

Abnormalities of Body-Fat Distribution

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Background

Abnormalities of body-fat distribution are a recognized complication of HIV infection and antiretroviral therapy (ART), and they are a common concern of patients. They include subcutaneous fat wasting (lipoatrophy) and central fat accumulation (lipohypertrophy). These morphologic changes are often referred to as lipodystrophy, though that term does not distinguish between the two phenomena. Abnormalities in fat distribution and body shape were noted in up to 40-50% of patients treated with older antiretroviral (ARV) medications (those available before the early 2000s); often those patients presented with more advanced HIV disease. The incidence of lipoatrophy appears to be much lower with the use of newer ARVs and with earlier initiation of ART, but it is unclear whether lipohypertrophy is less common.

Lipoatrophy and lipohypertrophy are associated with other metabolic abnormalities, such as dyslipidemia and insulin resistance, and visceral fat accumulation, in particular, has been shown to be a risk factor for cardiovascular disease, hepatic steatosis, and death. Severe lipoaccumulation can cause discomfort and, in some cases, impairment of breathing or other bodily functions. Both lipoaccumulation and lipoatrophy can be disfiguring, can damage self-image and quality of life, and can negatively influence ARV adherence.

The pathogenesis of lipoatrophy and lipohypertrophy in HIV-infected individuals is not well understood, but research to date suggests that the two processes have different but overlapping causes. They are multifactorial and may be associated with HIV-related immune depletion and dysregulation, treatment with ARV medications and resulting immune recovery, dysregulation of fat metabolism, hormonal influences, individual genetic predispositions, as well as aging, diet, and obesity. Lipodystrophy has been associated with low nadir CD4 counts as well as with gender (central lipohypertrophy may be more common in women) and age (it is more common in older patients), and longer exposure to ART.

- Lipoatrophy is strongly associated with nucleoside reverse transcriptase inhibitors (NRTIs), notably stavudine, as well as zidovudine and didanosine, and appears to occur rarely in persons who have never been treated with those agents. Efavirenz has variably been shown to worsen lipoatrophy in patients who also take NRTIs.
- Lipohypertrophy is associated with HIV treatment -- there is an increase in abdominal fat in many patients after initiation of ART -- but has not been proven to be related to specific ARVs or ARV classes (in the past it was variably attributed to treatment with protease inhibitors [PIs] and with NRTIs but studies have not demonstrated that these classes have more deleterious effects than others). The morphologic changes of lipohypertrophy also may develop in ARV-naive individuals.

Unfortunately, there are no standard clinical case definitions of lipodystrophy, lipoatrophy, or lipohypertrophy.

Lipoatrophy most commonly appears as the loss of subcutaneous fat in the face, arms, legs, and buttocks. It differs from the generalized wasting seen in advanced AIDS, because in lipoatrophy lean cell mass generally is preserved. In lipohypertrophy, the most common morphologic changes are a firm enlarged abdomen caused by central or visceral fat accumulation, breast enlargement (gynecomastia) in both men and women, development of a dorsocervical fat pad ("buffalo hump"), and neck enlargement. When lipohypertrophy and lipoatrophy occur together, the affected individuals show a mixed picture of abdominal obesity with thinning in the face, arms, and legs.

S: Subjective

The patient may report any of the following: sunken cheeks, decreased arm or leg circumference, prominence of veins in the arms or legs, or buttock flattening. Alternatively (or in addition), the patient may report abdominal fat accumulation with change in waist size, increased neck size, "buffalo hump," enlarged breasts, and reduced range of motion. Patient self-report of gains in abdominal fat has been correlated with visceral fat accumulation seen on radiographic imaging in HIV-infected patients on ART.

Determine CD4 cell count nadir and ARV medication history, with particular attention to past use of thymidine analogues (stavudine and zidovudine). Ask about past medical and family history, specifically regarding hyperlipidemia, diabetes or insulin resistance, other metabolic disorders, and cardiovascular disease. Evaluate the effect of body-shape changes on the patient's self-esteem, medication adherence, and interpersonal relationships.

O: Objective

There are no standard criteria for diagnosing lipoatrophy or lipohypertrophy on the basis of physical examination. Nevertheless, as a practical matter, clinical examination usually is the foundation of diagnosis. Serial examination often is helpful in determining the presence of fat loss or fat gain. Note that it may be difficult or impossible to differentiate lipohypertrophy and obesity without imaging studies.

Compare the patient's past and current weights. Calculate body mass index (BMI); see chapter [Initial Physical Examination](#) for information on BMI; note that BMI may not correlate with visceral lipoaccumulation.

Measure and document waist and hip circumferences. A waist circumference of >102 cm (39 inches) in men and >88 cm (35 inches) in women is the clinical definition of abdominal obesity and is associated with the metabolic syndrome. Waist-to-hip ratios of >0.95 in men and >0.85 in women have been associated with an increased risk of coronary heart disease. A study in HIV-infected persons (90% male) found that changes in waist circumference correlated with increases in abdominal fat on dual-energy x-ray absorptiometry (DEXA) or computed tomography (CT) after 96 weeks of ART.

