From Wasting to Obesity, Changes in Nutritional Concerns in HIV/AIDS

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KEYWORDS

• AIDS wasting syndrome • Malnutrition • Lipodystrophy • Frailty • HAART

KEY POINTS

- In the pre–highly active antiretroviral therapy (HAART) era, a wasting syndrome was the predominant nutritional alteration in human immunodeficiency virus/AIDS.
- The early HAART was complicated by the frequent development of a lipodystrophy syndrome related to medications, host factors, and disease characteristics.
- Frailty, associated with sarcopenia, is becoming a common nutritional and clinical problem in the current treatment era.

INTRODUCTION

An adage popular in the early part of the nineteenth century stated, *if you understand syphilis, you understand all of medicine*. In the latter part of nineteenth century the adage evolved to state, *if you understand tuberculosis you understand all of medicine*. In the current era, it can be said that *if you understand human immunodeficiency virus (HIV)/AIDS, you understand all of medicine*. These all are multifaceted diseases affecting multiple organ systems, and the implications span multiple levels within the health care system.

The history of HIV infection in the developed world can be divided into 2 eras, one preceding (1981–1996) and the other following (1996) the availability of highly active antiretroviral therapy (HAART). Much of the developing world remains in the pre-HAART

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era, although the number of treated patients has increased progressively over the past 10 years. In contrast, untreated patients, either through the lack of diagnosis or unwillingness to adhere to treatment, continue to be seen in the developed world, including severely malnourished patients, similar to those seen in the pre-HAART era.

Nutritional consequences in HIV infection have been recognized since early in the epidemic. Protein-calorie malnutrition (wasting) with depletion of lean mass, fat, and micronutrients was the most common problem in the pre-HAART era and led to shortened survival and diminished quality of life.[1] The pathogenesis of wasting is multifactorial and related mainly to altered caloric intake, intestinal injury with nutrient malabsorption, and/or increased metabolic demands from the active infections.[2] Although the specific disease complications are limited to patients with AIDS or other immune deficiency states, the clinical-pathological correlations of malnutrition are the same as in nonimmune deficiency–mediated conditions. Also, as in non-AIDS patients, wasting exacerbates the immune deficits, promotes debility and dependency, and shortens the lifespan.[3] The success of HAART in reconstituting immune function and reducing morbidity ultimately allows HIV-infected individuals in North America to live as long as the general population.[4]

The widespread use of HAART has markedly improved clinical outcomes and decreased the prevalence of wasting. However, many treated patients develop a cluster of other nutritional alterations, including changes in body fat distribution, as well as dyslipidemia and insulin resistance, without wasting of muscle or other lean tissues.[5,6] The lipodystrophy syndrome, as it has come to be called, has attracted considerable clinical and experimental attention.[7,8] The causes are multifactorial, which led to a wide-ranging discussion about cause and effect and the relative roles of host, disease, and treatment in its pathogenesis.

The initial responders to the AIDS epidemic were in a unique situation in that they faced a brand new disease, with no evidence base for evaluation and management to help or hinder them. It soon became clear that the clinical manifestations represented disease complications and that the underlying disease and its causes had to be distinguished from the clinical complications of immune deficiency. For example, there was an initial reluctance by some surgeons to perform major surgery on patients with HIV/AIDS because of reports of poor clinical outcomes, whereas later observations showed that the poor results were related to protein calorie malnutrition and not to HIV/AIDS per se. The perceptions that progressive wasting is a universal phenomenon and that everyone with immune deficiency has intestinal dysfunction were subjected to clinical investigation and were shown not to be true.[9,10] In fact, the approach to nutrition in HIV/AIDS fits the classic clinical conundrum: How is what we are seeing the same as in other diseases, and how is it different?

Initially, there was little to go on other than the classic teachings of medicine. The situation fostered inductive reasoning as well as the performance of clinical trials to develop an evidence base. The response to HIV/AIDS was the first clinical condition in which nonmedical activists came to play an important role in the design and implementation of clinical trials, and they also played a crucial role in promoting acceptance and participation by HIV-infected people worldwide.

In this article, the authors describe the current knowledge on nutrition in the setting of HIV/AIDS, both in the presence and absence of antiretroviral therapy. The authors provide clinical descriptions and discuss pathogenic mechanisms, evaluation, and management of wasting and of lipodystrophy. The authors also briefly discuss the topic of nutritional assessment. The discussion of many topics, such as diabetes mellitus, cardiovascular disease, fat distribution, and so forth, is limited, as they are covered in greater detail elsewhere in this issue.

