Current perspectives on HIV-associated lipodystrophy syndrome

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Introduction

Lipodystrophy in human immunodeficiency virus type 1 (HIV-1)-infected patients is now considered to be an adverse effect of antiretroviral therapy, not limited to a specific drug or a class of drugs.

HIV-associated lipodystrophy may affect up to half or even more HIV-infected patients receiving antiretroviral therapy.1,2 Antiretroviral drugs, which have a variety of effects, may play a role in the pathogenesis of body fat changes. However, at present it is not known whether lipodystrophy is a unique syndrome or several different overlapping syndromes. Several metabolic features (such as dyslipidaemia and insulin resistance, and body fat abnormalities consisting of a generalized decrease in subcutaneous fat with or without intra-abdominal, breast or dorsocervical accumulation) have been commonly reported, although the intensity and the associations of those changes have been highly variable. Other derangements such as hyperlactataemia, decreased bone mineral density, avascular necrosis, hypogonadism and hypertension have been described, although their relationship with the lipodystrophy syndrome has not been clearly established. The consequence of body fat changes is social stigmatization that may lead to poorer adherence and the failure of antiretroviral therapy. Moreover, metabolic abnormalities may increase the risk of cardiovascular disease.3 The knowledge of some aspects of this problem has increased in recent years, but many important questions still remain to be answered.

Definition of lipodystrophy

Lipodystrophy emerged as an unexpected problem in the field of HIV disease. It is not surprising that the method used most extensively to define lipodystrophy includes the subjective description of body fat changes. Two multicentre studies have been recently performed with the objective of reaching a definition of lipodystrophy. The Lipodystrophy Case Definition Study compared patients with and without evident clinical signs of lipodystrophy, concordant between the patient and the doctor. Laboratory testing, anthropometry and radiology (including computed tomography scanning and dual X-absorptiometry or DEXA) data were compared between both groups of patients, to try to establish the difference as an equation.4 The definition of lipodystrophy generated had 80% sensitivity and specificity, but it has proved to be too complex to be used in clinical practice. The Fat Redistribution and Metabolic Changes in HIV Infection (FRAM) study compared laboratory testing, anthropometry and radiology data from HIV-infected and non-infected subjects irrespective of body fat distribution. The FRAM study has shown that the only distinctive body fat change associated with HIV infection is generalized

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lipoatrophy, not lipohypertrophy. The results of the FRAM study do not explain why the prevalence of intra-abdominal obesity is so high in HIV-infected individuals. However, other studies agree that lipoatrophy is the hallmark of body fat changes in HIV-infected people. These studies represent great progress, but we still need a simple, easy, sensitive and specific definition of lipodystrophy.

Measurement

The word lipodystrophy has a vague meaning, as the problem has proved to be more complex than initially thought. The description of lipoatrophy and/or fat accumulation in specific areas and the degree of intensity of changes agreed by the clinician and the patient remain the best way to define the problem in a given patient. However, objective criteria for diagnosing lipodystrophy have not yet been established. The lack of standardized values of fat in the general population and the heterogeneity of clinical manifestations of lipodystrophy complicate this further. There is no gold standard method for measuring body fat. However, several techniques have been used: anthropometry, bioimpedance analysis, DEXA, computed tomography, magnetic resonance imaging (MRI) and ultrasonography. Anthropometry and bioimpedance analysis cannot measure regional body fat. Computed tomography and MRI are expensive, and their use may be restricted. Ultrasonography is promising because of its simplicity, safety, availability and low cost, although it may be more operator-dependent than the other techniques. It can also be used to measure perirenal fat diameter, which may be an early predictor of lipodystrophy. DEXA has gained popularity and is probably extensively used at present. Few data are available on the comparison of these objective techniques for measuring regional body fat. It seems that the measurement of only absolute values of regional fat is highly correlated, but that does not seem to be the case for detecting fat changes.

Another important issue is whether it is necessary to incorporate objective measurements of regional body fat into clinical practice, beyond investigational purposes. The availability and cost of current objective techniques are certainly important obstacles. However, the evolution of even minimal changes of body fat need to be detected and measured objectively, in order to prevent or diminish further evolution and also in order to evaluate accurately any possible intervention. We strongly believe that clinicians and healthcare providers should try to incorporate a readily available objective technique, to be performed as a part of standard procedures in the care of HIV-infected patients.

Managing HIV lipodystrophy

So far, there has been no adequate treatment to resolve lipodystrophy. Diet is of no use, unless dietary abnormalities are present. Exercise may lead to a partial beneficial decrease in central fat accumulation and triglyceride levels, but at the expense of increased peripheral fat wasting.

