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Lipodystrophy Syndrome: Diagnostic, Clinic and Therapeutic Aspects

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Abstract

Lipodystrophy (LD) in HIV-infected patients receiving HAART is a novel, polymorfic clinical entity that needs to be clearly defined. Its prevalence and diagnosis are not well established so far. It includes several disturbances, such as lipoatrophy and fat accumulation at different sites, and lipid and glucose metabolism alterations, including hyperlipidaemia, insulin resistance and lactic acidaemia. Several factors have been implicated, and no single etiological hypothesis has been able to account for the wide range of clinical manifestations. In fact, different entities could be underlying the process. However, little doubts remain as to the crucial role being played by protease inhibitors (PI) and nucleoside reverse transcriptase inhibitors (NRTI). Objective criteria to assess body-shape changes have not been defined. Morphological changes have psychological, social and treatment-adherence consequences, and there are very few therapeutic options currently available. Metabolic abnormalities may increase cardiovascular risk over the long term in some patients. A higher rate of coronary events and atherosclerotic disease in HIV+ patients under HAART are of great concern. For this reason, an adequate management of these disorders is decisive, to prevent cardiovascular morbidity and mortality in the future. Lactic acidaemia is a frequent complication associated with NRTI, but its clinical relevance is uncertain at the moment. Its most severe presentation is lactic acidosis, which requires a prompt diagnosis and treatment, given its fatal prognosis. Finally, less toxic antiretroviral strategies and/or a delay in its prescription might be warranted.

Key words

Lipodystrophy. HAART. Antiretroviral toxicity. Dyslipidaemia. Cardiovascular risk. Lactic acidaemia.

Introduction

Since highly active antiretroviral treatment (HAART) became available in 1996, the metabolic profile of HIV-infected patients has changed notably. Previously, when effective virus suppression was not achievable, HIV+ subjects frequently presented several nutritional disturbances, malnutrition and wasting syndrome being the most frequent[1]. After the introduction of potent antiretroviral therapies, the incidence of these nutritional disorders, together with opportunistic events, has declined remarkably. However, in 1997 various morphologic and metabolic alterations, including body fat accumulation and lipoatrophy at different sites, hyperlipidaemia and glucose metabolism abnormalities, were recognized in association with HAART intake. They constitute a new syndrome of lipodystrophy (LD), which still continues to be an intriguing and concerning issue[2-7].

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LD was at first related to protease inhibitors (PI), as the identification of the initial cases was recorded shortly after the beginning of their use[2,5,8,9].

Later on, nucleoside reverse transcriptase inhibitors (NRTI) were implicated too, LD features having been described in patients under HAART but never exposed to PI[10-12].

More recently, we have learned that HIV+ patients receiving HAART are at higher risk of bone demineralization, either osteopenia or osteoporosis, a fact that might be linked to LD[13-15]. Although firstly related to PI, the etiology of HAART-related bone toxicity needs further clarification.

A validated case definition of LD is lacking for the moment. It includes both morphologic and metabolic alterations. Different related syndromes might be involved and various pathogenic mechanisms and diverse risk factors have been postulated. Among them, major attention has been paid to certain antiretroviral drugs, but HIV infection *per se,* cytokines, genetic factors, gender, age, diet and premorbid body weight could also play a role.

Physical changes

Diverse LD morphologic alterations may become readily apparent after several months under HAART (Table 1). The LD body-shape changes most frequently observed are lipoatrophy (peripheral fat loss in the face, buttocks and limbs), and central fat accumulation (within the abdomen, breasts, and over the dorsocervical spine [so-called "buffalo hump"], as well as other lipomata)[3,16-18]. Fat accumulation may predominate in women[9]. Breast enlargement has been found mainly in women[9,19], but in men too[20,21].

Metabolic abnormalities

High triglycerides (Tg) and low cholesterol (Chol) levels had been related to HIV infection *per se* prior to the introduction of HAART[22,23]. However, the alterations in the lipid profile associated with LD comprise hypertriglyceridaemia and elevation of total Chol, VLDL and LDL fractions[2,5,7,8,23-25]. Moreover, subjects receiving PI frequently develop insulin resistance (hyperinsulinaemia and elevated C-peptide), either with or without glucose intolerance, and sometimes diabetes mellitus[2,5,7,8,23-27]. The nucleoside abacavir has also been reported to cause reversible hyperglycaemia[28]. Lactic acidaemia is another metabolic disturbance linked to the use of NRTI[29,30] (Table 2).

Diagnosis

Body fat alterations, high lipid levels and insulin resistance are commonly accepted as the most important features of LD, although not all of them need to be present simultaneously. A LD working classification was proposed by the Antiretroviral Treatment-Associated Lipodystrophy European Comparative Study (ALECS) group, at the First European Symposium on Lipodystrophy and HIV infection held in Marrakech during March 2000. This descriptive classification takes into account morphologic changes (lipoatrophy, fat accumulation, or both) defined on physician's and patient's observation, and metabolic alterations (hypercholesterolaemia, hypertriglyceridaemia, and hyperglycaemia). According to these parameters, each patient would be assigned a sort of code depending on the abnormalities detected. However, its complexity precludes its widespread use.

Before LD diagnosis, the presence of recent diseases or AIDS-defining events causing weight loss, or the use of anabolics, glucocorticoids or immunemodulators should be ruled-out[7,24].

