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Pathogenesis and Treatment of HIV Lipohypertrophy

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Abstract

Purpose of Review—This review addresses our current understanding of the pathogenesis of HIV associated lipohypertrophy, and describes an evidence-based approach to treatment.

Recent Findings—Although the pathogenesis of HIV associated lipohypertrophy remains elusive, recent clinical and laboratory investigations in fatty acid metabolism and growth hormone dynamics have furthered our understanding of the condition. These findings have also paved the way for new therapeutic interventions, of which tesamorelin, an analogue of growth hormone-releasing hormone, has gained recognition as a promising treatment strategy against visceral fat accumulation. Recent randomized placebo-controlled trials of tesamorelin demonstrated significant reductions in visceral adipose tissue, improvement in lipid parameters, and no adverse effects on glucose tolerance. Optimal therapeutic dosing and treatment duration, though, are not yet known. Whether treatment with GHRH-analogues will translate into improved long-term metabolic and cardiovascular outcomes also remains to be seen.

Summary—Although the pathogenesis of HIV lipohypertrophy remains unclear, several theories and observations have led to the development of treatment strategies to counter fat accumulation and its accompanying metabolic complications. Based on clinical trials, analogues of the GH/GHRH axis appear to be most effective in reducing visceral adipose tissue.

Keywords

lipohypertrophy; visceral adipose tissue; HIV; lipodystrophy; tesamorelin

Introduction

With the advent of potent antiretroviral therapy for HIV infection in the mid-1990s, descriptions of morphological changes and metabolic disturbances in treated patients began to emerge. Initially the observed lipoatrophy and central fat accumulation were referred to collectively as “HIV-associated lipodystrophy”. In recent years, there has been increasing recognition that fat loss and fat gain likely represent distinct entities with unique pathogenic mechanisms.

Lipoatrophy is characterized by generalized loss of subcutaneous fat, most evident in the face, arms, legs, and/or buttocks without substantial loss of lean tissue mass.

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Lipohypertrophy is characterized by excess fat deposition in abdominal visceral adipose tissue (VAT), as well as in the dorsocervical region (i.e. buffalo hump), trunk and/or breasts. There may be co-existing fat deposition in the liver, muscle [1], myocardium, and epicardium [2].

The clinical implications of HIV-associated fat redistribution are both psychosocial and medical. Patients with abdominal obesity report poorer self-image [3], and may be less inclined to initiate or maintain adherence to antiretroviral treatment. The accumulation of VAT is of particular concern from a medical standpoint due to the often concomitant presence of insulin resistance and dyslipidemia [4,5], a clustering of abnormalities akin to the metabolic syndrome. In the general population, the metabolic syndrome significantly increases the risk of incident cardiovascular disease and mortality [6–8], with waist circumference being increasingly recognized as an independent risk factor for myocardial infarction [9]. In a recent report, coronary artery calcium scores were strongly associated with lipohypertrophy, providing evidence for the link between VAT and CVD risk in HIV-infected individuals [•10]. From both psychosocial and medical perspectives then, there has been an urgency to develop treatment strategies to counter the morphologic and metabolic complications of fat accumulation. This review will focus on proposed pathogenesis mechanisms and current treatment options for HIV-associated lipohypertrophy.

Pathogenesis

Epidemiological studies suggest that host factors (e.g. female sex and increasing age), markers of HIV infection itself (e.g. HIV viral load and nadir CD4 count), duration and possibly type of antiretroviral therapy are associated with lipohypertrophy [11]. While protease inhibitors (PIs) as a class have been most cited in the development of lipohypertrophy [11], trunk fat and waist circumference tend to increase after initiation of ART regardless of the type of regimen [12,13]. Based on these epidemiological observations, investigators have proposed a number of theories to explain the pathogenesis of lipohypertrophy, or, more generally, altered fat distribution (lipodystrophy) in HIV-infected patients.

