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Counteracting Muscle Wasting in HIV-infected Individuals

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ORIGINAL RESEARCH

Counteracting muscle wasting in HIV-infected individuals

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HIV-infected persons often experience a loss of lean tissue mass, which includes decreases in skeletal muscle mass. This HIV-associated wasting is significant because it has been associated with accelerated disease progression and increased morbidity. Signalling related to several circulating molecules, including tumour necrosis factor (TNF)-α, growth hormone, insulin-like growth factor (IGF)-1 and testosterone, has been associated with the aetiology of muscle wasting. Additionally, nutritional status related to malnutrition and specific dietary deficiencies may be involved. In an attempt to counter muscle wasting in HIV-infected persons, treatments have been suggested that target these mechanisms. Nutritional supplementation, cytokine reduction, hormone therapy and resistance exercise training are potential treatments for this condition. Resistance exercise training, which is more easily accessible to this population than other treatments, holds promise in counteracting the process of HIV wasting, as it has been successfully used to increase lean tissue mass in healthy and clinical populations. This review will explore the HIV/AIDS muscle-wasting syndrome, its aetiology, and the treatments used to counteract wasting.

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Introduction

The Centers for Disease Control and Prevention define HIV/AIDS wasting syndrome as an involuntary weight loss of greater than 10% baseline body weight during the previous 12 months or a 5% loss of weight during the previous 6 months. It has been estimated that nearly 20% of those infected with HIV suffer from wasting, even with the widespread implementation of highly active antiretroviral therapy (HAART) [1]. The wasting in HIV/AIDS is characterized by reductions in lean body mass or fat-free mass [2]. Skeletal muscle represents between 50 and 54% of lean body mass [3,4], and thus wasting is accompanied by decreased muscular strength and functional performance, and is associated with disease progression [2]. Fever (documented for more than 30 days), chronic weakness and/or chronic diarrhoea (two loose stools or more per day for at least 30 days), independent of any conditions other than HIV infection, are common with this syndrome and may lead to the observed weight loss [5]. Lean body mass loss can occur independent of total body weight changes, making the diagnosis of this condition even more difficult. This type of loss has been described as cachexia, but this new classification has yet to be fully accepted in the treatment and diagnosis of HIV/AIDS wasting [6].

The significant loss of metabolically active lean tissue greatly increases morbidity and mortality [5]. Both before and after the introduction of HAART, there has been a strong association between wasting and negative outcomes including increased mortality [7], impaired functional status [6], and accelerated disease progression [8]. HIV-infected persons also demonstrate a progressive depletion of body cell mass (intracellular mass of all metabolically active tissues in the body) near death, and body cell mass and body weight at death have been found to be only half the ideal values [9]. HIV RNA levels also correlate positively with weight loss and body mass index. However, an inverse relationship exists between CD4 lymphocyte cell counts and weight loss [10]. In the light of the significant impact of wasting in HIV-infected persons, research has addressed this syndrome in the hope of improving the health of those with HIV wasting. This review will investigate the proposed aetiologies of HIV/AIDS wasting and the effectiveness of current treatments in counteracting HIV/AIDS wasting.

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Aetiology of HIV/AIDS wasting

The aetiology of the HIV-associated wasting syndrome is yet to be fully defined, but potential contributing factors

include malunitrition, abnormal cytokine production and endocrine dysfunction (Table 1). Thus, it appears that there are numerous interactions influencing protein turnover, an integral component of lean tissue maintenance [11]. Protein turnover is normally balanced between protein degradation and protein synthesis, which allows lean tissue maintenance. During muscle wasting in HIV/AIDS there is a shift towards excess protein breakdown [12]. Therefore, wasting treatments should aim to decrease protein degradation and/or stimulate protein synthesis.

Malnutrition

Altered metabolism

Elevated resting energy expenditure (REE) is commonly found in HIV-infected individuals [13–15], and can be 10 to 35% higher than in uninfected controls. In fact, during periods of acute opportunistic infection, conditions such as infection with *Pneumocystis carinii*, *Mycobacterium avium* complex (MAC) and cytomegalovirus (CMV) can all cause further increases in REE [13,16,17]. Gender may play a role in the altered metabolic response to chronic HIV infection, as asymptomatic HIV-infected men demonstrate higher REE values than asymptomatic HIV-infected women [18]. Finally, elevated REE is seen in patients presenting with lipodystrophy compared with HIV-infected patients with no signs of this syndrome [19].

