , . malnutrition adversely affects immunocompetence and may, in turn, contribute to progression of AIDS itselfw Since death from wasting is ultimately related to the magnitude of tissue depletion irrespective of etiology,5 preservation and/or restoration of body cell mass may enhance survival.

Although weight loss is a well recognized clinical complication of HIV infection, the degree and composition of the weight loss has not been well defined by controlled prospective studies. Weight change has been documented in most of the studies of body compositionmi10 Unfortunately, many of these investigations have been retrospective, have relied on self-reported weight changes and have not considered important factors which might impact on weight and body composition including: concurrent infections and their treatment, stage and duration 0fi11ness,antiviral therapy, nuttitional interventions, die tary habits and lifestylesgbiw

Mechanisms of weight loss in AIDS

The mechanism of weight loss in AIDS has not been clearly elucidated. As in the

case of cancer cachexia, the etiology is likely to be multifacton’al, the result of interactions
between decreased caloric intake, malabsorption, and alterations in energy expenditure secondary to hormonal and/or metabolic abnormalities.

Abnormalities in energy intake

Anorexia is widely believed to be a major contributor to the wasting seen in association _with HIV infection. In spite of the popularity of this view, there is scanty published data to support this belief. Koiter, et al reported normal caloric intake in five AIDS patients with stable weight as compared to homosexual and heterosexual controls.11 Dietary intake was estimated by a three-day dietary record in the research unit and could not therefore take into account the substantial variability in food intakes of free living subjects. Divorken, et a1, using 72 hour diet records, found no differences in energy intake in clinically stable patients with AIDS as compared to patients with ARC 0r asymptomatic HIV-seropositive controls.12 Similarly, Seaton, et al reported similar mean protein (exceeding RDA guidelines) and total caloric intakes in clinically stable patients with AIDS, ARC and asymptomatic HIV positive controls.13 In all of these investigations, the subjects studied had stable weight and therefore may not be appropriate models for evaluating catabolism in HIV infection. Little published data is available concerning food intake in HIV infected patients with greater than 5% loss of body weight.

In addition :0 the presumed metabolic abnormalities responsible for decreased food intake, psychosocial factors, mechanical impediments to food intake and other gastrointestinal symptoms may severely restrict oral intake. Innumerable esophageal and oral conditions associated with HIV infection may make eating painful or unpleasant;

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examples include aphthous stomatis, herpetic mucositis or esophagitis, esophageal cytomegalovirus infection, oral or esophageal candidiasis, oral herpes, bulky oral pharyngeal
Kaposi’s sarcoma or non-Hodgkins Lymphoma. Severe weakness and debilitation, dementia due to HIV encephalopathy or other CNS pathogens and depression not infrequently contribute to decreased oral intake. Early satiety from hepatomegaly or extensive gastric infiltration by malignancy, severe diarrhea and nausea and vomiting related to opportunistic
infections or therapies further compromise oral intake.
The gastrointestinal tract is frequently affected in patients with HIV infection. - Diarrhea is the most common symptom, is frequently difficult to treat and often becomes the major debilitating aspect of the patient’s illness. Diarrhea occurs in at least 50% of
patients with HIV infectionf; It is often accompanied by weight loss, malnutrition and impaired sense of weH-beingf5 In some cases, death has resulted from dehydration from the voluminous diarrhea. 16
Some of the diarrheal syndromes in AIDS may be due to infiltration of the intestine by the HIV itself. Using in vitro hybridization techniques, one group demonstrated evidence
of HIV infection in both the lamina propria and the crypts of the small intestine in some patients with AIDS and gastrointestinal symptoms, but failed to identify viral proteins in
others.17 Ulhich has suggested that HIV may cause a maturational defect in enterocytes. 18
In a study of small intestine structure and function in 45 HIV infected patients with gastrointestinal complaints, snail bowel biopsies of patients without intestinal infections as
compared to controls. had sitiilz crypt depths, decreased villous surface and significantly
decreased mitotic figures per :rypt.

Absorption may be further impaired in patients with AIDS by the deveIOpment of gastrointestinal mucosal edema associated with the decreased albumen seen in cn’tically 1 11 patients. Furthermore, mainutn’tion itself may impair intestinal function and contn’bute to the malabsorption and diarrhea in AIDS. Decreased oral intake can lead to decreased pancreatic enzyme secretion and intestinal brush border enzyme activity.