METHODS TO ASSESS NUTRITION

Although the high prevalence of weight loss and protein-calorie malnutrition was obvious from the earliest description of patients with AIDS, the only literature to guide the early clinicians was a subjective diagnosis of *slim disease* in a report from Africa. HIV/AIDS was one of the first diseases to be studied nutritionally using quantitative measures of body composition other than body weight.

Initial clinical studies, performed mainly on inpatients, demonstrated the weakness of using weight-based measures to estimate nutritional status.[1] Because of the wide ranges of premorbid body weights or body mass index (BMI) values as well as normal values, it may be difficult to detect wasting from a single measurement. The assessment of body weight provides no information about body composition: It cannot distinguish fat from muscle; it cannot distinguish lean mass from excess fluid, and it cannot detect micronutrient deficiencies at all. Body weight measurements were frequently difficult to interpret in patients with AIDS, especially hospitalized patients in whom wide swings in body weight resulted from diarrheal illnesses and from intravenous fluid administration. Quantitative measures of body composition had been developed more than 30 years before but had few clinical applications other than in examining the changes that occur during critical illness, aging, and obesity.

Wang and colleagues[11] organized body composition analysis by categorizing the measurements by level: atomic, molecular, cellular, tissue/organ, and whole body (**Table 1**). For example, the measurement of total body nitrogen by neutron activation analysis is part of the atomic level of measurement, whereas the measurement of total body water by isotope dilution is part of the molecular level of measurement and so forth. The 2 major rules of this organization are that the sum of all of the components within any level should equal the body weight and that one cannot use measurements from different levels in the same equation. However, one can derive predictive equations from one level to estimate the size of a compartment in another level (eg, total body protein = total body nitrogen $\times$ 6.25 or lean body mass = total body water/0.732).

Many techniques have been applied to the estimation of nutritional status in HIV/AIDS: (1) four-skinfold method, (2) hydrodensitometry, (3) neutron activation analysis, (4) bioelectrical impedance analysis (BIA), (5) dual-energy X–ray absorptiometry (DEXA), and (6) cross-sectional imaging (ie, computed tomography [CT]/magnetic resonance imaging [MRI]).[12–20] Because of their ease of use, BIA, DEXA, and CT/MRI have been used in clinical practice and research. Of note, the optimal methods to assess wasting are different from those used to assess lipodystrophy, with techniques to assess nonadipose tissue cellular mass or skeletal muscle mass being more important for protein-calorie malnutrition, whereas cross-sectional imaging

Table 1
Levels of body composition analysis

Level	Components
Atomic	Oxygen, carbon, hydrogen, nitrogen, potassium, sodium, phosphorus, chlorine, calcium, magnesium, sulfur, other atoms
Molecular	Water, lipid, protein, minerals, glycogen, and other molecules
Cellular	Body cell mass, adipocytes, extracellular fluid, extracellular solids
Tissue/organ	Skeletal muscle, adipose tissue, bone, viscera, other tissues
Whole body	Head, trunk, appendages

and DEXA are better at demonstrating alterations in body fat distribution in patients with HIV-associated lipodystrophy.

NUTRITIONAL ALTERATIONS IN THE PRE-HAART ERA

In 1987, the Centers for Disease Control and Prevention established HIV-associated wasting (defined as involuntary weight loss of greater than 10% from baseline plus either diarrhea or fever for 30 days or more) in the absence of a diagnosed concurrent illness as an AIDS-defining condition.[9,21,22] There have been no substantive changes in the definition since that time. However, many patients lose weight in the presence of a concurrent illness and also can be considered malnourished; clinical evaluation in others may be inadequate to detect the specific cause. The goal of the definition was to categorize patients as having AIDS, rather than HIV infection, both for reporting purposes as well as qualifying for medical and other entitlements. It provided no information about the cause or appropriate management.