Enteropathy

Disease of the digestive tract is referred to as enteropathy. There is a high prevalence of gastrointestinal (GI) disorders in the HIV-infected population and these can include swallowing disorders (47%), abdominal pain and cramping (20%), diarrhoea (77%), oral and perianal disease (74%), oral lesions (54%), oral candidiasis (34%) and hairy leucoplakia (27%) [20–22]. Xerostomia (dry mouth), caused by infections, medications, smoking and dehydration, is also found in many HIV-infected persons (29%) [23]. Saliva is essential to normal digestion and immune function as it contains enzymes (lingual lipase and salivary amylase) and immune cells [producing antibodies, immunoglobulin A (IgA) and salivary leucocyte protease inhibitor] responsible for neutralizing parasites, bacteria and viruses; therefore, decreased saliva production can contribute to disorders of digestion and malabsorption, as well as increase the risk of opportunistic infections.

Alterations of the intestinal lining make infected persons more susceptible to infections and diarrhoea, thereby decreasing nutrient absorption [24,25]. HIV itself can cause atrophy of digestive tract villi, decreasing the surface area through which absorption takes place. The resultant decrease in intestinal enzyme activity can cause further maldigestion, diarrhoea and steatorrhoea (fatty stool) [26,27]. Diarrhoea can exacerbate symptoms of dehydration, further decreasing saliva production and increasing the incidence of malnutrition and secondary infection.

Physical impairment

Physical impairment in this context refers to a decreased ability to physically chew and swallow food and a decreased ability to perform activities of daily living related to nutrition and hygiene. Oral and oesophageal conditions common in this population can make swallowing painful, and oral and oesophageal lesions can cause dysphagia and anorexia by physically blocking the glottis and limiting the size of the oesophagus [20,28]. Fatigue and reduced functional capacity are often found in this population and have been shown to decrease the ability of the HIV-infected individual to complete essential activities of daily living, such as preparing meals or shopping for nutritious foods [29].

Neurological impairment

HIV/AIDS-related nerve complication occurs throughout the course of the disease, often causing dementia, sensory impairments and neuropathy. Dementia occurs at later stages of the disease in up to 50% of HIV-patients [30], and this decreased mental capacity may result in forgetting to eat and poor medication adherence [31]. Some HIV-infected individuals experience visual and olfactory decrements secondary to cranial nerve damage. Sensory impairments can make foods look, taste and smell different, reducing hunger and placing patients at risk for malnutrition [32]. Neuropathy of the cranial nerves, usually occurring later in the course of the disease and associated with CMV co-infection, is another potential cause of functional impairment [33]. Loss of cranial nerve function responsible for chewing, taste, swallowing and salivary gland stimulation (cranial nerves V, VII and IX) can prevent complete mastication, cause food to be dry and tasteless, and prevent completion of the normal swallowing reflex.

Medication-related side effects

HIV-infected individuals are on complex antiretroviral drug regimens. While these combinations help keep CD4 cell counts high and decrease viral load, HAART causes GI disturbance and leads to nutritional deficiencies. In fact, the most common side effects reported with HIV medications are diarrhoea, anorexia, vomiting, abdominal pain and cramping, steatorrhoea and GI upset, all of which affect calorie consumption and nutrient absorption.

Cytokines

Several cytokines, in particular tumour necrosis factor (TNF)-α, have been implicated in skeletal muscle degra-

dation. In HIV/AIDS [34], as well as other diseases such as cancer [35], chronic obstructive pulmonary disease (COPD) [36] and congestive heart failure [37], skeletal muscle catabolism has been attributed to TNF-α. TNF-α can inhibit the secretion of the hormone testosterone, which regulates muscle mass, affects tissue sensitivity to hormone signalling, and directly stimulates protein degradation [38,39]. Serum concentrations of soluble TNFs 55 and 75, which reflect TNF-α release, are elevated in HIV-infected patients compared with healthy control subjects [40]. In HIV-infected men, circulating TNF-α has been shown to be inversely associated with changes in lean body mass [41].

Cortisol

Those infected with HIV experience changes at multiple levels of the hypothalamic pituitary adrenal axis (HPAA), resulting in elevated cortisol levels [42]. The chronic stress experienced by these persons along with the elevation of TNF-α leads to activation of the HPAA, causing excess cortisol release [43]. Cortisol is a potent catabolic hormone, which increases rates of protein degradation and slows protein synthesis rates, especially in skeletal muscle, and thus is implicated in the wasting associated with HIV infection [43].

