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REVIEW

New and emerging agents in the management of lipodystrophy in HIV-infected patients

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Abstract: Lipodystrophy remains a major long-term complication in human immunodeficiency virus-infected patients under antiretroviral (ARV) therapy. Patients may present with lipoatrophy or lipohypertrophy or both. The choice of treatments to improve fat redistribution depends on the form of lipodystrophy and its duration. Measures known to improve lipoatrophy are switches in ARV therapy (stavudine or zidovudine to abacavir or tenofovir) and filling interventions. Pioglitazone may be added to these measures, although any benefits appear small. Uridine and leptin were found to be disappointing so far. Regarding lipohypertrophy, diet and exercise, recombinant human growth hormone, and metformin may reduce visceral fat, but may worsen subcutaneous lipoatrophy. Surgical therapy may be required. Attractive pharmacologic treatments include growth hormone-releasing factor and leptin. Adiponectin and adiponectin receptors are promising therapeutic targets to explore.

Keywords: lipoatrophy, lipohypertrophy, lipodystrophy, treatment, HIV, AIDS

Introduction

Lipodystrophy remains a major concern for human immunodeficiency virus (HIV)-infected patients, although its incidence tends to decrease with the use of new antiretroviral (ARV) combinations. The negative impact of lipodystrophy on quality of life of patients, sexual function, and adherence to ARV treatment has been widely documented.[1–9]

Management of lipodystrophy includes ARV switch strategies, lifestyle modifications, pharmacologic interventions, and surgical or cosmetic corrective treatments.

After a few reminders on the definition, incidence, pathogenesis, and diagnosis of lipodystrophy, this review will focus on new and emerging therapeutic strategies.

Definition

Lipodystrophy includes fat loss (lipoatrophy) and fat accumulation (lipohypertrophy), which may exist separately or be combined (mixed syndrome) in a single patient. Despite some anthropometric measurements and/or imaging could detect fat mass changes earlier than physical examination, the current definition and classification are based on the patients' self-assessment confirmed by the physician during a detailed physical examination.[10]

Lipoatrophy occurs on the face, the buttocks, the arms, and the legs, whereas lipohypertrophy may be revealed by abdominal obesity, mammary hypertrophy, accumulation of fat on the neck or the suprapubic region, and localized or generalized lipoma.

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A diagnosis model including demographic, clinical, biological, and radiological parameters has been proposed by Carr et al.[11] This model has a sensitivity of 79% and a specificity of 80%;[12] however, its complexity makes it impractical for routine use.

Incidence

The overall prevalence of lipodystrophy remains high in HIV-infected patients upon ARV treatment. The incidence of lipoatrophy is still high in countries where thymidine analogs (stavudine and to a lesser extent zidovudine) are frequently prescribed.[13–16] Because standardized criteria for the definition of lipodystrophy are lacking, the frequency of lipodystrophy observed in major clinical studies varies from 2% to 84%, with a mean prevalence of 40%–60%.[17–22] The significant variations found among different studies may also be explained by the composition of the populations (different gender, age, race, or ethnicity), the ARV used, and the duration of observation.

The prevalence of lipoatrophy is also widely variable, from 13% to 67%.[23–28] It has been estimated that 16%–29% of patients present lipoatrophy after 3 years of ARV treatment.[29,30] However, these studies have been conducted in the late 90s and early 2000s, and the regimens have evolved. Besides, some recent studies that have evaluated new drug combinations suggest lower incidence.

Differences in frequency of lipoaccumulation reported throughout various studies are even more important, from 6% (in men) to 93% (in women).[23–28] Once again wide variations may be explained by the definition criteria used, populations studied, and the duration of observation.