Effects of HIV/AIDS on Macronutrient Status

The earliest nutritional studies were performed in severely ill, hospitalized patients with AIDS before the availability of any antiretroviral agents and demonstrated protein depletion (ie, transferrin, albumin) and muscle wasting (ie, midarm circumference).[22] In contrast, weight gain was often noted during hospitalization as a result of intravenous hydration in the presence of hypoalbuminemia. Although weight loss was often profound, the depletion of lean mass was even more striking; in contrast, body fat content was not severely depleted in many patients.[1] These studies were performed before the identification of HIV as the etiologic agent of AIDS and represent the natural history of tissue depletion at the start of the epidemic in New York City. Body composition studies performed in patients with wasting syndromes in the absence of nutritional support demonstrated that magnitude of weight loss and the severity of body cell mass depletion correlated with the timing of death.[3] Later studies demonstrated that depletion of lean mass occurs early in the disease course and may precede the development of weight loss.[23] The loss of lean mass is concentrated within the body cell mass, the metabolically active components of the muscles and visceral organs. The composition of weight loss differs in men and women, with men losing more lean mass and less body fat than do women.[24] However, clinical stability was associated with nutritional stability, indicating that wasting is not a universal phenomenon in HIV-infected individuals.[9] Weight loss from opportunistic infections is episodic and rapid, whereas weight loss related to malabsorption tends to be more chronic and slowly progressive.[25] Other factors, both behaviors and comorbidities, may also affect nutritional status, independent of HIV infection.

Effects of HIV/AIDS on Micronutrient Status

Many studies of micronutrients have been published but mostly in untreated patients. Low levels of several micronutrients have been reported, including vitamin B12, selenium, zinc, vitamin B6, other B vitamins, and fat-soluble vitamins, including vitamin A and vitamin D.[26] Vitamin A deficiency was associated with increased mortality in Africa and with an increased risk of maternal child transmission of HIV infection.[27] Selenium deficiency is recognized to occur commonly in HIV infection and was significantly associated with an increased relative risk of mortality.[28] Several studies have shown that HIV/AIDS is associated with enhanced oxidative stress. Antioxidant deficiency is potentially important because inflammatory mediators promote HIV replication.[29]

Nutrition and Wasting

Malnutrition is multifactorial in HIV infection, and the pathogenic mechanisms are similar in HIV and non-HIV infected people. Although some nutritional and metabolic alterations can be identified during the preclinical stage of disease, progressive malnutrition is limited to patients with a severe, chronic disease complication and, usually, severe immune depletion. The pathogenic processes underlying wasting involve alterations in caloric intake, nutrient absorption, or energy expenditure. Weight loss, ultimately, is a consequence of negative caloric balance, irrespective of cause. The relative roles of altered energy intake and expenditure have been examined. Grunfeld and colleagues[30] demonstrated that caloric intake was more important than resting energy expenditure in predicting short-term (1 month) change in body weight. Macallan and colleagues,[31] using the technique of doubly labeled water measurement, found that total energy expenditure was decreased in weight-losing patients and that the loss was confined to voluntary energy expenditure. However, caloric intake was decreased to a greater extent than was voluntary energy expenditure. Simply maintaining caloric intake by nonvolitional feeding does not necessarily replete lean mass (see later discussion).

There are several causes for reduced food intake, including local pathological conditions; focal or diffuse neurologic diseases; severe psychiatric disease; food insecurity because of psychosocial or economic factors; and anorexia caused by medications, malabsorption, systemic infections, or tumors (**Box 1**). Malabsorption in HIV/AIDS is usually related to small intestinal infections, usually protozoal, with partial villus atrophy and crypt hyperplasia (**Fig. 1**). Cryptosporidiosis is the most well known of these infections (**Fig. 2**). This organism causes a self-limited infection in immune-competent people and in most HIV-infected patients with peripheral blood CD4 lymphocyte counts greater than 200/mm^3 but it is progressive and ultimately fatal in the absence of HAART therapy. *Isospora belli*, microsporidia, and *Cyclospora cayetanensis* (**Figs. 3** and **4**) are other protozoa that localize in small intestinal mucosa. *Mycobacterium avium* complex infection (**Fig. 5**) of the small intestine promotes malabsorption, particularly of fats, because of lymphatic obstruction and exudative enteropathy. Patients with HIV/AIDS also develop a variety of systemic infections with fever, hypermetabolism, and anorexia.

Other metabolic alterations not necessarily associated with opportunistic infections include elevated resting energy expenditure, hypertriglyceridemia, and decreased serum cholesterol concentrations.[32] Hypertriglyceridemia is associated both with decreased clearance of chylomicrons as well as increased de novo fatty acid synthesis and elevated serum concentrations of bioactive interferon alpha.[33] Alterations of the hypophyseal pituitary adrenal and gonadal axes are common; deficiencies in testosterone and other endogenous anabolic factors may occur and promote protein depletion.