Growth hormone/growth factors

Growth hormone maintains bone and skeletal muscle mass through the stimulation of insulin-like growth factor (IGF)-1 release from the liver. IGF-1, an anabolic agent active in the regulation of protein metabolism, has been shown to stimulate replication and differentiation of myogenic (muscle) precursor cells necessary for muscle growth and repair [44]. Additionally, IGF-1 produced locally in the muscle is a potent regulator of muscle mass [45]. Growth hormone release is depressed in obese persons and malnourished persons suffer from growth hormone resistance as a result of impaired IGF-1 signalling. Therefore, HIV-induced lipodystrophy and nutrient malabsorption can cause significant alterations in growth hormone and IGF-1 function that will ultimately influence lean tissue mass. Persons with HIV/AIDS wasting also demonstrate growth hormone resistance, which manifests itself in increased growth hormone levels and decreased IGF-1 levels, and may be attributable to malnutrition [46]. Thus, alterations in growth hormone release and utilization present in HIV/AIDS wasting may be attributable to malnutrition and/or lipid disorders.

IGF-1 can exert its function by directly binding to the IGF-1 receptor, but its action can be modified by IGF-binding proteins (IGFBPs). These IGFBPs, of which there are six, can enhance or inhibit the biological activity of IGF-1 [47]. IGFBP-3 is the major binding protein in the circulation and is responsible for binding 90% of IGF-1, ensuring efficient delivery of the hormone to target tissues. HIV infection can increase the proteolysis of IGFBP-3, thereby decreasing IGFBP-3 levels. This may explain the lack of growth hormone-induced increase in IGF-1 seen in HIV-infected persons, and possibly contribute to a decrease in protein synthesis that may lead to muscle wasting [48,49].

Testosterone

Decreased circulating testosterone levels also correlate with body mass loss, lean tissue mass loss, and decreased exercise capacity in HIV-infected persons [46]. Thirty to 50% of HIV-infected men may suffer from low testosterone levels, which puts them at greater risk for muscle wasting [49]. Testosterone is a potent regulator of skeletal muscle mass that acts via multiple pathways. Testosterone binds to skeletal muscle receptors, thus directly influencing protein expression [50]. Testosterone stimulates the release of growth hormone from the pituitary, thereby increasing the expression of IGF-1, resulting in increased protein synthesis [51]. Additionally, testosterone can influence lean tissue mass by exerting an antiglucocorticoid (anticatabolic) effect [52].

Treatments for muscle wasting

It has been proposed that many factors are involved in the mechanisms that lead to the muscle wasting observed in HIV/AIDS. No definitive aetiology has been established, and, given the interactive nature of the proposed mechanisms of muscle wasting, it is likely that the cause is multifactorial. Therefore, numerous treatments for HIV/AIDS muscle wasting have been proposed and studied. These treatments include nutritional interventions, hormone therapy, cytokine treatments and resistance exercise training (Table 2).

Nutritional strategies

Nutritional counselling for 8 weeks, resulting in an increase in calorie intake of 600 kcal/day, was shown to increase fat free mass in HIV-infected patients ($n = 24$) with recent weight loss ($> 5\%$). Supplementation with a high-calorie drink ($n = 26$) also increased fat free mass in HIV-infected persons [53]. HIV-infected malnourished patients given supplementation with a polymeric diet (containing a balance of standard nutrients) also demonstrated significant increases in body weight, fat mass (skin fold

Table 1 Anabolic and catabolic factors associated with HIV/AIDS wasting

Agent	Action	Implications in HIV/AIDS wasting
Anabolic agents		
Testosterone	↑ developmental protein expression Stimulation of growth hormone release Antiglucocorticoid effects	Testosterone is decreased in men with wasting
Growth hormone	↑ protein synthesis ↑ collagen synthesis Stimulation of release of IGF-1	Growth hormone resistance has been observed in wasting, resulting in decreased IGF-1 production
Insulin-like growth factor-1	↑ protein synthesis Stimulation of replication and differentiation of muscle precursor cells	IGF-1 is decreased in wasting Increased degradation of binding proteins in wasting leads to decreased IGF-1 activity
Catabolic agents		
Tumour necrosis factor α	Stimulation of protein degradation Alteration of hormone receptor sensitivity Decrease in anabolic hormone levels Indirect stimulation of cortisol release ↑ in resting energy expenditure	TNF-α levels are elevated in wasting
Cortisol	Inhibition of protein synthesis ↑ protein degradation ↑ proteolytic enzymes	Elevated cortisol levels are common in persons with wasting

IGF, insulin-like growth factor; TNF, tumour necrosis factor.

measurement), energy balance and nitrogen balance following a 45-day intervention [54].