Mitochondrial dysfunction

Mitochondrial dysfunction induced by NRTIs, specifically the thymidine analogues stavudine and zidovudine, has been implicated in the pathogenesis of lipoatrophy [14–16]. Some patients could have preserved visceral fat in the setting of subcutaneous fat loss if there is relative resistance of visceral fat to mitochondrial toxicity. In one study, patients were found to have increased expression of adipogenic transcription factors in abdominal subcutaneous adipose tissue (SAT) after two months of ARV initiation but decreased expression in thigh SAT suggesting that ARVs may have tissue-specific effects leading to lipoatrophy, lipohypertrophy, or a combination of both [17]. The technical challenge of acquiring visceral fat tissue from HIV-infected subjects for laboratory investigation has limited investigation in this area.

Impaired fatty acid metabolism

One model of HIV-associated fat redistribution cites dysregulation of fatty acid metabolism in the adipocyte as the underlying defect in promoting lipodystrophy. This model is based on the finding that patients with HIV lipodystrophy have significantly increased rates of basal lipolysis in the fasted state, increased intra-adipocyte re-esterification and net increase in free fatty acid release into the plasma pool without a proportionate increase in fatty acid oxidation [18]. Furthermore, a study involving ingestion of labeled triglyceride demonstrated that clearance from the plasma chylomicron pool was markedly reduced in

patients with HIV-associated fat redistribution [19], implying that there is also a profound defect in fat storage.

To explain the development of lipohypertrophy, Sekhar et al. hypothesize that a defect in peripheral adipocytes results in a greater availability of fatty acids in the circulation. The available fatty acids are then selectively deposited in visceral adipose tissue owing to the higher rate of lipid turnover and uptake in visceral adipocytes [20]. The putative cause of this dysregulation is not apparent but could be related to the effects of HIV itself via the HIV-1 accessory protein Vpr [21] or the effects of specific antiretrovirals.

Adiponectin

Adiponectin is an adipocyte-derived hormone that functions as an insulin sensitizer by reducing triglyceride levels and inhibiting gluconeogenesis in the liver. Adiponectin deficiency has been implicated in obesity, insulin resistance and type 2 diabetes in the general population [22,23], and has also been found to correlate inversely with VAT in patients with HIV-associated fat redistribution [24]. Since adiponectin expression is higher in SAT than VAT in obese humans [25], the adiponectin deficiency observed in HIV lipodystrophy may result from the accumulation of VAT in conjunction with the loss of SAT.

Leptin

Leptin is a hormone involved in central regulation of energy homeostasis and insulin resistance. In human obesity, leptin levels are elevated, likely representing a state of leptin resistance [26]. In HIV-infected individuals, leptin levels seem to correlate with body fat phenotype, with the lowest levels seen in patients with lipoatrophy, and the highest levels in patients with lipohypertrophy [27]. Elevated leptin levels can be attributed to increased secretion by adipocytes and/or resistance at the leptin receptor level in those with lipohypertrophy. Whether these alterations in adiponectin and leptin are a cause or consequence of fat redistribution is unclear, but therapeutic interventions to correct their levels are being explored.

Cortisol

Owing to phenotypic similarities with Cushing's syndrome, the role of cortisol in the pathogenesis of lipohypertrophy has been investigated. Though circulating levels of cortisol are not elevated [28], investigators have found higher ratios of urinary cortisol: cortisone metabolites and higher mRNA levels of 11β-hydroxy-steroid dehydrogenase type 1 (11β-HSD1) in the SAT of patients with HIV-associated lipodystrophy [29]. 11β-HSD1 is an enzyme that catalyzes the conversion of inactive cortisone to cortisol, and its overexpression in transgenic mice leads to visceral obesity, diabetes and dyslipidemia [30]. These data suggest that alterations in intra-abdominal glucocorticoid signaling could account for the Cushingoid characteristics of patients with HIV-associated lipohypertrophy.