Box 1
Causes of poor food intake

- Local pathologic conditions affecting chewing, swallowing, or gastrointestinal motility
- Focal neurologic disease affecting food intake
- Diffuse neurologic disease affecting the perception of hunger or ability to eat
- Severe psychiatric disease
- Food insecurity because of psychosocial or economic factors
- Anorexia caused by medications, malabsorption, systemic infections, or tumors

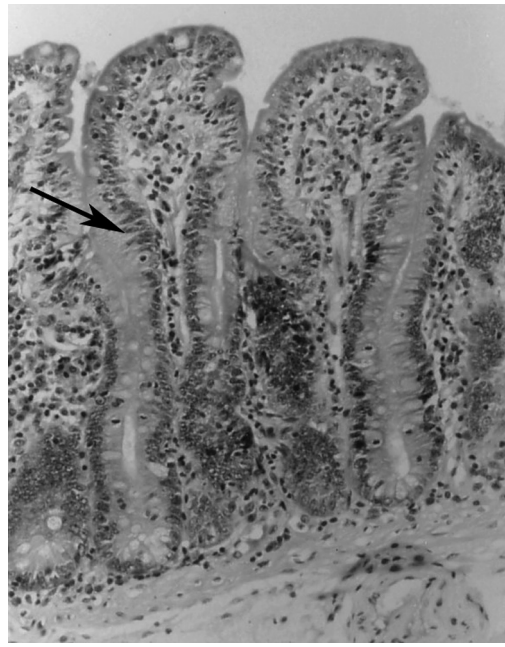

Fig. 1. A small intestinal biopsy demonstrating marked crypt hyperplasia and partial villus atrophy. The arrow is placed at the approximate level of the crypt/villus junction (hematoxylin and eosin, original magnification ×250).

Nutritional Management of Wasting

The rationale for nutritional therapy to patients with AIDS is straightforward: malnutrition has adverse consequences that can be prevented by improving nutritional status. Concepts guiding the decisions to provide nutritional support in HIV-infected patients are the same as in anyone with a chronic illness.

There are no data to support the standard use of oral supplements in HIV-infected individuals, in the presence or absence of wasting, though they often are prescribed in patients complaining of fatigue. There is little consensus about the use of

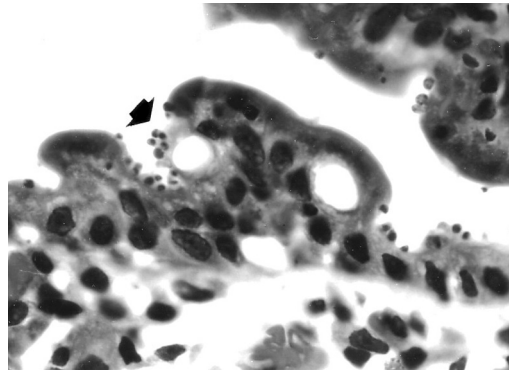

Fig. 2. A small intestinal biopsy from a patient with cryptosporidiosis, demonstrating the organisms (*arrow*) at the brush border level, where they invade and damage the apical portion of the enterocyte (acid fast stain, original magnification ×400).

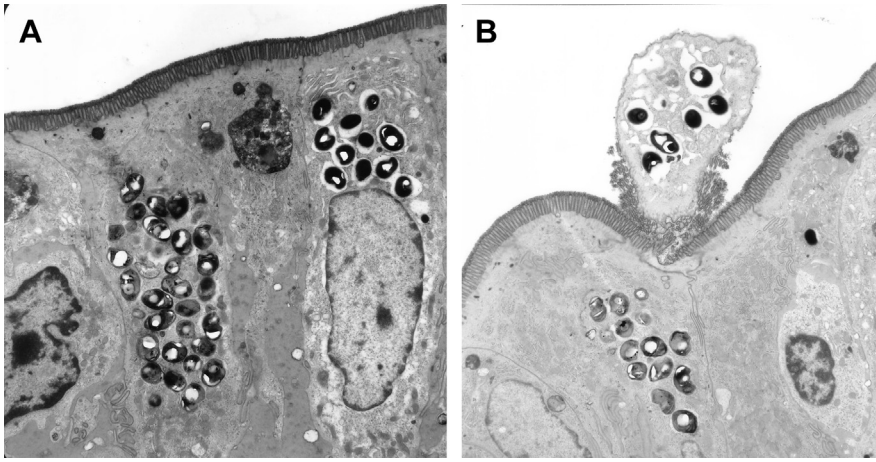

Fig. 3. (*A*) A small intestinal biopsy from a patient with microsporidiosis. Spores of *Enterocytozoon bieneusi* are seen in the cytoplasm of epithelial cells. The organisms may be difficult to detect on light microscopy. (*B*) A small intestinal biopsy from a patient with microsporidiosis. A dying cell containing spores of *E bieneusi* (electron micrograph, original magnification ×3500).