The prevalence of mixed syndrome has been found to range from 20% to 29%.[23,24,26–28] The prevalence reported at 3 years has varied from 8% to 12.5%.[30,31]

Pathogenesis and risk factors

The pathogenesis of lipoatrophy and lipohypertrophy is multifactorial, and common risk factors have been identified as the patient, HIV infection, and ARV drugs.[32–35]

Potential host risk factors include age, sex, race, or ethnicity.[22,29,36,37] Genetic components have also been reported. Lipodystrophy is more common in older patients. Fat accumulation is more common in women and fat loss in men. In one study, Caucasians exhibit more lipoatrophy, whereas non-Caucasians develop more lipohypertrophy.[23] Several polymorphisms were identified as being involved in the development or severity of lipodystrophy, whereas others seem to have a protective role.[38–45]

HIV infection can increase expression of antiadipogenic and proinflammatory genes and inhibit the expression of proadipogenic genes and genes coding for adiponectin and leptin.[35] In multivariate analysis, advanced stage of HIV infection (established AIDS), longer duration of HIV infection, low nadir CD4 cell count, decrease in CD4 cell count, and high viral load have been identified as risk factors for lipodsytrophy.[17,23,24,46–49] The role of hepatitis C virus coinfection in the development of lipodsytrophy is controversial.[50,51]

Different effects on adipose tissue have been described according to the family of ARV drugs. Moreover, among different members of an ARV family, the magnitude of these effects is very variable. Thymidine analogs and, especially, stavudine have been shown to be involved in the development of lipoatrophy.[27,52–56] These molecules act essentially through a mitochondrial toxicity by inhibiting DNA polymerase γ.[57–62] In addition, thymidine analogs altered adipocyte functions, reduced lipid content, reduced adiponectin and leptin release, and in parallel, increased ROS production and monocyte chemoattractant protein-1 and interleukin-6 release.[63] The association of oxidative stress and lipodystrophy has been confirmed in a recent clinical study in HIV-infected men.[64] Protease inhibitors (PIs) are more closely associated with lipoaccumulation but may also participate in lipoatrophy.[65,66] PIs inhibit adipocyte differentiation.[67,68] They may also exert a deleterious effect on mitochondrial function.[69] Moreover, some PIs inhibit the glucose transporter isoform Glut4 at physiological concentrations.[70,71] Finally, some PIs alter adipokine secretion and lipid content through ROS production in human subcutaneous adipocytes.[63] An additive, even synergistic, toxicity of nucleoside reverse transcriptase inhibitors (NRTIs) and PIs on peripheral fat tissue has been observed *in vivo*.[33] The role of non nucleoside reverse transcriptase inhibitors (NNRTIs) on adipose tissue is unclear. In a recent comparative prospective study, the incidence of lipoatrophy was higher among patients receiving efavirenz (EFV) than in those receiving PIs.[72] Regarding the most recent drugs (fusion inhibitors, integrase inhibitors, and CCR5 chemokine receptor agonists), they do not seem to exert a deleterious effect on adipose tissue.

Diagnosis

In most studies, the diagnosis of lipodystrophy is based on clinical grounds that include signs and symptoms (Table 1).[34,35,73,74]

The diagnosis of lipoatrophy is currently accepted if weight loss (due to loss of body fat) located on the face (Bichat's ball and temporal areas) and/or buttocks and/or

Table 1 Diagnostic methods of lipodystrophy

Clinical assessment by the patient and the physician
Fat loss (lipoatrophy)
Face: sunken, hollow temples, sunken eyes, prominent zygomatic arch
Extremities: prominent veins, skinny or muscular appearance
Fat accumulation (lipohypertrophy)
Increased abdominal girth
Supraclavicular fat pad
Dorsocervical fat pad
Anterior neck fat accumulation
Chest enlargement (gynecomastia and lipomastia)
Hypertrophy of the parotid areas
Suprapubic fat accumulation
Single or multiple lipomata
Anthropometric measurements
Bicipital, tricipital, subscapular, and suprailiac folds
Waist-to-hip ratio
Imaging methods
Dual-energy X-ray absorptiometry
Echography
Computed tomography
Magnetic resonance

lower limbs and/or upper limbs is reported by the patient (or his/her entourage) and confirmed by the physician.[17,75,76] However, the finding of fat loss by the patient and the physician is already witnessing an advanced lipoatrophy. Fat loss in the limbs often results in an apparent hypertrophy of the venous system sometimes described as "venomegaly".

The diagnosis of lipohypertrophy is also based on the patients' complaints confirmed by clinical examination by the physician. Clinical features may include abdominal girth, dorsocervical fat pad (buffalo neck), supraclavicular fat pad, anterior neck fat accumulation, chest enlargement (gynecomastia or lipomastia), hypertrophy of the parotid areas, suprapubic fat accumulation, and single or multiple lipomata.[75,76]

In some studies, anthropometric measurements are used as diagnostic criteria.

