

Lipodystrophy: focus on HIV Lipodystrophy

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Abstract

Lipodystrophy is a rare condition which can be inherited or acquired, localised or generalised. It is characterised by abnormal adipose tissue distribution and in some cases underlying metabolic derangement, including diabetes mellitus, hypertriglyceridemia, hepatic steatosis, polycystic ovaries and acanthosis nigricans. Today, most cases of lipodystrophy are associated with human immunodeficiency virus (HIV).

This article gives a review of the possible mechanisms associated with HIV lipodystrophy, namely HIV infection itself, genetic susceptibility to HIV lipodystrophy and effects of treatment with highly active antiretroviral therapy (HAART). Treating HIV lipodystrophy is challenging. The various treatment options currently available for treating lipodystrophy are reviewed.

Key Terms

lipodystrophy, human immunodeficiency virus (HIV), highly active antiretroviral therapy (HAART), protease inhibitors (PI), Nucleoside reverse transcriptase inhibitors (NRTI)

Introduction

Lipodystrophy is a rare disorder. In recent years it is most often seen in association with human immunodeficiency virus (HIV). Recognising this syndrome is of importance because it has a psychological impact due to body shape changes and also because of the underlying metabolic abnormalities, which are linked with increased morbidity and mortality.

Lipodystrophy is characterised by generalised or partial loss of adipose tissue. There are different extents of adipose tissue loss, with some having loss from discrete areas (localised lipodystrophy), others from the limbs (partial lipodystrophy) whilst others having loss from most of the body (generalised lipodystrophy).¹ In localised lipodystrophy, usually there are only cosmetic implications. However, in the partial and generalised forms, an association with severe metabolic derangement exists, including diabetes mellitus, hypertriglyceridemia, hepatic steatosis, polycystic ovaries and acanthosis nigricans.

Lipodystrophy can be inherited (monogenetic), or acquired (autoimmune or idiopathic), in patients who do not have a clear inheritance pattern. Therefore lipodystrophy can be classified into the following 4 main categories: congenital generalised lipodystrophy (CGL), familial partial lipodystrophy (FPL), acquired generalised lipodystrophy (AGL) and acquired

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partial lipodystrophy (APL). Lipodystrophy in patients receiving highly active antiretroviral therapy (HAART) has become the most common form of lipodystrophy.¹⁻²

Presentation and diagnosis

HIV-associated lipodystrophy refers to both lipohypertrophy, where there is abnormal fat accumulation usually in the dorsocervical fat pad, neck, breasts and around abdominal viscera³, and lipoatrophy with loss of subcutaneous fat around the face, arms, legs and buttocks. Facial fat loss can be very severe and psychologically disturbing to patients, as it carries a social stigma. This may limit compliance to HAART. In fact lipodystrophy has also been associated with lower reported quality of life.⁴ Patients report reduced satisfaction with their body image, self-esteem, problems with social relationships, less confidence about their health and embarrassment due to body changes. Many patients also develop hypertriglyceridemia and some also develop impaired glucose tolerance and insulin resistance.¹

The diagnosis is mainly clinical, but additional tests for glucose intolerance, serum lipids, liver function and hyperuricaemia are indicated.¹ Some tools that are used to help make a diagnosis are: anthropometry, bioelectrical impedance analysis (BIA), imaging techniques such as dual-energy X-ray absorptiometry (DEXA), magnetic resonance imaging (MRI) and computed tomography (CT). Both CT and MRI demonstrate accumulation of intra abdominal visceral fat and minimal subcutaneous fat.^{3,5-6}

Pathogenesis

Lipodystrophy has a multi-factorial aetiology, including HIV infection itself, genetic susceptibility and effects of HAART. HIV infection itself may contribute to fat redistribution by infecting macrophages in adipose tissue, which release pro-inflammatory cytokines and enhance local inflammation.⁷ This is supported by increased tumour necrosis factor-alpha (TNF- α) expression observed in HAART-naive HIV-infected patients, a pro-inflammatory cytokine that initiates adipocyte apoptosis.^{2,7} In a study by Castilhos et al⁸ genetic variability in the adiponectin receptor, which is a circulating peptide secreted by mature adipocytes that acts as a regulator of glucose and lipid metabolism, appears to be associated with different

anthropometric and metabolic phenotypes in HIV infected patients on HAART.