micronutrient supplements, such as antioxidant and vitamins, in the face of a nutritious diet. A study of vitamin A supplementation in African mothers with HIV/AIDS demonstrated a significant decline in vertical HIV transmission.[34] Micronutrient supplementation has the greatest impact in patients with micronutrient deficiencies at baseline, even in the absence of antiretroviral therapy, though the effect may not be adequate if protein and caloric deficiencies persist.[35]

Several appetite stimulants have been studied or used in HIV-infected patients. The synthetic progestin, megestrol acetate, increases caloric intake and promotes weight gain and improved quality of life.[36] Dronabinol, a synthetic derivative of *Cannabis sativa* (marijuana), is approved for appetite stimulation in AIDS-related anorexia.

Several studies examined the effects of nonvolitional feeding on wasting. A prospective, open-label study in the pre-HAART era demonstrated gains in body cell

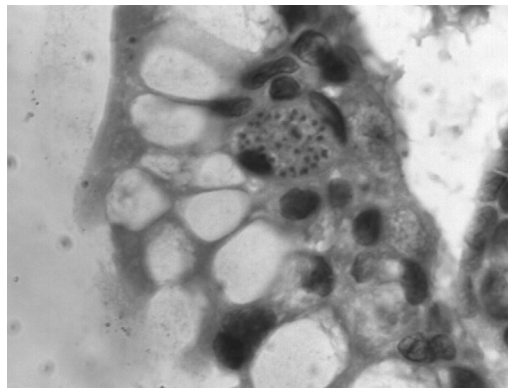

Fig. 4. A small intestinal biopsy from a patient with *Isospora belli* infection demonstrating the microgametocyte stage of infection (hematoxylin and eosin, original magnification ×1000).

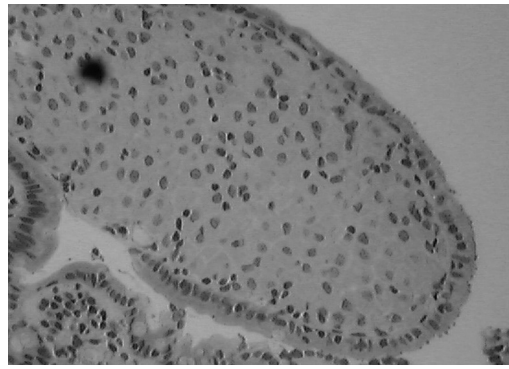

Fig. 5. A small intestinal biopsy from a patient with *Mycobacterium avium* complex infection. The villus is thickened and infiltrated with macrophages (foam cells) containing acid-fast bacilli. Of note, the patient has coexisting cryptosporidial infection (hematoxylin and eosin, original magnification ×250).

mass and body fat after percutaneous endoscopic gastrostomy (PEG) tube feeding.[37] Ockenga and colleagues[38] compared the clinical courses of patients with AIDS and non-AIDS patients who accepted or declined PEG feedings. Treatment was equally safe in both groups and led to nutritional benefits, but survival was not different in patients accepting or refusing PEG feedings. Total parenteral nutrition (TPN) was also studied in the pre-HAART era and promoted weight gain caused by an increase in body fat, without a change in lean mass.[39] However, patients with malabsorption syndromes or eating disorders responded well to TPN, with significant increases in body cell mass, whereas patients with systemic infections continued to lose body cell mass while gaining body fat. Thus, the response to TPN is related to the underlying condition rather than to the specific TPN formula. These results show that, although inadequate caloric intake is the most important promoter of weight loss, simply providing calories is not sufficient to reverse the loss of lean mass.