Lipoatrophy may be evaluated by measuring bicipital, tricipital, subscapular, and suprailiac folds.[77]

Waist and hip circumferences and waist-to-hip ratios have been used to evaluate fat accumulation. Waist-to-hip ratios greater than 0.95 in men and 0.85 or 0.90 in women are indicators of lipohypertrophy.[34,78]

The European AIDS Clinical Society recommends monitoring for changes in body composition of HIV patients by using body mass index, waist circumference, waist-to-hip ratio, and clinical lipodystrophy in all patients at HIV diagnosis, before starting highly active antiretroviral therapy (HAART), and annually thereafter.[79]

The most reliable means to assess lipodystrophy are undoubtedly imaging studies. However, they are not always readily available in routine and are sometimes expensive. Most of them could be reserved for research studies.

Dual-energy X-ray absorptiometry (DXA), ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI) have all been used for the objective measurement of the fat composition of particular body regions or given compartments in patients with lipodystrophy syndrome.

DXA can detect fat modifications earlier than clinical assessment,[80] although a significant negative correlation exists between DXA-measured limb fat and lipoatrophy scores generated by either the patients or the physicians.[81]

Fat mass ratio (equals to ratio of percentage of trunk fat mass to the percentage of lower limbs fat mass) measured by DXA may be useful for detecting early (subclinical) lipodystrophy and its evolution.[80,82,83]

In recent studies, lipoatrophy was defined as a reduction of 20% or more in limb fat measured by DXA. However, there is a weak correlation between lipoatrophy, using this definition, and clinical lipoatrophy as perceived by the patient. Indeed, loss of body fat of at least 35% is required for it to become clinically evident.[84]

Some authors have reported a good correlation between subcutaneous fat measurement using ultrasonography and other methods of diagnosing lipoatrophy.[85,86]

CT and MRI are particularly useful for measuring the intra-abdominal fat mass.[85–87]

Treatment

Conventional and old strategies

ARV switch strategies

Lipoatrophy

As PIs have been first suspected to be the only agents responsible for lipoatrophy, the first therapeutic strategy for HIV-associated lipodystrophy proposed was the substitution of the PI with an NNRTI (Table 2). Unfortunately, this strategy did not lead to significant gain in limb fat.[88–90]

The association of thymidine analog NRTIs with lipoatrophy was shown in subsequent *in vitro* and *in vivo* studies. Therefore, it was logical to explore the efficacy of switching from these drugs to alternative NRTIs or NRTIs-sparing regimens in order to try to reverse lipoatrophy. A modest but significant gain of limb fat has been reported in several studies.[72,91–98] However, this gain was not clinically relevant in most studies, probably, because the duration of follow-up was too short. Anyway, it was demonstrated that lipoatrophy was (at least partially) reversible when switching from thymidine analogs to other NRTIs. The speed and the

Table 2 Therapeutic strategies for HIV-associated lipodystrophy

Type of treatment	Effects of treatment on lipodystrophy	
	Lipohypertrophy	**Lipoatrophy**
Switch strategy	Not proved to be effective (further studies needed with new ARV families)	May be beneficial, particularly if early intervention
Diet and exercise	May reduce visceral adiposity	May worsen subcutaneous fat loss
Surgical and corrective cosmetic measures	To be strongly considered if excess of abdominal subcutaneous fat. May be the best therapeutic option for breast enlargement, buffalo hump, lipomas, and various localized fat deposits	May be the only effective option and give immediate results (facial lipoatrophy)
Pharmacologic treatments	–	–
Thiazolidinediones	–	–
Rosiglitazone	No effect, despite improvement of peripheral insulin sensitivity	No effect, despite improvement of peripheral insulin sensitivity
Pioglitezone	No effect	Small but significant improvement of limb fat atrophy as measured by DXA, no clinical benefits perceived by the patients (after 48 wk of treatment)
Statins	–	–
Pravastatin	No effect	May decrease subcutaneous fat
Metformin (Kohli R HIV Med 2007)	May reduce visceral adipose tissue and total adipose fat	May induce additional loss in limb fat
Recombinant human growth hormone (somatotropin)	Decreases visceral adipose tissue	May worsen subcutaneous lipoatrophy
Growth hormone-releasing factor	Decreases visceral adipose tissue	No effect on lipoatrophy
Testosterone	No effect	No effect
Uridine	May increase visceral fat	Small and not sustained improvement in limb fat
Leptin	Decrease visceral fat	No effect
Acetyl-L-carnitine	No effect	May increase leg fat
Adiponectin and adiponectin receptors	Investigational	
TNF-α antagonists	Not studied and not recommended in HIV-infected patients	
IGF-1/BP-3	No effect	No effect