Examine the face and extremities for subcutaneous fat loss (e.g., in the cheeks, temples, limbs, and buttocks). Examine the head, neck, back, breasts, and abdomen for fat accumulation, especially looking for the presence of a dorsocervical fat pad and enlargement of face, neck, breasts, or abdomen. Palpate the abdomen -- central fat gain that presents as an expansion of the abdomen deep to the abdominal wall (as distinguished from an accumulation of subcutaneous fat) suggests the presence of lipohypertrophy. It can be helpful to compare the patient's current appearance with that shown in past photographs.

Review laboratory history (glucose, lipid panel) to identify other metabolic disorders. (See chapters [Dyslipidemia](#) and [Insulin Resistance, Hyperglycemia, and Diabetes on Antiretroviral Therapy](#).)

A: Assessment

No uniform criteria are available for defining or grading lipoatrophy or lipohypertrophy in clinical practice. Clinicians must base their assessment on patient self-report, physical examination (e.g., for characteristic body-shape changes and changes in waist circumference), associated symptoms, and psychological consequences.

In research settings, modalities such as DEXA, CT, and magnetic resonance imaging (MRI) have been used to characterize and quantify lipoatrophy and lipoaccumulation. Anthropometric measurements may be made in the clinic by trained personnel (e.g., nutritionists), but do not measure visceral fat directly. Measurements such as waist circumference do not directly assess visceral fat accumulation but may be a proxy measure. In HIV-uninfected individuals, waist circumference measures have been validated as an assessment of cardiovascular risk (see chapters [Dyslipidemia](#) and [Coronary Heart Disease Risk](#)). Bioelectrical impedance analysis (BIA) does not measure regional body composition and thus is not used to measure abnormal body-fat changes.

Differential diagnosis of lipoatrophy includes weight loss and wasting.

Differential diagnosis of lipohypertrophy includes obesity or excess weight gain, ascites, and Cushing syndrome.

P: Plan

Diagnostic Evaluation

Laboratory

Check for other metabolic abnormalities, such as dyslipidemia and impaired glucose metabolism (check fasting lipids and random or fasting glucose). See chapters [Dyslipidemia](#) and [Insulin Resistance, Hyperglycemia, and Diabetes on Antiretroviral Therapy](#) for further information about workup and treatment.

Imaging

CT or DEXA could be considered if diagnosis of abdominal hypertrophy is uncertain and if these modalities are available (see “Assessment,” above).

Treatment

Treatments for lipohypertrophy and lipoatrophy have not reliably and fully reversed body-shape changes once these changes have occurred. In general, treatment interventions have shown poor results in patients with marked or severe fat maldistribution and responses have been inconsistent or limited in those with milder conditions. *The best approaches to managing both lipoatrophy and lipohypertrophy are prevention and early intervention.*

Clinicians can help to prevent body fat abnormalities by avoiding, whenever possible, ARV agents known to confer a greater risk of this disorder (note that the ARVs currently recommended for initial treatment are rarely associated with lipoatrophy, and no specific ARVs are associated with lipohypertrophy). All patients should be monitored carefully for the development of fat maldistribution. If abnormalities related to ARVs are noticed, the suspect ARV should be discontinued and a more benign ARV started in its place, if possible.

The optimal management strategy for established lipoatrophy or lipoaccumulation is not known, although the following approaches can be considered (see below). Also consider referring the patient to clinical studies of lipodystrophy treatment, and refer for psychological or adherence support and counseling, if indicated. If the patient is distressed enough to consider discontinuing or interrupting ART, review with the patient any gains he or she has made on ART and discuss treatment options (see below). In some cases, the patient may insist on discontinuing ARV medications; in this situation, carefully review the risks of treatment interruption as well as the alternatives to discontinuing treatment.

ARV Substitutions

Avoiding thymidine analogue NRTIs, particularly stavudine, and avoiding the NRTI combination stavudine + didanosine have been shown to reduce the risk of lipoatrophy (note that these NRTIs are no longer recommended for ART).

In patients with lipoatrophy, modest slow improvement in limb fat has been demonstrated after switching from thymidine analogues (stavudine, zidovudine) to nonthymidine NRTIs (such as abacavir or tenofovir) or to NRTI-sparing regimens. In patients with lipohypertrophy, similar NRTI switch strategies have had little or no effect on visceral or trunk fat. Studies in which PIs were eliminated from the ART regimen (e.g., by switching to an integrase inhibitor) also generally have not shown significant effects on body fat measures.

Before switching therapies, carefully assess the potential risk to the patient's long-term HIV management.