HIV type 1 (HIV-1) protease inhibitors (PI) are a class of drugs used in HIV⁹. They inhibit viral replication by selectively binding to viral proteases, therefore blocking proteolytic cleavage of protein precursors necessary for the production of infectious viral particles. Nucleoside reverse transcriptase inhibitors (NRTIs), another class of drugs used in patients infected with HIV⁹, block the reverse transcriptase enzyme, which controls the replication of HIV genetic material. Both these drugs are particularly implicated in HAART-induced lipodystrophy.

One mechanism thought to be implicated in the pathogenesis of PI-induced lipodystrophy is the down-regulation of peroxisome proliferator-activated receptor gamma (PPAR- γ), (a nuclear-receptor which regulates adipocyte differentiation and maintenance) by the up-regulation of the Wnt-related integration site (wnt)/ β -catenin signalling pathway.¹⁰ One of the functions of this pathway is to inhibit adipogenic gene expression.¹¹ Another effect of PI is the down-regulation of essential adipogenesis transcription factors like CCAAT-enhancer-binding proteins (C/EBP)- α , which have major adipogenic function.⁹ This down-regulation creates reactive oxygen species, which may induce insulin resistance by inhibiting glucose transporter 4 (GLUT-4), together with impaired leptin and adiponectin production. PIs share similar sequence homology with 2 proteins involved in lipid metabolism, namely cytoplasmic retinoic acid-binding protein type 1 (CRABP-1) and low-density lipoprotein receptor-related protein (LDLR-RP). Inhibition of the former leads to decreased fat storage and adipocyte apoptosis with subsequent release of lipids into the blood and the latter induces hyperlipidaemia by inhibiting hepatic and endothelial removal of chylomicrons and triglycerides from the circulation.¹²⁻¹⁴

NRTIs, especially zidovudine and stavudine, are thought to inhibit mitochondrial polymerase- γ and cause mitochondrial dysfunction, ultimately leading to apoptosis and loss of fat cells. This in turn causes insulin resistance and secondary dyslipidaemia.^{6,15}

Since PI and NRTI are usually prescribed simultaneously, it is difficult to predict which drug is responsible for which phenotypic appearance, although it is likely that PI induce peripheral

lipoatrophy and metabolic abnormalities whereas NRTIs may be responsible for the lipohypertrophy with accumulation of fat in the neck region.¹ Newer HIV drugs are less likely to cause the condition: old NRTIs such as zalcitabine, didanosin, stavudine and zidovudine are more prone to lipodystrophy than the newer NRTIs lamivudine, abacavir and tenofovir.^{6,16} The older agents have been phased out in most developed countries but are still in use in low-resource settings.

Epidemiology

The global prevalence of lipodystrophy among HIV patients ranges considerably and studies quote very differing rates (1-84%).⁶ Gender influences mode of presentation: women tend to be more likely to report fat accumulation in the abdomen and breasts, whereas men are more likely to notice the loss of fat from the face and other extremities.¹⁷

Risk factors for HIV-induced lipodystrophy include the duration of antiretroviral therapy (particularly receiving treatment for 2 years or more), female sex, obesity, higher triglyceride level, white race, older age and low CD4 count.¹⁸

Management

Treatment can be challenging. First and foremost, it should be targeted at managing the underlying metabolic derangements of glucose and lipids aggressively.¹ Diet and exercise have been proven to improve insulin sensitivity but no controlled clinical trials have been conducted to guide treatment for the metabolic complications in patients with lipodystrophy.