Abbreviations: HIV, human immunodeficiency virus; ARV, antiretroviral; DXA, dual-energy X-ray absorptiometry; TNF-α, tumor necrosis factor-α; IGF-1/BP-3, insulin-like growth Factor-1/binding protein-3.

magnitude of the recovery depend on how early the switch is made.[82]

Lipohypertrophy

There is no published evidence that NRTI switching leads to significant changes in trunk or visceral fat, and consequently, to an improvement of lipohypertrophy.

There are conflicting results concerning the effects on fat accumulation of switching from PI to EFV or nevirapine or abacavir. An improvement of lipohypertrophy, if any, appears to be weak. Most studies exploring this strategy are summarized by Baril et al.[34] The results of PI switch studies (in which a boosted PI is replaced by atzanavir/ritonavir) are divergent.[99,100]

Lifestyle modifications

Lipoatrophy

Exercise and diet may induce modifications of the appearance of limbs by a gain of muscular mass. However, there are no data showing any substantial gain in peripheral fat by modifying lifestyle. Consequently, changes in lifestyle are not part of the measures recommended to improve lipoatrophy.

Lipohypertrophy

Several studies have documented effects of diet and exercise on central fat accumulation.[101–103] Regular exercises can reduce intra-abdominal lipoaccumulation and improve muscle strength, lean mass, and blood lipids. However, it can aggravate lipoatrophy. A diet, rich in fiber, adequate in energy and protein can reduce fat depot, but a beneficial effect on insulin resistance is not always reported.[104,105]

Pharmacologic interventions

Lipoatrophy

Adipose cell function in patients with lipoatrophy is partially restored by the peroxisome proliferator-activated receptors-γ agonists, thiazolidinediones.[106] Thus, it is hypothesized that treatment with thiazolidinediones could improve, at least partially, the subcutaneous lipoatrophy. A recent meta-analysis

of clinical trials of thiazolidinedione therapy for HIV lipoatrophy concluded that patients receiving pioglitazone had significantly higher limb fat mass gain compared with those receiving placebo, whereas patients on rosiglitazone did not. Interestingly, the effectiveness of glitazones did not vary according to whether the patients were receiving thymidine analogs.[107,108] Moreover, glitazones can decrease bone formation and accelerate bone loss. This could be particularly deleterious in HIV-infected patients in whom a preexisting osteopenia is frequently observed. The effects of pioglitazone are detailed in section "New and emerging agents".

There are few studies exploring the effects of statins on body composition in HIV-infected patients. Mallon et al[109] showed that apart from lowering lipids, pravastatin can also increase subcutaneous fat and limb fat. Improvement of lipohypertrophy by pravastatin treatment was not confirmed by Macallan et al[110] and Calmy et al.[111]

Whether uridine is a promising or disappointing treatment of lipoatrophy will be discussed later.

Lipohypertrophy[112]

Insulin sensitizers such as metformin have been used to treat HIV lipodystrophy in which fat accumulation and insulin resistance are prominent factors. Some studies indicated that treatment with metformin can reduce visceral adipose tissue, total adipose fat, waist circumference, and/or waist-to-hip ratio in HIV-infected nondiabetic patients with lipohypertrophy.[113,114] However, other studies did not show any change in waist-to-hip ratio, and rather, worryingly additional loss in limb fat.[115–117]

Statins have been used for lowering lipid levels in HIV-infected patients. However, there are no data supporting their use in the treatment of visceral fat and trunk fat accumulation.[109]

Several clinical trials demonstrated a significant loss of visceral fat content in HIV-infected patients treated with recombinant human growth hormone (rhGH; somatotropin).[118–122] However, an increase in insulin resistance is often noted, which limits, of course, the use of this drug in this indication.