In five malnourished (as a result of absorption or food intake problems) AIDS patients, body cell mass was significantly increased, as were body weight and body fat content, following 4–42 weeks of home total parenteral nutrition (as many calories as tolerated up to 35 kcal/kg of body weight) [55]. The same intervention in seven subjects with wasting caused by severe systemic infections resulted in increases in body weight and fat mass, but not lean tissue mass. These data, collected prior to the introduction of HAART, showed that nutritional support is successful at countering weight loss by restoring fat mass, and possibly lean tissue mass. However, common side effects of HAART include nausea, vomiting and diarrhoea, which can decrease appetite and alter nutrient absorption. Thus, its effectiveness at restoring body weight in HIV-positive persons receiving HAART is unknown.

Other nutritional treatments aimed at combating muscle wasting in HIV-infected individuals have focused on specific deficiencies within the diet, rather than overall caloric intake. The need for L-glutamine, an essential amino acid that is required for protein synthesis, exceeds the rate of production during stress and inflammation, and thus skeletal muscle is catabolized to provide this necessary amino acid to other parts of the body [56]. L-glutamine is also necessary for many other metabolic processes, including tissue repair, but to complete its function it must be present with other necessary amino acids. Most parenteral nutrition solutions and enteral feeding formulas do not contain L-glutamine, potentially explaining their lack of success in increasing lean tissue mass. Additionally, reactive oxygen species have been found to be associated with HIV/AIDS wasting and overall weight loss [57]. In the light of these findings, a combined L-glutamine and antioxidant supplement was administered to 21 HIV-infected individuals with documented wasting (> 5%) for 12 weeks. Subjects receiving the treatment increased body weight by 2.2 kg compared with a nonsignificant 0.3-kg gain in the controls. Bioelectrical impedance analysis (BIA) revealed a significant increase of 1.8 kg in body cell mass versus a 0.4-kg change in the controls. No changes in diet were found according to a 3-day dietary recall [58]. Eighteen of the 21 subjects were receiving HAART, and the subjects did not report any side effects during the study.

A mixture of beta-hydroxy-beta-methylbutyrate (3 g), L-glutamine (14 g) and L-arginine (14 g) was used as a nutritional supplement in patients with AIDS (all receiving antiretroviral therapy) who had muscle wasting [59]. Beta-hydroxy-beta-methylbutyrate is thought to provide protective benefits to skeletal muscle by limiting proteolysis [60], while L-arginine is a precursor to nitric oxide, which may have nitrogen-sparing effects [61]. Treatment subjects ($n = 22$) received supplements twice daily for 8 weeks, while control subjects ($n = 21$) received a placebo containing maltodextrin (easily digestible carbohydrates). The treatment subjects gained 3.0 ± 0.5 kg body weight compared with 0.37 ± 0.84 kg ($P = 0.009$) in the control subjects. There was no change in fat mass in either group ($P > 0.20$), and computed tomography (CT) scans revealed that the increase in body weight in the treatment group was predominantly lean body mass (2.55 ± 0.75 kg) compared with a loss of lean tissue (-0.70 ± 0.69 kg; $P = 0.003$) in the controls [59]. Even with the limited published

information, these results indicate that correcting specific dietary deficiencies may be effective in restoring lean tissue mass in HIV-infected persons. However, no federally funded programmes for identifying and treating nutritional deficiencies in HIV-infected persons exist, and thus the practicalities of analysing and prescribing corrective nutrition to large numbers of HIV-infected persons are questionable.

Hormone therapy

Testosterone

Administration of testosterone has resulted in increased muscle mass and strength in several clinical populations, including hypogonadal elderly men [62], COPD patients [63] and persons with autoimmune diseases receiving glucocorticoids [64]. Testosterone therapy therefore has potential for treating HIV/AIDS muscle wasting. Kong and Edmonds [65] reviewed the effects of testosterone therapy in HIV wasting. This meta-analysis revealed that oral testosterone administration resulted in increases in body cell mass [mean 1.22 kg; 95% confidence interval (CI) 0.23 – 2.22 kg] for all groups, but those who received intramuscular injections experienced a greater increase (mean 1.99 kg; 95% CI 0.23–3.76 kg). An interesting finding was that only one trial included women [66], and if they were excluded from the analysis the change in body cell mass increased even further (mean 2.63 kg; 95% CI 1.42–4.06 kg). There was an overall mean increase of 1.04 kg (95% CI −0.01 to 2.10 kg) in total body weight, and again exclusion of women produced greater increases (mean 1.54 kg; 95% CI −0.03 to 3.10 kg). The assessment of muscle function/strength was not uniform across the reviewed studies, making meta-analysis for this variable impossible; however, three of the studies reported an improvement in strength [67–69]. Because of reporting inconsistencies, meta-analysis of adverse events was impossible to assess, but the authors indicate that the most common reports were of acne, gynaecomastia and breast tenderness. Overall, analysis was difficult because of heterogeneity of participants (in terms of gender, age, pre-intervention testosterone level, etc.), treatments (mode of delivery and dosage) and outcome measures (lean tissue mass vs body cell mass). However, the reviewed literature indicates that testosterone therapy can positively influence lean tissue mass and total body weight in those with HIV/AIDS wasting [70].