Management of severe lipodystrophy needs to involve modifying the treatment regimen, especially if an older drug is being administered. If this is not possible, using a lower dose of the drug will need to be considered. In a meta-analysis of trials comparing doses of stavudine which is an older NRTI (40mg vs 30mg) in high income countries, there was strong evidence that the lower 30 mg dose of stavudine was associated with lower rates of side-effects including lipodystrophy, and similar efficacy in suppressing HIV viral load, compared to the 40 mg dose.¹⁹ These findings informed the WHO recommendations for lower dose stavudine in 2007 and the subsequent discontinuation of stavudine due to severe side-effects in 2009.²⁰ In a study HIV-infected adults were switched from

stavudine/didanosine to the newer agents tenofovir/lamivudine. There was an increase in limb fat mass and total fat mass, as measured by DEXA 48 weeks after the regimen change.²¹ Thus the newer NRTI agents are recommended.

No controlled clinical trials have been conducted to guide drug therapy for metabolic complications. For severe hypertriglyceridemia, fibrates and fish oil should be used and may be combined with a statin.¹ Metformin remains the first-line treatment for diabetes and insulin resistance, when tolerated. Studies of thiazolidinedione treatment for HIV lipodystrophy have shown conflicting results. A meta-analysis has shown that pioglitazone may be safer than rosiglitazone but any benefits on improved fat deposition in lipodystrophic regions were small.²² In many patients with diabetes, insulin therapy is needed and since patients usually require high doses of insulin, highly concentrated insulin such as U-500 insulin should be used, due to the difficulty in injecting a large volume of insulin whilst having no subcutaneous fat in the abdomen or thighs. GLP-1 analogues may also be considered in selected patients.²³

Tesamorelin, a synthetic form of growth hormone-releasing hormone, which was approved by the Food and Drug Administration (FDA) in 2010, seems to have some role in decreasing visceral adipose tissue.²⁴⁻²⁵

Leptin therapy (Metreleptin) was approved by the FDA in 2014 for treating generalised lipodystrophy with or without metabolic complications but not associated with HIV.²⁶⁻²⁷ In patients with lipodystrophy a state of leptin deficiency occurs due to lack of adipocytes. Leptin regulates appetite by allowing negative feedback via the hypothalamus. Patients with leptin deficiency lose this regulation causing hyperphagia. However due to the lack of adipocytes, which usually store the excess food ingested, this fat is deposited in abnormal places, leading to the typical appearance in patients with lipodystrophy. Leptin therapy was found to improve the overall clinical picture of the metabolic syndrome; namely the hyperglycaemia and insulin resistance, the hyperlipidaemia and hepatosteatosis.

Plastic surgery procedures, namely liposuction and lipectomy did not yield very positive cosmetic results, as lipohypertrophy usually recurs. For lipoatrophy, free flaps, lipotransfer (transplantation

of fat harvested during liposuction of the dorsocervical fat pad), and commercial fillers such as Poly-L-lactic acid (Sculptra®) have been approved by the FDA as treatment for facial lipotrophy in HIV-positive patients.^{3,28}

In addition to the physical consequences of lipodystrophy, an important component to clinical management is the evaluation of the impact of lipodystrophy on emotional well-being and quality of life.⁴

Prognosis

There might be some regression of HIV-associated lipodystrophy on stopping the implicated PI or NRTI therapy. To date, there has been no studies determining the morbidity and mortality from the body morphologic changes of HIV associated lipodystrophy per se. However the excess morbidity and mortality is attributed to atherosclerotic cardiovascular disease secondary to insulin resistance, hyperglycaemia and hyperlipidaemia.

Conclusion

HAART is the gold standard treatment for HIV/AIDS care and treatment, however adverse treatment related outcomes, including lipodystrophy are relatively more common in low and middle-income countries, due to the use of older drugs. This has considerable implications in view of the increased risk of metabolic disease, quality of life and drug adherence. With early detection of HIV and longer lifespans of infected individuals, the length of HAART exposure and the burden of related metabolic complications are also expected to rise. More evidence based interventional studies are needed in this respect to reduce the burden of HIV and lipodystrophy.

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