Although in epidemiological studies, serum total and free testosterone concentrations have been inversely correlated with intra-abdominal fat mass, and testosterone administration to middle-aged men is associated with decreased visceral fat, there are no convincing data on the beneficial effects of testosterone in HIV-infected patients.[123] In a small study, transdermal administration of testosterone failed to demonstrate a decrease in visceral fat in HIV-infected men with abdominal obesity.[124]

Surgical or cosmetic corrective treatments

Lipoatrophy

Various injectable fillers have been used to treat facial lipoatrophy.[125] Permanent fillers are synthetic materials that are designed to provide a sustained filling of the space vacated by the loss of facial fat. They include purified silicone oil, polymethylmethacrylate, polyalkylamide, and polytetraflurorethylene. There are limited data in HIV-associated lipoatrophy. None of these products are approved by the Food and Drug Administration (FDA).

Temporary fillers need to be reinjected at regular intervals. To date, two products are approved by the FDA in the treatment of HIV-associated facial lipoatrophy: poly-L-lactic acid (PLLA; Sculptra or New-Fill™; sanofi-aventis, Bridgewater, NJ) and calcium hydroxylapatite (Radiesse™; Bioform Medical Inc., San Mateo, CA). Several (small) studies have been performed to assess their effectiveness.[126–132] HIV-infected patients treated with PLLA or calcium hydroxylapatite for facial lipoatrophy have reported more satisfaction with their physical appearance and improvement in their quality of life.[125]

Use of autologous fat implantation can be a suitable method to correct facial lipoatrophy in patients who have sites with sufficient subcutaneous fat to donate.[133–138] Unfortunately, available donor sites are lacking in most HIV-infected patients suffering from lipoatrophy.

Other temporary fillers including bovine or human collagen and hyaluronic acid have been used with limited experience in HIV-infected patients with facial lipoatrophy, and are not approved by the FDA.[139]

Finally, silicone gluteal prosthesis can be proposed for patients with fat loss in the buttocks, who complain of painful sitting down or who present trophic cutaneous disorders.[140]

Lipohypertrophy

Liposuction has been used successfully to treat dorsocervical fat accumulation (buffalo hump), gynecomastia, or increased abdominal contour.[141–144]

Surgical breast reduction (mammoplasty) is an alternative for women with breast enlargement. Other surgical resections could be indicated for lipomas and various localized fat deposits.[145]

New and emerging agents

Treatment of lipoatrophy

Pioglitazone

The effects of pioglitazone on lipoatrophy have been briefly described in "Conventional and old strategies".

However, among the glitazones, the newest and most promising data concern pioglitazone than rosiglitazone.[146] Therefore, these results are detailed here. Thus, in a recent study, pioglitazone 30-mg daily (n = 64) was compared with placebo (n = 66) in patients with lipodsytrophy, changes in limb fat between weeks 0 and 48 were measured using DXA. Subcutaneous and visceral fat was measured using single-slice CT. Pioglitazone was associated with an increase in limb fat of 0.38 kg vs 0.05 kg of placebo ($P = 0.05$) at 48 weeks. Among patients not receiving stavudine (n = 48 vs 46), the increase was 0.45 kg in the pioglitazone group vs 0.04 kg in the placebo group ($P = 0.013$), whereas among those receiving stavudine (n = 16 vs 20), the increase was 0.17 kg in the pioglitazone group vs 0.07 kg in the placebo group ($P = 0.40$). Piogitazone was also associated with an increase in thigh circumference (1.4 cm vs 0.2 cm; $P = 0.017$). However, all these changes in body composition were not sufficient to be detected clinically by patients. The differences observed between groups in changes in visceral adipose tissue (5.3 cm^2 vs 7.7 cm^2) or abdominal subcutaneous tissue (16.3 cm^2 vs 7.8 cm^2) were not statistically significant. The lipid profile was not significantly different at week 48 except for levels of high-density lipoprotein (HDL) cholesterol, which was improved in the pioglitazone group (+0.08 mmol/L vs −0.08; $P = 0.005$). However, despite significant changes in limb fat, there were no statistical significant differences in clinical manifestations. Pioglitazone, unlike rosiglitazone, is metabolized by cytochrome P450 3A4 enzymes and thus has potential for pharmacokinetic interactions with PIs. A recent meta-analysis performed by SH Sheth and RJ Larson[108] concluded that rosiglitazone should not be used in HIV-associated lipodystrophy syndrome, pioglitazone may be safer, and any benefits appear small.