The use of recombinant human growth hormone (rhGH) can be beneficial in patients with increased visceral abdominal fat and/or buffalo hump, but it is not recommended for the treatment of lipotropic aspects of lipodystrophy syndrome, as it may lead to a decrease in peripheral fat. The safety of this drug and its long-term efficacy are of concern due to a high rate of dropout and adverse reactions in several trials using high doses of rhGH.

Epidemiological data show an increased risk of HIV-associated lipodystrophy in women, older patients, lower nadir CD4 cell count, lower body mass index and/or AIDS diagnosis, as well as hepatitis C virus co-infection. Patients with higher risk require closer follow-up, and since it is so difficult to obtain lipodystrophy reversion, it is important to try to prevent it by choosing an optimal treatment with a lower incidence of lipodystrophy.

The impact of switching antiretroviral drugs that are supposed to be involved in lipodystrophy has been commonly assessed in different studies. The majority of these studies and the first performed historically were those concerned with discontinuing protease inhibitors. In general, switching protease inhibitors may improve metabolic abnormalities, particularly those induced or increased by protease inhibitor therapy, but the impact on body fat is very small or nil. Switching thymidine analogues (most data coming from stavudine discontinuation or dose reduction) has been the only intervention to improve lipoatrophy in different independent studies.

The effect of discontinuing all antiretroviral therapy on the evolution of lipid abnormalities and body fat is poorly known. There are some preliminary data obtained from a group of well-controlled patients with primary HIV infection that have shown gain of total and regional fat during consecutive cycles of structured treatment interruptions (STIs). This issue will be addressed in the now ongoing large scale studies, such as the SMART study. Although STIs can be an attractive strategy to prevent or treat lipodystrophy they may also have unfavourable consequences, such as HIV drug resistance emergence, and immunological and virological disease progression. Because of this, patients have had to be closely monitored and chosen from the group of immunologically preserved HIV-infected patients in which even prolonged STIs have been shown to be generally safe.

Treatment with thiazolidinediones and leptin has shown good results in the group of non-HIV-infected patients with familial and autoimmune lipodystrophy.

Moreover, two small uncontrolled studies suggested that rosiglitazone might contribute to fat gain regardless of ongoing antiretroviral therapy. However, randomized, placebo-controlled studies have shown that rosiglitazone does not improve fat mass in HIV lipoatrophy, and may even worsen dyslipidaemia despite the improvement of insulin sensitivity.

The lack of the effect of rosiglitazone seems to be related to the continued exposure to thymidine analogue therapy.

Data from randomized studies comparing the effects of metformin, gemfibrozil and placebo in the group of patients receiving highly active antiretroviral therapy (HAART) found less fat loss with gemfibrozil than with placebo, and no effect of metformin, but all patients lost fat over time, which, although it may reduce cardiovascular risk parameters, leads to aggravation of peripheral lipoatrophy. Therefore, there are too few reasons to support widespread therapeutic interventions with metabolic drugs, except on an individual basis.

Since there is no effective and quick solution for lipodystrophy, there is a growing demand for interventions with immediate results. This explains why the advances in the field of plastic and reparatory surgery are such attractive treatment options. Liposuction performed in some patients with severe buffalo hump as well as increased subcutaneous fat depots gave good results in the short-term, but some patients re-accumulated fat in the following months. Unfortunately, excision or liposuction is not a treatment option in patients with visceral fat accumulation.
Implant surgery for lipoatrophy can be performed using permanent or biodegradable implants such as poly-l-lactic acid or hyaluronic acid. The treatment of facial lipoatrophy by injecting autologous adipose tissue (Coleman’s lipostructure) seems to be a satisfactory and cost-effective option to treat facial lipoatrophy if there is a source of fat graft existing. Prospective studies are ongoing to assess the durability, complications and potential differences among surgical procedures.

Conclusions

Huge improvements in the understanding of lipodystrophy have been achieved. However, much remains to be learned. A definition of lipodystrophy is yet to be established. There is still no clinically proven definitive treatment for any feature of lipodystrophy.

The only intervention that has been shown to revert lipoatrophy is the discontinuation of thymidine analogues, but the results obtained are partial and slow at best. Structured therapy interruption has become an increasingly popular strategy aimed at preventing antiretroviral drug toxicity, but few objective data exist on its impact on the body composition of HIV-infected patients. At present, the only available solution is plastic surgery, which may at least give satisfactory aesthetic results in the absence of other definitive options.

References