Growth Hormone

In obese subjects, the amount of GH secreted per burst is decreased [31], and the response to GHRH and arginine stimulation testing is significantly blunted [32]. Subsequent studies in patients with HIV-associated lipodystrophy have shown similar alterations in GH dynamics. In comparison with age and body mass index-matched HIV-negative men and HIV-infected men without lipodystrophy, pulsatility of GH is maintained in overnight frequent sampling, but mean concentrations of GH are reduced by approximately 50% [33]. Affected patients also show suboptimal GH response to standard GHRH and arginine stimulation testing [34]. Increased somatostatin tone, decreased ghrelin concentrations and direct suppression of GH

by elevated free fatty acids may all contribute to impaired GH secretion in HIV-infected men with lipodystrophy [35].

Immune Reconstitution

Finally, immune reconstitution from effective antiretroviral therapy and residual inflammation and immune activation in the setting of suppressed HIV replication could contribute to lipohypertrophy. While there is no direct evidence to support this theory, there is precedent in the oncologic literature where adult survivors of childhood cancers and adults who have undergone bone marrow or stem cell transplantation appear to have a higher prevalence of obesity and metabolic syndrome than the general population [36,37].

Treatment

Because of the potential metabolic and cardiovascular risk posed by fat accumulation, there has been significant interest and research on the treatment of HIV lipohypertrophy, especially in the reduction of VAT (Table).

Switching antiretrovirals

Unlike lipoatrophy, there is no clear association between fat accumulation and specific antiretrovirals. While PIs have been implicated historically, switching PIs out of cART regimens have yielded inconsistent results in reducing adipose tissue [51]. In one small study, switching from lopinavir/ritonavir to atazanavir/ritonavir, a PI that does not affect insulin stimulated glucose uptake *in vitro* [52–54], resulted in increased muscle glucose uptake, decreased visceral adiposity and improved lipid parameters [55]. Due to inconsistency of results, however, we do not recommend switching antiretrovirals to combat lipohypertrophy. It is not known if choice of contemporary cART regimen affects the likelihood of developing lipohypertrophy or whether earlier initiation of HIV therapy could reduce the incidence of lipohypertrophy.

Diet and Exercise

Lifestyle changes are likely to provide some benefit in treating HIV-associated lipohypertrophy and associated metabolic abnormalities, though data are limited. A small study involving 17 HIV-infected patients with lipodystrophy who underwent a supervised aerobic training program demonstrated a mean decrease of 12.8% in total adipose tissue and 12% in visceral adipose tissue at 4 months [38]. Another study of 40 HIV-infected women who underwent 16-week exercise training program demonstrated improvements in muscle strength, cardiorespiratory fitness, endurance, and a reduction in waist circumference, but ultimately no change in VAT [39]. Since diet and exercise are typically well-tolerated and confer other health benefits, they are recommended in the initial treatment approach to lipohypertrophy.

Metformin

A number of clinical trials have explored the use of metformin in the treatment of lipohypertrophy with most showing modest reductions in waist circumference but inconsistent effects on VAT [40–42, 56]. Metformin use has led to proportionate reductions of SAT and VAT, and documented loss of limb fat in one study [42]. Consequently, metformin should be avoided in patients with concurrent lipoatrophy.

Thiazolidinediones (TZDs)

Several studies have investigated the use of TZDs for HIV-associated lipoatrophy with mixed results and no clear benefit in a recent meta-analysis [57]. Neither rosiglitazone nor

pioglitazone significantly reduces VAT in this population. In light of recent data from a meta-analysis suggesting that rosiglitazone may increase cardiovascular risk [58], there does not appear to be a role for TZDs in the treatment of HIV-associated lipohypertrophy.

Testosterone

In a study of 88 HIV-infected men with abdominal obesity randomized to receive testosterone gel or placebo, the testosterone group experienced reductions in total body subcutaneous fat, but did not show any statistically significant reduction in visceral abdominal fat [59].