Nandrolone decanoate

Another anabolic steroid, nandrolone decanoate (ND), a testosterone analogue, appears to be effective in increasing lean tissue mass and muscular strength in men with HIV infection. The rationale for using ND in treating HIV/AIDS wasting is that it has high androgenic/anabolic activity accompanied by fewer androgenic side effects than testosterone. A 12-week regimen of intramuscular ND administration increased lean tissue mass [3.9 ± 2.3 kg; dual energy X-ray absorptiometry (DXA)], body cell mass (2.6 ± 1.0 kg; BIA) and quadriceps and hamstring muscle area [$P < 0.001$; magnetic resonance imaging (MRI)] in 15 subjects (most receiving antiretroviral therapy) [71]. The subjects receiving ND significantly improved strength from baseline in eight of nine exercises as determined by one repetition maximum (1-RM) lifts. Side effects of the therapy included development of acne (one subject) and testicular shrinkage (eight subjects). Subjects with AIDS-related wasting (mean CD4 count 90 ± 24 cells/μL; > 5% weight loss) with low testosterone (< 25th percentile for age) received a low dose (65 mg/week) or a high dose (195 mg/week) of ND over a 14-day period [72]. They were found to show an increase of 0.5 or 0.9 kg in lean tissue mass per week, respectively, and the increased lean tissue correlated with significant nitrogen retention.

Gold *et al.* examined the use of ND in patients ($n = 17$) with HIV-related wasting (5–15% loss of body weight) who were unable to gain weight via nutritional therapy and education [73]. Following 16 weeks of bi-weekly 100 mg/mL intramuscular ND injections, anthropomorphic, BIA, total body water and neutron activation measurements revealed significant increases in body weight (mean 0.14 kg/week) and lean body mass (mean 3 kg overall). The results indicate that ND supplementation appears to be effective at increasing weight in HIV-infected persons with wasting, and a significant portion of this weight gain is lean tissue mass.

Growth hormone

Growth hormone therapy is another strategy used in the treatment of HIV/AIDS wasting. Short-term (7 days) administration of growth hormone to six HIV-infected persons (pre-HAART) with wasting (average 19% below ideal body weight) resulted in increased body weight (2.0 ± 0.3 kg) and decreased urinary nitrogen excretion (288 ± 17 mmol/day), despite increased resting energy expenditure (7.5%). These results indicated that short-term growth hormone administration was able to increase protein anabolism and body weight, which theoretically will result in increased body cell mass with long-term administration [74]. These results were attained pre-HAART, so the outcomes must be viewed cautiously given the influences of HAART on fat distribution [75] and skeletal muscle function [76].

Growth hormone at a low dose (1.4 mg/day) was administered to patients who had progressed to AIDS

(CD4 count < 200 cells/μL) and were suffering from wasting (> 10% weight loss) [77]. After 6 weeks of treatment the growth hormone group ($n = 12$) significantly increased lean body mass ($P = 0.002$) and body weight ($P = 0.02$); however, at 3 months subjects no longer showed significant changes in lean body mass or weight. Muscle function, assessed by computerized isotonic dynamometry, with muscular power as the endpoint measure of interest, revealed that the growth hormone group had increased upper body and lower body power at 6 weeks, but only upper body power at 12 weeks. Given the small number of subjects and the significant side effects of the growth hormone therapy (jaw pain, $n = 4$; myalgia/arthralgia, $n = 4$), the results of this study should be interpreted with caution.

Growth hormone administered at a dose of 0.1 mg/kg/day to HIV-infected persons with documented wasting (> 10% loss of ideal body weight) for 3 months resulted in significant increases in weight and lean body mass ($P < 0.001$) [78,79]. Subjects who received the same dose for 6 months showed no difference ($P = 0.25$) in lean tissue mass compared with those who received 3 months of growth hormone [79]. This dose also resulted in a significant improvement ($P = 0.039$) in work output (cycle ergometer) after 3 months [78]. Side effects occurred in 15 of the 90 subjects randomized to receive growth hormone, with arthralgia, myalgia, fluid retention and diarrhoea being the most commonly reported side effects [78]. These data indicate that increases in lean body mass can be sustained, and the most significant effects of growth hormone, both on lean tissue mass and on muscular strength, are observed in the early phases (3 months) of treatment.