In a prospective randomized trial, TPN was compared with an oral, semielemental diet.[40] Although both the oral diet and TPN reversed weight loss in patients with AIDS with malabsorption, the caloric intake and weight change were both greater in the TPN group, whereas the quality of life was higher and health care costs lower in the oral-diet group. In a meta-analysis of nutritional therapy in patients with HIV, although energy and protein intake were increased in patients who had been supplemented with specific macronutrients, the outcomes were not different.[41]

A recurring theme in nutritional studies is that weight loss includes lean mass, especially skeletal muscle mass, although treatment-associated weight gain involves mainly body fat. For this reason, studies of anabolic agents were an area of active research in the pre-HAART era. Recombinant human growth hormone (rhGH) was shown to promote repletion of lean mass in studies performed both in the pre-HAART and HAART eras.[42,43] The increase in lean mass was associated with improvements in quality of life and physical performance. Anabolic steroids, including testosterone and its derivatives, were also studied in men and women and promoted lean mass repletion.[44,45] Because proinflammatory cytokines influence the wasting process, studies of cytokine inhibitors, antioxidants, omega-3 fatty acids, pentoxifylline (Trental), and thalidomide were performed, though with little evidence of benefit. However, resistance training exercise has been demonstrated to promote skeletal muscle repletion without systemic toxicity or potential for adverse interactions.[46]

THE LIPODYSTROPHY SYNDROME

Soon after the introduction of HAART, clinicians began to notice a constellation of metabolic and morphologic changes in treated patients.[47] A loss of subcutaneous adipose tissue, especially in the face, often associated with a gain in visceral and dorsocervical adipose tissue and no loss of lean mass, is common in HAART-treated patients.[48] The term *lipodystrophy* has been applied based on similarities to congenital or acquired conditions that include lipoatrophy and lipohypertrophy (**Fig. 6**) associated with dyslipidemia and insulin resistance, among other alterations.[7] Epidemiologic studies identified several risk factors (**Box 2**). Although the changes tend to cluster, they have some distinctive pathogenic pathways and may occur independently of one another.

The medical consequences of body fat redistribution have been known for more than one-half century since the French investigator, Jean Vague,[49] applied quantitative measures of body fat content in women with 2 different phenotypes, upper body and lower body obesity, which he termed android and gynoid, respectively. Upper body obesity was associated with adverse health outcomes, including diabetes mellitus and cardiovascular disease, whereas lower body obesity was not, despite having equivalent total body fat contents. The obvious conclusion, replicated many times since then, is that body fat distribution is more important than is total body fat in promoting adverse health outcomes. Initial observations suggested that lipoatrophy and lipohypertrophy in HIV/AIDS are closely linked, whereas epidemiologic studies suggest that these distinct compartments are affected differently by various influences (see later discussion). Premorbid body composition also strongly influences the clinical picture, with prior obesity associated with lipohypertrophy.

The major metabolic alterations seen in HAART-treated patients are similar to that seen in the general population, including dyslipidemia (elevated triglycerides and total cholesterol, decreased high-density lipoprotein [HDL] cholesterol) and insulin resistance. Generally, around 25% of treated patients with HIV fit the metabolic syndrome definition, similar to that of the normal population.[50] The incidence of hypertriglyceridemia varies by treatment regimen and is most common with certain protease

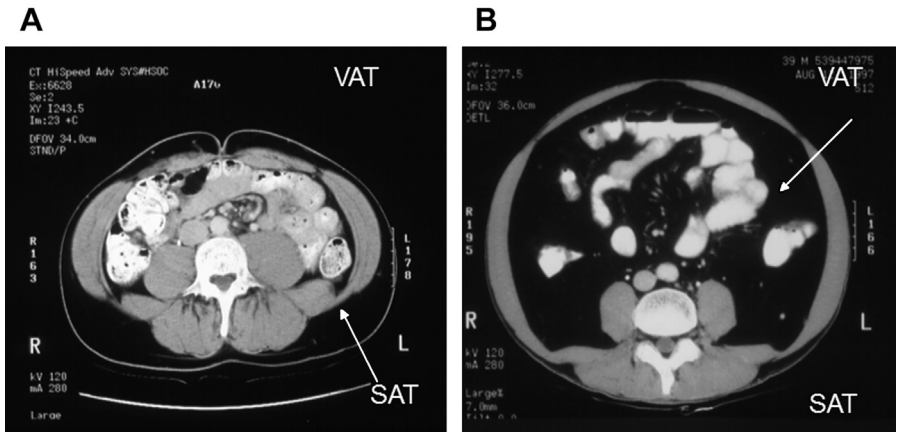

Fig. 6. (*A*) The abdomen in a young healthy male patient. Note the moderate amount of subcutaneous adipose tissue (SAT) (*black*) and very little visceral adipose tissue (VAT). (*B*) The abdomen in a patient with HIV-associated lipodystrophy. Note the virtual absence of subcutaneous adipose tissue (*black*) and the large amount of visceral adipose tissue. The *arrows* point to the correct compartment – SAT and VAT.