Leptin

One small study looking at leptin replacement in HIV-infected patients with lipoatrophy found a decrease in truncal fat by 14.6% though no significant change in VAT [43]. In a more recent study of 8 patients with lipoatrophy, hypoleptinemia and insulin resistance, recombinant human leptin decreased visceral fat by 30% with no exacerbation of lipoatrophy [44]. Although these patients were selected for the presence of lipoatrophy, average values for VAT at baseline were comparable to those seen in other studies targeting patients with central fat accumulation. While these positive findings are worthy of further investigation, we are not aware of any ongoing trials of leptin replacement that will definitively assess its role as a potential treatment for lipohypertrophy.

Recombinant human growth hormone

Based on anecdotal observations of improvements of lipohypertrophy in patients receiving recombinant human growth hormone (rhGH) for AIDS-related wasting and the subsequent observation of a relative GH deficiency in HIV-infected patients with fat redistribution, the GH axis has become a target of pharmacologic strategies to reduce visceral fat. In the largest randomized controlled trial, supraphysiologic doses of recombinant human growth hormone (rhGH) at 4mg daily reduced visceral abdominal fat by approximately 20% and improved lipid profiles [45]. However, this relatively high dose of rhGH worsened insulin sensitivity and caused significant side effects of arthralgias, peripheral edema, and carpal tunnel syndrome. Studies of lower rhGH doses [46,47], including physiologic dosing to achieve IGF-1 levels in the upper range of normal [48], have been less robust in reducing VAT but are better tolerated and have modest if any effects on insulin sensitivity. Unfortunately the effects of rhGH wane after treatment discontinuation, with body composition returning to baseline at 12 weeks in several studies. Drug development of rhGH for lipohypertrophy is no longer being pursued.

Recombinant human growth hormone releasing hormone

Tesamorelin, an analogue of growth hormone-releasing hormone, augments endogeneous GH pulsatility with preservation of the negative feedback inhibition by IGF-1 (Figure). In an initial phase III trial, 412 ARV-treated patients with excess abdominal fat were randomized to tesamorelin at 2mg daily vs. placebo for 26 weeks. At the end of the study, visceral fat decreased by 15% in the treatment group with only a marginal reduction in abdominal SAT and limb fat. Triglyceride levels also declined on tesamorelin, and glucose metabolism was not adversely affected [49]. A second large Phase III study randomized 404 patients to tesamorelin or placebo during a 6 month efficacy phase. In a second 6 month extension phase, 265 patients were re-randomized to continue on tesamorelin or switch to placebo. Patients who received tesamorelin for the entire study period of 12 months demonstrated an overall 18% reduction of VAT. Those who switched from tesamorelin to placebo, however, experienced a reaccumulation of VAT to baseline levels [••50], indicating that treatment effects are not sustained after discontinuation of the medication.

Potential limitations of GH or GHRH therapies include cost and uncertainty regarding optimal dosing and duration of treatment. Long-term safety has also not been established. In the first Falutz study, 49% of the patients who received the drug developed IgG antibodies against tesamorelin, and a hypersensitivity reaction was seen in 6 patients, all of whom tested positive for IgG antibodies against tesamorelin [49]. The consequences of antibody development against tesamorelin are unknown, and it is unclear if antibody production is responsible for the predisposition to atopy observed in the tesamorelin group. Other theoretical concerns about the long-term administration of GH or GHRH analogues include increased risk of pituitary neoplasms or other cancers through excessive IGF-1 stimulation.

In June 2010, an FDA advisory committee voted unanimously for the approval of tesamorelin for the treatment of excess abdominal fat in HIV lipodystrophy, and an official decision from the FDA is expected in the latter half of 2010.