A low dose of growth hormone (30–40 μg/kg/day) was tested for 6 months in HIV-infected persons ($n = 5$) during the HAART era [80], and increases in lean body mass (62.9 ± 6.4 to 68.3 ± 9.1 kg; $P = 0.03$) were observed in a comparison of baseline and 6-month results. It should be noted that arthralgia, oedema in the extremities, and fasting hyperglycaemia did develop in these subjects to the extent that some had to reduce the growth hormone dose to 1.5 mg/day. These data show that increases in lean body mass with growth hormone administration can be attained at lower dosages, and can be expected in persons receiving HAART.

In a study that included patients on HAART, a high dose of growth hormone (6 mg/day) was administered for 6 months, a 12-week wash-out period was implemented, and then 4 mg of growth hormone was administered every other day for 6 months [81]. The primary goal of the study was to observe changes in body fat, but DXA scans also revealed an increase in lean tissue mass during the high-dose intervention, at 3 months (60.7 ± 9.7 kg at baseline vs 65.8 ± 10.8 kg at 3 months) and at 6 months (66.0 ± 11.3 kg) ($n = 19$). The low-dose intervention ($n = 9$) also produced increases in lean tissue mass at 3 months (60.6 ± 8.6 kg at the start of the low-dose treatment vs 63.4 ± 7.2 kg at 3 months) and at 6 months (63.2 ± 8.3 kg), although the changes were not as great as in the high-dose treatment. Nine subjects experienced adverse events during the high-dose phase to the extent that dosages were reduced, and 13 participants experienced side effects at some point during the study.

Insulin-like growth factor-1

Research has revealed that IGF-1 is not as effective as growth hormone at increasing nitrogen retention [82] and subjects frequently experience hypoglycaemic effects along with myalgia, gynaecomastia and headaches. Additionally, IGF-1 administration has only shown transient increases in lean tissue mass, with no apparent improvements in muscle function [77]. However, the combination of growth hormone and IGF-1 has produced a lean tissue mass increase of 3.2 kg, which is greater than the increase obtained with either agent alone in these studies [83,84]. Limited data are available regarding the effects of IGF-1 on increasing lean tissue mass, and thus it is too early to speculate on its effectiveness.

Cytokine treatments

Research has shown that proinflammatory cytokines (specifically TNF-α) can induce catabolic pathways in skeletal muscle and suppress the expression and function of the anabolic hormone IGF-1 [85]. Additionally, TNF-α has been shown to be elevated in patients with AIDS and AIDS-related weight loss [86]. Thus, cytokine therapies may be beneficial in combating muscle wasting in HIV-infected individuals. Treatment with thalidomide (which suppresses TNF-α production *in vitro*) has demonstrated effectiveness in promoting weight gain in patients with HIV disease [87]. Twenty-eight AIDS patients with documented wasting (> 10% loss) on antiretroviral therapy received either 400 mg of thalidomide ($n = 14$) or placebo ($n = 14$) daily for 12 weeks [88]. Significant weight gain was seen in eight (57%) treatment subjects while only one placebo subject gained weight. Shorter treatment periods (14 days) with thalidomide in HIV-infected subjects without wasting also increased body weight ($P = 0.002$) [89]. This weight gain was associated with increased nitrogen retention ($P = 0.017$), suggesting that a portion of the weight gain may be lean tissue mass.

Pentoxifylline, another cytokine modulator, decreases TNF production and has been effective in decreasing TNF mRNA levels as a result of thrice-daily doses in AIDS

patients [90]. Ketotifen, an inhibitor of TNF-α release from peripheral blood mononuclear cells, has also been used as a treatment in HIV-infected individuals. Daily doses of ketotifen for 12 weeks resulted not only in decreased TNF-α release, but also in weight gain [91]. Thus, thalidomide, pentoxifylline and ketotifen appear to be effective in increasing body weight, but the effects on lean tissue mass and muscle function are yet to be characterized.

Resistance exercise training

Resistance exercise training is known to increase skeletal muscle mass and strength in numerous healthy and clinical populations regardless of gender, age or race [92]. Resistance exercise serves to improve muscle protein balance via a number of mechanical and chemical signals, and therefore maintains and/or increases muscle mass [93]. Thus, resistance exercise training has the potential to be a viable alternative to pharmacological treatments for maintaining and increasing lean body mass and muscular strength in HIV-infected persons.