Uridine

In vitro studies suggest that the compound uridine, a pyrimidine precursor, can reverse mitochondrial toxicity induced by ARV pyrimidine analogs such as zalcitabine and stavudine with cell restoration, notably in adipose tissue. NucleomaxX ™ (Pharma Trade Healthcare AB, Spänga, Sweden) is a sugar cane-derived dietary supplement that increases uridine levels. The preliminary results of small studies in HIV patients receiving stavudine or zidovudine-containing ARV therapy show that a dietary supplement with NucleomaxX (36 g, twice a day) is well tolerated and improves lipoatrophy scores generated by patients and physician or increases limb fat.[147,148] Unfortunately, it also increases visceral fat. This can be particularly annoying in patients who have already a mixed lipodystrophy.[147] Furthermore, in contrast to *in vitro* data, NucleomaxX supplementation did not lead to changes in fat or blood mitochondrial DNA levels.[148] These promising data on lipoatrophy improvement are not fully confirmed in a larger prospective, randomized, placebo-controlled multicenter trial (ACTG study A5229).[149] In this study, the results demonstrate that in HIV lipoatrophy, despite a small increase in limb fat after 24 weeks with as-treated analysis, the effect was not sustained through 48 weeks of uridine.[111,149]

Leptin

Leptin is a protein hormone that plays a key role in regulating energy intake and energy expenditure, including appetite and metabolism. It is one of the most important adipose-derived hormones. It has peripheral effects on skeletal muscle, liver, pancreas, adipose tissue, and other cell types where it acts to decrease anabolic pathways (such as glucose, lipid, and protein synthesis) and increase catabolic pathways (glucose and lipid utilization). Leptin therapy has been used successfully in patients with congenital and acquired non-HIV–related lipodystrophy.[150,151] In HIV-infected patients on HAART, leptin levels have been found to positively correlate with body mass. The rationale for using leptin to treat HIV-associated lipoatrophy is based on the results of cross-sectional studies showing that levels of both leptin and adiponectin are decreased in HIV-lipoatrophic patients and are inversely correlated with dyslipidemia and insulin resistance.[152,153] In fact, in HIV lipodystrophy, leptin administration is well tolerated, improves lipid profiles and insulin resistance, and decreases visceral fat, but has no significant effect on subcutaneous or peripheral fat deposition.[154–156]

Acetyl-L-carnitine

L-carnitine is a nonessential micronutrient that regulates fatty acid transport into the mitochondrial matrix for metabolism via β-oxidation. HIV-infected individuals on ARV therapy may become deficient in this cofactor, limiting mitochondrial fat metabolism. One small recent study showed that HIV-infected patients with lipodystrophy had an increase in the percentage of leg fat after a treatment of 8 months with L-carnitine (2 g/d).[157]

Treatment for lipohypertrophy

Human growth hormone-releasing factor

Human growth hormone-releasing factor (GHRH) analogs induce a more physiological release of GH, with normal feedback inhibition, and are, therefore, potentially less toxic than rhGH, previously used in the treatment of fat accumulation.

Compared with placebo, injectable GHRH analogs (Geref or GHRH 1–29 and Tesamorelin or TH9507) increase lean body mass, decrease visceral and trunk fat, and improve the ratio of visceral fat to lower extremity fat.[158–160] They have minimal effect on subcutaneous adipose tissue and did not alter glucose metabolism, in contrast to rhGH (see above).[158–160] Tesamorelin also improves lipid profiles; triglyceride levels and the ratio of total to HDL cholesterol decrease.[160] The benefit of tesamorelin is similar in men and women and is not affected by ARV therapy. Main adverse events leading to discontinuation are related to injection-site reactions. Serious adverse events are not significantly higher in the tesamorelin arm (5%) than in the placebo arm (2%).[159] Use of GHRH analogs require long-term treatment for continued benefit, as patients who stop treatment regain their visceral adipose tissue.[160] Finally, the cost of this treatment is very high, so its access could be restricted to few patients.