Box 2
Epidemiologic factors affecting the development of lipodystrophy

- Disease
  - Duration
  - Severity of immune deficiency
  - Magnitude of immune reconstitution
- Host
  - Age
  - Sex
  - Race
  - Family history, BMI
  - Diet
  - Exercise
  - Tobacco use
- Therapy
  - Specific agent
  - Duration of therapy

inhibitors. It is a direct effect of the drug as shown in a study of ritonavir administration to healthy HIV-seronegative volunteers.[51] In contrast to triglycerides, serum cholesterol concentrations are classically low in HIV-infected patients and increase during therapy, irrespective of the specific HAART regimen, as shown in an analysis of blood samples from a longitudinal cohort.[52] Seroconversion was associated with reductions in total, low-density lipoprotein (LDL), and HDL cholesterol concentrations. Total and LDL cholesterol levels increased during HAART, but LDL-cholesterol only increased to preinfection levels, which was interpreted as a return to prior health as opposed to drug toxicity. A similar argument has been made in the analysis of temporal trends in waist circumference.[53]

Alterations in glucose-metabolism first came to light with an alert from the Food and Drug Administration (FDA) about reports of diabetes mellitus associated with protease inhibitor use. Insulin resistance was found to occur in about one-half of protease inhibitor-treated patients compared with about one-quarter of patients on nucleoside analogue therapy in an early series.[54] Although asymptomatic, insulin resistance predicts a future risk of symptomatic atherosclerosis in non-HIV infected subjects.[55] Its genesis is multifactorial.[56] An acute, reversible effect of protease inhibitors on glucose transport into cells via glucose transporter type 4 (GLUT4) inhibition has been demonstrated.[57,58] Nucleoside reverse transcriptase inhibitors (NRTI) also promote insulin resistance, as shown in studies in healthy adults, an effect thought to be mediated by mitochondrial toxicity.[59] Other pathogenic factors include chronic inflammation, hepatitis C infection, elevations of free fatty acids caused by excess lipolysis, obesity with visceral fat accumulation, and others.

Pathogenesis

Several risk factors have been uncovered through epidemiologic investigations. Although most attention has been given to antiretroviral therapy, many host- and disease-related variables are important. Age, sex, race, premorbid weight and weight

change, a personal or family history of the metabolic syndrome, diet, and exercise may all affect the diagnosis, as may the duration of disease, the severity of immune depletion, and the magnitude of the immune reconstitution during antiviral therapy (see **Box 2**). A genetic predisposition to the development of lipodystrophy was shown in a prospective study of HAART therapy using cluster analysis. Treated patients were classified by developing morphologic and metabolic abnormalities while on therapy, which were found to cluster. Studies of selected candidates revealed a polymorphism in the resistin gene, which strongly predicted the development of the changes.[60]

There is substantial clinical and experimental evidence for direct metabolic effects of antiretroviral agents. Initial observations associated the development of hyperlipidemia, insulin resistance, and body composition changes and linked them to protease inhibitor use.[47] Protease inhibitors may affect hepatic very-low-density lipoprotein secretion through an inhibition in intracellular apoprotein B and may also decrease glucose uptake through a reversible inhibition of the glucose transport molecule GLUT4.[57] However, lipoatrophy was shown to occur in patients not taking protease inhibitors and even before the application of HAART.[61,62]

The development of lipoatrophy is related to mitochondrial DNA (mtDNA) depletion within adipose tissue and muscle cells.[59,63] The development of liver failure as a consequence of mitochondrial toxicity from nucleoside analogue therapy first came to clinical attention during studies of a fluorinated uridine developed to treat chronic hepatitis B infection.[64] Several nucleoside reverse transcriptase inhibitors inhibit human mtDNA polymerase gamma, leading to mtDNA depletion. Intraclass differences among the NRTIs in the ability to cause mitochondrial dysfunction and local factors limit the complication to specific tissues. Mitochondrial toxicity may be covert or overt, implying a threshold for clinical sequelae. A large body of corroborating evidence from many experimental models, ranging from cell culture to clinical trials, has been published.