Resistance training programmes have been used to combat muscle wasting in many clinical populations. A 12-week total body resistance training programme (three sets of eight repetitions at 80% of 1-RM, three times per week) involving patients (17 men and 19 women, over 50 years of age) with renal failure resulted in increases in total body potassium and muscle fibre cross-sectional area (muscle biopsy), and improvement in muscle strength compared with controls [94]. Similarly, Hakkinen *et al*. [95] implemented a 2-year total body resistance training programme (two sets of 8–12 repetitions, two times per week at 50–70% of 1-RM) for rheumatoid arthritis patients (31 subjects; 18 women). Those who completed the exercise training regimen exhibited significant increases in strength (19–59%); however, lean tissue measurements were not taken.

Prior to discussing the effects of exercise in HIV-infected populations, it should first be recognized that research has shown exercise to be safe in this population [96]. Exercise at low to moderate intensities does not increase the prevalence of opportunistic infections, does not increase viral load, and does not decrease CD4 cell counts [97]. Additionally, there have been no reports of adverse side effects to exercise interventions. That being said, as is the case in other clinical populations, the benefits of resistance exercise are also experienced by HIV-infected patients. Progressive resistance exercise programmes have resulted in increases in lean tissue mass and improvements in strength in HIV-infected persons, both with and without muscle wasting.

Roubenoff *et al*. [98] implemented an 8-week resistance exercise training programme in a group of 21 HIV-infected persons receiving antiretroviral therapy. The protocol consisted of three sets of eight repetitions at 50% of 1-RM during week 1, 60% of 1-RM during week 2, and 75–80% of 1-RM during the remaining weeks on both upper body and lower body exercises. Significant strength improvements (18–31%) were reported on all exercises, along with a significant increase ($P<0.0002$) in lean body mass (DXA). Roubenoff and Wilson also found that differential effects occurred between the wasting and nonwasting groups [99]. The subjects with muscle wasting had 16% greater strength increases and gained 3% more lean tissue mass. Another interesting finding was that both groups increased perceived physical functioning following the intervention.

Resistance exercise training and hormone therapy

A common trend in studying HIV/AIDS-associated wasting is combining resistance exercise training with androgen therapy. Bhasin *et al*. [68] tested the effects of a 16-week training programme (three times per week alternating between heavy days of four to six repetitions at 90% 1-RM and moderate days of four to six repetitions at 70% 1-RM) combined with testosterone supplementation in a group of HIV-positive men with wasting (5% or greater loss of body weight). Results showed that both exercise (29–36%) and testosterone therapy (17–28%) increased strength and both exercise ($P<0.03$) and testosterone ($P<0.001$) increased thigh muscle volume (CT). The interesting finding was that there was not an additive effect with the combination of therapies.

Sattler *et al*. [71] examined the effects of ND therapy and a resistance exercise training programme in HIV-infected men ($n=30$) over 18 years of age. After a 12-week period in which the exercise group performed three sets of eight repetitions at 80% 1-RM, the ND-only group showed increased lean tissue mass (3.9 ± 2.3 kg; DXA) and increases in quadriceps ($P<0.001$) and hamstring ($P<0.001$) muscle area (MRI). The exercise and ND group experienced the same increases in muscle area, but had an even greater increase in lean body mass (5.2 ± 5.7 kg).

Grinspoon *et al*. [67] tested the effects of testosterone and exercise for 12 weeks in a group of HIV-infected men with wasting. Subjects randomized to receive the exercise intervention completed 20 min of aerobic exercise followed by two sets of eight repetitions at 60% 1-RM during the first week, and then progressed to three sets of eight repetitions at 80% 1-RM during the final weeks. There was an increase in lean body mass (DXA) in the training group (mean 2.3 kg) and in the combined therapy group (mean 4.0 kg), showing an effect of testosterone; however,

Table 2 Effects of various therapies on body composition and muscular strength in HIV-infected persons with wasting

Therapy	Treatment duration (weeks)	Results					Side effects
		Weight	LTM	FM	BCM	Muscular strength	
Total parenteral nutrition	4–42	↑	NC	↑	↑	–	None reported
L-glutamine	12	↑	–	NC	↑	–	None reported
Testosterone/nandrolone decanoate		↑	↑	–	↑	↑	Acne, gynaecomastia, breast tenderness, testicular shrinkage
Growth hormone/IGF-1 fasting	1–24	↑	↑	–	–	NC	Jaw pain, myalgia, arthralgia, oedema, hyperglycaemia, diarrhoea, headaches
TNF-α blockers interference	2–12	↑	–	–	–	–	Potential innate immune system
Resistance exercise	8	↑	↑	–	–	↑	None reported
Resistance exercise and testosterone	8–16	↑	↑	NC	–	↑	See testosterone side effects

LTM, lean tissue mass; FM, fat mass; BCM, body cell mass; ↑ , increase following therapy; NC, no change following therapy; –, not measured; IGF, insulin-like growth factor; TNF, tumour necrosis factor.

isometric strength tests showed that neither training nor testosterone had a significant effect on muscle strength.