Abnormalities in energy output

The wasting associated with AIDS is characterized by a loss of body cell mass, primarily muscle protein. This is unlike the process of starvation in which lean body mas s ’ is preserved through adaptive mechanisms; a decrease in resting energy expenditure and a decrease in the percent of energy expenditure due to protein oxidation. The metabolic profile of AIDS patients varies with the clinical situation. In clinically stable AIDS pa tients with intestinal malabsorption and stable intake, Kolter has reported conservation of lean body mass as a result of hypometabolism, an appropriate metabolic response. (ref)ll These adaptive mechanisms are not consistently adopted in AIDS patients. Fevers, associated with severe wasting are not infrequent in this population. In patients with ac ute systemic illness, Kotler has reported increases in metabolic rates of 20-60% above predic ted values.H A number of investigations of resting energy expenditure in stable AIDS patients have suggested hypermetabolism as an important contn’butor to the wasting seen in AIDS patients. Melchoire, et a1, using indirect calorimetry assessed resting energy expenditur e in malnourished HIV infected patients, normal subjects and anorectic controls.19 The resting energy expenditure was highly correlated with lean body mass in all subjects. When expressed with respect to lean body mass, resting energy expenditure was specifically

elevated in HIV infected patients. Similarly, Hommes et a1, evaluated resting energy expenditure in HIV infected men free of clinically active infections and in healthy controls with similar food intake and body composition.20 Patients with AIDS or ARC had 9% higher rates of resting energy expenditure than controls. This difference was not associated with difference in levels of catecholamines or tn’iodothyronine. Energy balance studies were not done.

Altered lipid metabolism, such as fasting hypertriglyceridemia, has been observed in a cross section of HIV infected patients. A direct correlation between hypertriglycetidemia and wasting has not been established. Recently, Grunfeld, et al reported a significant correlation between increased triglyceride levels and levels of alpha-interferon, but not with TNF or IL-1.21 No relationship between circulating interferon-alpha or TNF levels and the presence of wasting was identified. This suggests that many aspects of metabolic regulation may be altered by the many cytokines which act as mediators in HIV infection. Lipid catabolism by lipoprotein lipase in fat cells in vitro is inhibited by multiple cytokines including TNF,IL-1 and interferons alpha, beta and gamma. Many 0fthese same cytokines stimulate hepatic lipogenesis in vivo. Although elevated serum levels of TNF have been identified in patients with AIDS, no clear association between TNF levels and weight change has been noted.23 It has been hypothesized that TNF contributes to the "futile cycling" of free fatty acids and m’acylglycerols by stimulating overproduction of lipids by the liver and increasing total body lipolysis. This might explain the preservation of fat mass in AIDS patients with weight loss.

Clearly, much remains to be learned about the mechanisms of altered metabolism

in AIDS patients with wasting. Hypermetabolism is not a consistent finding. It does not necessan’ly cause negative nitrogen balance or wasting because of the potential adaptations of increased intake and decreased energy expenditure due to protein oxidation. This is supported by a recent report by Grunfeld et al in which HIV positive subjects, controls, patients with AIDS without active infections and patients with AIDS and active secondary infections were evaluated on a metabolic ward.23 Resting energy expenditure and caloric intake were measured and conelated with weight changes over a four week period. Although resting energy expenditure was significantly elevated in HIV seropositive and AIDS patients with or without concurrent infections, as compared to controls, significant weight loss over the course of the study was only seen in AIDS patients with secondary infections. Hypermetabolism, per se, does not cause weight loss: no significant differences in caloric intake were noted in controls as compared to HIV seropositive patients or AIDS patients without secondary infections. Caloric intake in AIDS patients with concurrent opportunistic infections was reduced by 30%. A highly significant correlation was identified between 28 day weight loss and caloric intake, while no correlation was found between resting energy expenditure and weight loss.

Therapeutic Strategies

The mechanism of weight loss in patients who are HIV infected remains elusive. Reversal of the anorexia and cachexia seen would be of considerable value in the supportive management of these patients, whether or not weight gain contributes to improved survival and a decrease in opportunistic infections. Treatment of HIV infection and opportunistic infections has led to an improvement in weight. The initial report describing the use of

zidovudine for the treatment of HIV infection reported appetite improvement during the first six to eight weeks of treatment, with an average weight gain of 2.2 kg.24 Similar repletion of body mass has been reported during therapy for cytomegalovirus infections in patients with AIDS.25

Unfortunately, many patients experience anorexia and weight loss without easily identifiable and/or reversible causes. Enteral and parenteral nutrition, which are expensive, cumbersome and potentially morbid, are sometimes suggested as therapeutic options. Several agents ineiuding steroids, cyproheptadine, hydrazine sulfate and marijuana have . been used in an attempt to reverse cancer cachexia with thus far little or no long term ber1ef1t.26’29 With the exception of marijuana, which is currently under study, there is little data regarding the remainder of these agents for the use of HIV-related cachexia.