A consistent finding in antiretroviral treatment studies is that evidence of inflammation and immune activation may persist despite immune reconstitution and control of opportunistic conditions. There is a large body of literature linking inflammation and atherosclerosis in non-HIV situations and a growing body of information that suggests that a similar process occurs in HIV/AIDS. The field gained a strong impetus with the identification of microbial translocation and its association with immune activation.[65] Microbial translocation and immune activation have been associated with several long-term adverse outcomes beyond cardiovascular disease, including neurocognitive disorders, cancer, and frailty. Microbial translocation is now being sought and found in other diseases where its presence may affect outcomes.[66]

Diagnosis

Despite great interest and effort in understanding the nature of lipodystrophy, there has been little effort in deriving diagnostic criteria, leaving clinicians to manage the various alterations individually. Therefore, HIV medicine parallels the general practice of medicine; the HIV treater has had to become familiar with practice standards for general medicine. Identifying body composition alterations is especially difficult. Because there are no recognized normal values, the techniques for quantitating subcutaneous and visceral fat contents are not available for clinical use; surrogate measures, such as anthropometric analyses, are inaccurate.[67] In general, the diagnostic criteria for the metabolic alterations are the same as in the non-HIV population.

Consequences

Although there are many possible etiologic factors in the development of lipodystrophy, most are nonmodifiable, whereas drug therapy is modifiable. The recognition

of lipodystrophy has fueled changes in HIV management, including reevaluation of the appropriate time to start therapy, switching therapy, stopping therapy, and providing consistent therapy. Not all of these changes have had a beneficial effect. For example, intermittent therapy was tested as a possible means to mitigate heart attack risk; but that study demonstrated an increase in myocardial infarction in patients who stopped and resumed therapy, which convinced the field that HIV infection itself should be considered as a cardiac risk factor.[68] Most importantly, the recognition of lipodystrophy and its adverse consequences has led to the development of new agents and new classes of agents that are largely free of mitochondrial toxicity and other adverse metabolic consequences.

Several aspects of the lipodystrophy syndrome are of clinical interest: cardiovascular disease,[69–71] cerebrovascular disease, diabetes mellitus,[72,73] neurocognitive dysfunction, bone disease,[74–77] and frailty. Frailty is a distinct clinical syndrome encompassing weight loss, weakness, exhaustion, and decreased activity; linkage to immune activation has been postulated in both HIV and aging.[78] Frailty is an increasingly recognized problem in clinical medicine and includes decreased muscle mass and function. Therefore, it may well be the future face of HIV-associated nutritional disorders.

Therapeutic Options

There are 4 possible responses to the development of lipodystrophy: do nothing, stop HAART, switch HAART, or treat the individual abnormalities. Advances in the field have led to the development of treatment regimens that are relatively free of mitochondrial and other metabolic toxicities, so that patients with these problems likely have them as a legacy of prior therapies. Unfortunately, lipoatrophy is not reversible to any significant extent. Most clinicians approach the metabolic complications as they would in non-HIV infected individuals, with some extra attention of possible drug-drug interactions. Complementary therapies (eg, weight control, smoking cessation) should be stressed in all cases, as they likely have a greater influence on the outcome than the individual antiretroviral agent.

Dietary modification has only a modest effect on serum lipid concentrations. Fibrates decrease serum triglyceride concentrations but do not significantly affect serum cholesterol concentrations, whereas the 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins) decrease both serum cholesterol and, to a lesser extent, triglyceride concentrations.[79] However, the goals of clinical management of hyperlipidemia as defined by the National Cholesterol Education Program's criteria are often not reached in HIV-infected patients. The treatment of clinical diabetes mellitus is standard.[56] Most patients can be managed successfully with diet and oral agents. Diet and resistance training exercise are well known to affect total body and regional fat mass in non-HIV infected subjects and have similar effects in patients who are HIV+.[46,80] The FDA approved a growth hormone releasing factor to treat visceral fat accumulation in patients with HIV lipodystrophy.[81]

FUTURE CONSIDERATIONS/SUMMARY

Initially, HIV infection was seen as being different from other diseases. However, as clinical knowledge has grown, it has become clear that clinical alterations, including nutritional changes, in patients with HIV/AIDS occur by the same processes as in other diseases and that people who understand all of clinical medicine can understand HIV infection. Although wasting was the initial nutritional complication of HIV/AIDS to be recognized and lipodystrophy followed the initial application of HAART, sarcopenia and frailty may be the most important alteration in the near future. Further, some of

the knowledge gained in studies of HIV/AIDS, such as microbial translocation, has been used to further our understanding of non-AIDS diseases.

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