Nonpharmacologic Measures

Diet

The effects of diet on lipohypertrophy have not been evaluated thoroughly. In HIV-uninfected persons, improvements in visceral fat have been achieved through diets low in carbohydrates, saturated fats, and alcohol. It is reasonable to advise the patient to decrease intake of simple sugars, saturated fat, and alcohol; refer to a dietitian as indicated. If overall weight reduction is needed, recommend dietary changes and exercise. Avoid rapid weight loss plans, as lean body mass often is lost disproportionately.

Exercise

Regular, vigorous cardiovascular exercise may help control central fat accumulation, whereas resistance exercises (strength training) may improve the ratio of muscle to fat. Two small studies of exercise in persons with HIV and lipoaccumulation (done alone or in combination with diet) have shown a reduction in visceral fat accumulation with minimal or no changes in peripheral lipoatrophy, and with improvement in lipids and insulin resistance. Moderate aerobic exercise should be encouraged for all patients.

Pharmacologic Measures

Insulin-sensitizing agents

In diabetic and non-HIV-related lipodystrophy, treatment with thiazolidinediones may decrease visceral fat, increase peripheral fat, and improve glycemic control. In HIV-infected patients with lipoatrophy, studies of thiazolidinediones, specifically rosiglitazone and pioglitazone, have not demonstrated consistent or substantive improvement in body-fat abnormalities. Some studies have shown small increases in subcutaneous fat in patients who were not taking thymidine analogues, but these improvements were quite modest. Other randomized trials have found no significant increase in limb-fat mass. In patients with lipohypertrophy, thiazolidinediones have not reduced visceral fat accumulation.

Studies of metformin in HIV-infected patients with lipoaccumulation have not generally found improvement in visceral adiposity; and in some studies, metformin appeared to cause worsening of lipoatrophy.

Statins

Pravastatin and rosuvastatin have been studied for treatment of both lipoatrophy and lipohypertrophy but have thus far not been proven to be effective.

Growth hormone-releasing factor

Tesamorelin, a synthetic growth hormone-releasing factor analogue, is approved by the U.S. Food and Drug Administration (FDA) for treatment of excess abdominal fat in HIV-infected persons with lipodystrophy. In randomized controlled studies, it has been shown to reduce mean intraabdominal fat accumulation by about 18% and waist circumference by a mean of 3.4 cm

after 12 months of treatment, with no significant effect on subcutaneous fat. Treatment with tesamorelin resulted in a modest decrease in triglycerides and no significant worsening of glucose parameters. However, substantial mean increases in levels of IGF-1 were seen (the clinical significance of these is not known). Unfortunately, when tesamorelin was discontinued, patients' visceral fat returned to baseline levels within 13 weeks. That, along with its expense and the fact that it requires subcutaneous injection, has limited the use of tesamorelin. No long-term data (beyond 12 months) are available on the safety or possible clinical benefits of tesamorelin. Glucose and IGF-1 should be monitored before and during treatment with tesamorelin.

Recombinant human growth hormone

Treatment with recombinant human growth hormone (rHGH) has been shown to reduce visceral fat in many patients, with minimal impact on peripheral fat wasting. However, rHGH produces a high rate of adverse effects (including insulin resistance) and visceral fat frequently reaccumulates once rHGH is discontinued. rHGH is not approved by the FDA for treatment of lipohypertrophy.

Plastic and reconstructive surgery

For facial lipoatrophy, poly-L-lactic acid (Sculptra, formerly New-Fill) and a calcium hydroxylapatite preparation (Radiesse) are approved by the FDA as treatments. These injectable materials have shown good cosmetic results and often significantly improve patients' satisfaction with their appearance. Treatment effects of these agents typically wane with time and the procedures often must be repeated. Other facial fillers (used off-label), as well as cheek implants and autologous fat transfer, have been used successfully in some cases. For lipoaccumulation, treatments such as liposuction for focal areas of fat deposition (e.g., dorsocervical) and breast reduction may be effective in the short term, though fat often reaccumulates. Various other approaches and techniques have been investigated, but generally have limited applicability and efficacy.

These interventions may be covered by private- and public-payer sources, but still often are deemed to be the financial responsibility of the patient. In some cases, they may be only a temporary solution, because abnormalities may reappear after treatment.

Patient Education

- Instruct patients who are receiving ARV medications to inform their health care provider if they notice changes in the shape or appearance of their bodies.
- Review the importance and benefits of ART and assess adherence to the regimen. For patients with lipohypertrophy, recommend aerobic and resistance exercise to reduce fat and build muscle. Assess local resources for safe exercise options.
- If weight reduction is needed, refer to a dietitian for consultation. Remind the patient that quick weight-loss diets may result in excessive muscle loss.
- If ARV medications are thought to be contributing to lipoatrophy, consider changing ARVs if suitable alternatives are available; consult with experts.

- For patients with severe facial lipoatrophy, consider referral to an experienced dermatologist or plastic surgeon for restorative treatment.

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