Megestrol acetate, a synthetic orally active progestational agent, used widely for the treatment of advanced breast cancer, has been reported to stimulate appetite and weight gain. Multiple controlled randomized studies have demonstrated the benefit of megestrol acetate for cachexia in patients with non-hormone responsive tumors.30’32 A pilot study of megestrol acetate for the treatment of HIV-related cachexia was initiated in 1987.33 Twenty-two HIV positive patients who had lost at least 10% of their pre-illness body weight, were treated with megestrol acetate, at doses ranging from 320 to 640 mg. per day. Twenty-one of the 22 patients gained weight. The average weight gain was 7.3 kg (range -4.1 to 17.3 kg). Seven patients returned to within 1 kg of their pre-morbid body weight. No serious toxicity was associated with megestrol acetate therapy. Because of the appetite enhancing effects of megestrol acetate, its excellent tolerability and the potential importance of nutritional

status in HIV infected patients, a double-blind randomized placebo controlled tiial of megestrol acetate was initiated in patients with AIDS, anorexia and cachexia.
Two hundred and seventy-one patients, all with AIDS, anorexia and cachexia, were randomized in a double-blind fashion to receive placebo or 100 mg, 400 mg or 800 mg per day of megestrol acetate for 12 weeks. Weight change and percent weight change were analyzed. Anthropometric measurements and bioelectric impedance analysis were performed every four weeks to compaIe treatment groups with respect to changes in lean body mass and botiy fat.
Mean weight steadily increased over 12 weeks for patients treated with 400 mg or 800 mg of megestrol acetate. In the 400 mg megestrol acetate group, the mean weight increased from 130.71bs. at baseline to 1401135. at 12 weeks. In the 800 mg megestrol acetate group
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mean weight increased from 129 lbs at baseline to 140.81bs. at 12 weeks. In the placebo group, mean weight remained stable over the 12 week period. Maximum weight gain greater than or equal to 5 lbs was seen in 64% of patients in the 800 mg megestrol acetat
e
group as compared to 21.4% in the placebo group (P 6.0001) (See Table 1). None of the patients in the placebo group had weight gain greater than 15 lbs. compared to 22.6% in t
he
800 mg megestrol acetate group. The mean maximum weight change from baseline to last evaluation was 8.31bs in the 800 mg megestrol acetate and -1.1 lbs in the placebo group (P(0.001). The mean change in lean body mass from baseline to last evaluation was 2.51b. in the 800 mg megestrol acetate and -1.71bs in the placebo group (P $001). There was a significant improvement in appetite in patients receiving 800mg megestrol acetate compare
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to those randomized to the placebo aim of the study. At the time of maximum weight

change, 90.6% of the patients in the 800 mg megestrol acetate group reported an improvement in appetite compared to 42.9% of those receiving placebo (PQDOI). Mean change in daily calorie intake from baseline to time of maximum weight change, as measured by a three day intake diary, was 629.3 calories in the 800 mg megestrol acetate group, compared to a -111 calories in the placebo arm (P:0.004).

No significant toxicity was observed with megestrol acetate therapy. Increasing doses of megestrol acetate were not associated with increased edema. Additionally, there was no worsening of disease symptoms or increase in opponunistic diseases in patients receiving megestrol acetate compared to those receiving placebo.

This study convincingly demonstrates the effectiveness of megestrol acetate for the treatment of AIDS-reiated anorexia and cachexia. The results are similar to those reporte d
by Loprinzi, et al in megestrol acetate treated patients with cancer cachexia.3O

Conclusion

Anorexia and cachexia remain important clinical problems for patients with HIV infection. To date, megestroi acetate is the only drug which has convincingly demonstrate d
benefit for the treatment of HIV-related anorexia and cachexia. The optimal dose of megestrol acetate for the treatment of cachexia remains unclear. Unfortunately, their remain a significant minority of patients (34%) who do not respond to megestrol acetate therapy. Further evaluation of treatment failures and a better understanding of the mechanism of weight gain with megestroi acetate therapy may shed some light on the mechanism of HIV-cachexia itself. Replenishing body cell mass in patients with AIDS or neoplastic disease has not yet been shown to prolong survival. Future studies will be nee ded

to assess the impact of improved nutritional status on immune function, infection n’sk an
d
survival for persons with HIV infection.
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Mean maximum
weight change
% of patients with
weight gain 3 5 lbs.
Mean change in f
6.001
lean body mass
% of patients
reporting appetite
improvement
TABLE 1
Summag of Treatment Results
Placebo
-l.11bs
21.4%
-1.71bs
42.9%
11
800 mg megestrol acetate
8.3 lbs
64%
2.51bs
90.6%
40.001
dMIJOl
40.001

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