Summary

It is evident from the data presented above that there exist many methods of increasing lean tissue mass and improving muscular strength in HIV-infected persons both with and without wasting (Table 2). Basic nutritional supplementation, while accessible to many persons, appears to result in increased body weight, but mainly via increases in body fat stores. Other nutritional interventions, such as those that analyse dietary intake and supplement for specific amino acid deficiencies, can increase lean tissue mass in HIV-infected populations; however, the availability of these types of services limits the applicability of this type of intervention.

Blocking catabolic factors, such as TNF-α, with the use of pharmacological agents has been effective at increasing body weight in HIV-infected persons. Further research is needed, however, to determine whether these increases in weight are attributable to lean tissue or fat mass gains. Furthermore, this population is already burdened with medications for treating HIV infection, so the feasibility of administering additional drugs is questionable. Finally, this population already experiences decreased immune function. Therefore, decreasing TNF-α, which is a vital cytokine in the innate immune system, may lead to additional immunological complications.

Results indicate that growth hormone at higher doses (0.1 mg/kg/day) provides benefits to those with HIV/AIDS wasting, regardless of disease severity, by increasing protein anabolism and thus increasing lean tissue mass. An inconsistency, however, is the relationship between the increased lean tissue mass and muscle function. Additionally, it is unclear if these increases in lean body mass are actually skeletal muscle, because it has yet to be verified that these increases are concurrent with increases in muscle function. The major limitation of this research is that many of the studies occurred before the HAART era, and thus results must be cautiously interpreted. Additionally, while the listed side effects may not seem severe, if added to the side effects of HIV infection itself, and those of HAART, they may be considered too burdensome. Finally, growth hormone costs approximately $42/mg, making the average cost $252/day, or $21 000 for a 12-week treatment course. This makes growth hormone inaccessible to most HIV-infected persons.

Androgen therapy, with either testosterone or ND, has been successful in increasing lean tissue mass and muscular strength in HIV-infected persons with and without wasting. A minimal effective dose is yet to be determined, and this is a significant hurdle because the side effects (gynaecomastia, acne and breast tenderness with testosterone and acne and testicular shrinkage with ND) can further decrease the quality of life in this population, who already experience HIV-related problems and antiretroviral treatment-related side effects. Further, research has yet to show the effects of treatment cessation (e.g. endogenous testosterone production, lean tissue mass changes and mood alterations), which could place these persons in even more compromising situations than prior to therapy.

Exercise training studies, although few in number, show that resistance exercise training at high intensities (~80% 1-RM) for relatively short periods is successful at increasing lean tissue mass in HIV-infected patients with and without wasting. These improvements in lean tissue mass are also associated with significant increases in muscular performance, as evidenced by gains in muscular strength. Also, these beneficial effects occur without compromising immune function and are independent of the side effects common to hormone therapies.

Conclusions

Muscle wasting in HIV/AIDS is a major public health problem because the loss of muscle mass is a predictor of morbidity and mortality, and the corresponding decline in muscular strength can be debilitating. Nutritional therapies, pharmacological agents that decrease TNF-α levels, androgen supplementation, growth hormone administration and resistance exercise have all shown varying levels of success in increasing lean tissue mass in HIV-positive persons. However, resistance exercise appears to be a very effective treatment because it is less expensive than other treatments, debilitating side effects are virtually nonexistent, and it is available to a far greater portion of the population. Additionally, quality of life and physical functioning have also been positively affected by exercise training programmes.

Given the influence of HAART on body composition and muscle function, many early exercise and HIV studies need to be revisited. It is also unknown whether disease status affects exercise training results. Additionally, the underlying mechanism(s) involved in the exercise-induced increase in lean tissue mass is yet to be defined. Further, it is yet to be determined whether increases in lean tissue mass can be attained at lower training intensities, which may increase retention rates. Finally, no long-term studies examining the effects of resistance training in HIV-infected populations exist; it is therefore unknown whether the benefits can be sustained over time, or whether further adaptations occur.

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