IGF-1/IGFBP-3

In patients with pituitary GH deficiency, treatment with recombinant IGF-1 has been shown to increase lean muscle and reduce body fat [60]. In a recent pilot study 13 HIV-infected men with excess central fat and insulin resistance were treated with IGF-1 complexed to its major binding protein, IGF-binding protein-3 (IGFBP-3) to prolong its half-life. After 3 months of treatment, glucose tolerance and peripheral insulin sensitivity improved but visceral adiposity remained unchanged [61].

Surgical interventions

Surgical procedures for fat deposition in the head and neck using liposuction techniques may help some patients. A small case series reported efficacy for dorsocervical fat pad liposuction, though 3 of 10 patients developed a partial late recurrence at 1 year [62].

Conclusions

The pathogenesis of HIV-related lipohypertrophy has been attributed to several complex processes, but ultimately is most likely multi-factorial in nature. Ongoing research may yield important insights into visceral obesity and the metabolic syndrome in the general population. Despite limited understanding of the mechanisms underlying lipohypertrophy, investigators have made advances in treatment strategies for this complication. A reasonable treatment approach to lipohypertrophy is to initiate standard methods of weight reduction through diet and exercise. In patients with concomitant type 2 diabetes, metformin can be considered if there is minimal, if any, lipoatrophy. Of the potential treatments on the horizon, tesamorelin appears to be the most promising though its optimal use requires further study.

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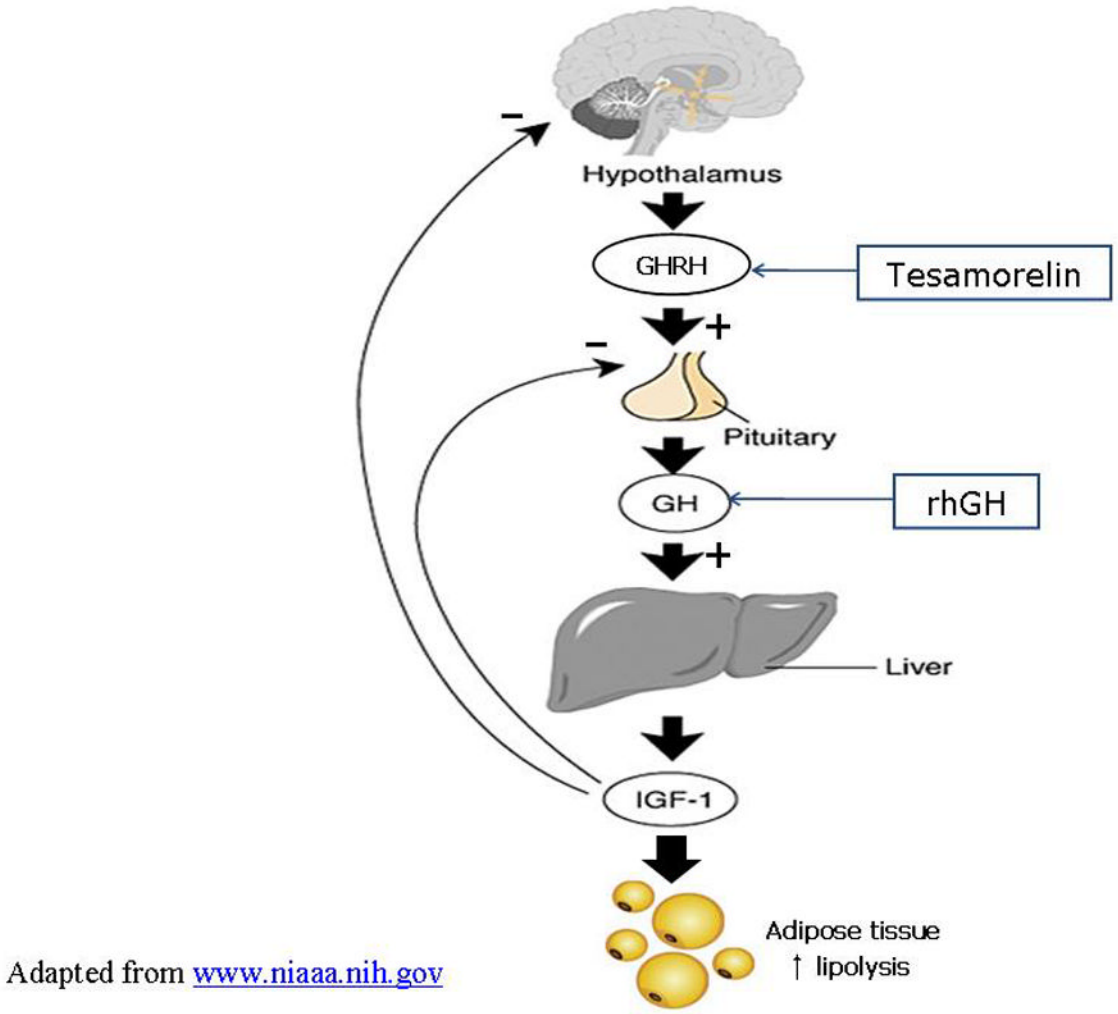