Leptin

It has been shown that leptin therapy can decrease visceral fat without significant effect on subcutaneous or peripheral fat deposition[156] (see "Treatment of lipoatrophy").

Adiponectin

Adiponectin is a cytokine exclusively secreted from adipose tissue. It modulates a number of metabolic processes, including glucose regulation and fatty acid catabolism. Adiponectin acts via two receptors; AdipoR1 located in skeletal muscle and AdipoR2 located in the liver.[33] The level of adiponectin is reduced in visceral obesity.[161] HIV-associated lipodystrophy is associated with low plasma adiponectin levels and low expression of adiponectin in adipose tissue.[162–164] Thus, adiponectin and its receptors are attractive future targets for drug development in the treatment of HIV-related lipohypertrophy.[165]

Tumor necrosis factor-α antagonists

Tumor necrosis factor-α (TNF-α) is a proinflammatory cytokine overexpressed in fat tissue of obese patients, especially in subcutaneous fat and even further in omental fat.[166] TNF-α may be the link between visceral obesity and development of insulin resistance, dyslipidemia, type 2 diabetes, and cardiovascular diseases.[33] TNF-α also induces apoptosis, which might underline the lipoatrophy caused by NRTIs.[167]

It has been suggested that TNF-α-238 promoter region gene polymorphism increases the risk of developing ARV-related lipodystrophy.[168] Nevertheless, the use of TNF-α antagonists has been disappointing in obese non-HIV patients with type 2 diabetes mellitus.[169] Moreover, there is no trial assessing the benefit of TNF-α antagonists in the treatment of HIV-associated lipodystrophy, given the risks of causing opportunistic infections.

Insulin-like growth factor-1/binding protein-3

To date, we have found only one small, open-label study on the use of insulin-like growth factor-1/binding protein-3 (IGF-1/BP-3) therapy in HIV-infected patients with visceral fat accumulation and insulin resistance. Upon treatment with IGF-1/BP-3, insulin resistance and trunk fat decrease, whereas no decrease in visceral adipose tissue is observed.[170] These results are not encouraging for the design of future studies with this compound in the field of HIV-associated lipodystrophy.

Conclusion

The best strategy to prevent HIV-associated lipodystrophy is to avoid, if possible, ARV therapies, which are known to be associated with fat modifications. Some NRTIs, especially thymidine analogs, are associated with lipoatrophy and must be avoided to prevent peripheral fat loss. Concerning lipohypertrophy, there is no proven strategy to prevent it. Not only PIs but also EFV have been implicated in the development of lipohypertrophy. Some new ARVs (integrase inhibitors and CCR5 coreceptor antagonists) could induce fewer changes in fat distribution and deserve further attention.

If lipodystrophy is detected at an early stage, a switch of ARV drugs makes sense to avoid worsening. Early use of pioglitazone must be considered in patients with lipoatrophy. In patients with fat accumulation, diet, exercise, and metformin may be beneficial; however, in patients with mixed lipodystrophy, they may worsen lipoatrophy.

If lipodystrophy is supported at a late stage, a switch of ARV therapy should still be warranted particularly in cases of lipoatrophy. Surgical or cosmetic corrective treatments are often required. Additional pharmacologic interventions such as the use of pravastatin and pioglitazone should be considered for the treatment of lipoatrophy. For patients who have only lipohypertrophy, exercise and diet may be proposed, as well as the administration of metformin or rhGH. Finally, for patients who have mixed form of lipodystrophy, promising pharmacologic treatments, which may improve lipohypertrophy without worsening lipoatrophy, include GHRH and leptin. If lipoatrophy is predominant, L-carnitine could be beneficial without increasing visceral fat accumulation. Adiponectin and its receptors are also attractive targets for the treatment of HIV-related lipodystrophy.

Disclosure

The author reports no conflict of interest in this work.

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