Figure.
Sites of pharmacologic intervention for HIV lipohypertrophy in the GH/GHRH axis. Tesamorelin preserves the negative feedback of IGF-1 on the pituitary.

TABLE

Summary of interventions for HIV-associated visceral adiposity

Intervention	Selected Studies	N	Dose	VAT outcome
Diet and exercise	Thoni 2002 [38]	17	Individualized aerobic training program x 4 months	Reduction in VAT by 12%
	Dolan 2006 [39]	40	Home exercise training program x 4 months	Decrease in waist circumference, but no change in VAT
Metformin	Hadigan 2000 [40]	26	Metformin 500mg bid vs. placebo x 3 months	Reduction in VAT by 6.3%
	Driscoll 2004 [41]	37	Metformin 500mg bid (increased to 850mg bid) +/− exercise training x 3 months	Combination of metformin and exercise training decreased VAT by 8.5%
	Kohli 2007 [42]	48	Metformin 500mg bid (increased to 1500mg bid) vs. placebo x 6 months	No significant decrease in VAT compared to placebo after adjusting for age, height, baseline VAT and insulin AUC
Leptin	Lee 2006 [43]	7	Recombinant human leptin at 0.02mg/kg bid x 2 months	Decrease in truncal fat by 14.6%, but no significant decrease in VAT
	Mulligan 2009 [44]	8	Recombinant human leptin at 0.01 mg/kg bid x 3 months, then 0.03 mg/kg bid x 3 months	Average reduction in VAT by 32% after 6 months
Recombinant human growth hormone	Grunfeld 2007 [45]	325	rhGH 4mg daily vs. placebo x 12 weeks induction	Reduction in VAT by 20.3%
	Luzi 2005 [46]	30	rhGH 0.028 IU/kg/day vs. placebo x 6 months	Reduction in truncal fat but no specific data on VAT
	Hansen 2010 [47]	46	rhGH 0.7mg/day vs. placebo x 10 months	Decrease in VAT by 11%
	Lo 2008 [48]	56	rhGH titrated to upper quartile of normal IGF-1 range (average dose 0.33mg/day) x 18 months	Decrease in VAT by 8.5%
Tesamorelin (growth hormone-releasing factor)	Falutz 2007 [49]	412	Tesamorelin 2mg daily vs. placebo x 26 weeks	Reduction in VAT by 15.2%
	Falutz 2010 [50]	404	Tesamorelin 2mg daily vs. placebo x 6 months (efficacy phase)	Reduction in VAT by 10.9% during efficacy phase
		265	Re-randomization to tesamorelin 2mg daily vs. placebo x another 6 months (safety extension phase)	Overall reduction in VAT by 17.5% in those treated with tesamorelin x 12 months. Return to baseline VAT in group switching from tesamorelin to placebo.