At the moment, there are no measurable, objective parameters for the diagnosis of LD body-shape alterations, which is based on self-reported changes by the patient, confirmed on physical examination. Both criteria don't always correlate[24,31]; therefore, objective assessment of both visceral and subcutaneous fat tissue compartments is warranted, for clinical and research purposes. Anthropometric evaluation is easily available, although the technique shows different results when performed by either the same or different clinicians. Longitudinal studies have pointed-out that weight changes, and modifications of both waist circumference and abdominal skin-folds, predict alterations in subcutaneous and visceral fat tissues with a sensitivity comparable to MRI[32]. However, other authors have not found such a good correlation be-

Table 1. *Body-shape changes in HIV-associated lipodystrophy syndrome.*

- Peripheral lipoatrophy
  - Subcutaneous fat loss in face, buttocks and limbs.
- Central fat accumulation
  - "Buffalo hump" (dorsocervical fat pad enlargement).
  - Intra-abdominal.
  - Breast enlargement.
  - Other lipomata.

Table 2. *Metabolic abnormalities in HIV-associated lipodystrophy syndrome.*

- Hypertriglyceridaemia
- Hypercholesterolaemia
- Insulin resistance (insulin and C peptid elevated)
- Glucose intolerance / diabetes mellitus 2
- Lactic acidaemia

tween anthropometric assessment and LD clinical manifestations[33].

Bioelectrical impedance analysis and DEXA (dual-energy x-ray anthropometry) are helpful diagnostic tools to evaluate lean-body mass and fat tissue. Unlike bioelectrical impedance, DEXA can differentiate various parts of the body in determining fat loss and fat accumulation. The amount of fat tissue present in visceral and subcutaneous locations can also be assessed by image techniques, such as CT-scan or MRI. Nevertheless, these two techniques and DEXA should not be considered for routine practice, as they are not always affordable or available. In this regard, sonography is more readily available and can be useful in assessment of regional fat thickness, especially for the subcutaneous compartment[34].

Prevalence

Regarding body-shape changes, data on the prevalence of LD are widely variable, from 10 to 80%[2,9,11,24]. The large series from the Australian survey[35], the Swiss HIV cohort[36] and the US HOPS cohort[37], have all shown prevalence rates in unselected patients of 40-50%. In patients who have received combination therapy, this is about 70%. The variability of LD prevalence is partly due to the absence of objective diagnostic criteria. In addition, LD is more frequent in those studies with more prolonged follow-up periods[2,24]. In patients who begin HAART, a 20% rate of morphologic changes have been reported after two years of treatment[38]. In another survey, 17% of patients who started HAART early after seroconversion developed clinical LD after a mean follow-up of 19 months[39]. Mixture patterns of lipoatrophy plus fat accumulation seem to be the most common, followed by either lipoatrophy or fat accumulation.

Dyslipidaemia is present in up to 70% of subjects under PI-containing HAART regimens[24,25,40], and in half of those receiving non-nucleoside reverse transcriptase inhibitors (NNRTI) instead of PI[41,42]. Lipid abnormalities with NNRTI therapy are largely due to efavirenz. Hypercholesterolaemia is more prevalent than hypertriglyceridaemia[25,40,42], and they frequently coexist. Impaired glucose tolerance and diabetes are recorded in 15-45 % and 8-10% of subjects following a PI-containing combination, respectively[5,7,24-26].

Clinical implications

In the long-term, the clinical consequences in subjects with LD are unknown. Hyperlipidaemia and insulin resistance are independent cardiovascular risk factors. In HIV+ subjects under HAART with dyslipidaemia, other cardiovascular risk factors such as a family history of cardiovascular disease, smoking, physical inactivity or being overweight, are commonly present[43,44]. There is a major concern that these disturbances will lead to an epidemic of cardiovascular disease, mainly because the life expectancy in HIV+ persons has been remarkably improved with the new antiretroviral therapies. Preliminary data show a significant increment of coronary events in HIV- infected individuals[45], and the prolonged use of PI has been related to a higher incidence of myocardial infarction[46]. This fact may be related to increased survival, and not necessarily due to the drugs. PI also seem to induce endothelial dysfunction[47]. In addition, a higher than expected prevalence of atherosclerotic disease in HAART recipients has been found[48,49]. A significant association of carotid lesions with the usage of PI has been reported[48]. All these findings should alert clinicians to the importance of paying attention to cardiovascular aspects in HIV+ patients under HAART, as a routine part of their total healthcare needs.

Hypertriglyceridaemia is quite prevalent in patients under HAART. This condition warrants an appropriate management, as high levels of Tg predispose to pancreatitis[50,51].

Lactic acidaemia, defined as lactic acid levels above 2 mmol/l, is frequently recognized in subjects receiving NRTI. It is moderate and asymptomatic in most cases[29,52]. A classification of this disturbance has been proposed, on the basis of plasmatic concentrations of lactate and the presence of acidosis and symptoms[53] (Table 3).

Lactic acidosis, though rare in frequency, is by far the most severe complication of NRTI. It has been described in patients following treatment with ZDV, ddI, d4T or 3TC for several weeks or months. Its clinical presentation includes malaise, nausea, vomiting, abdominal pain and hyperventilation[30,54,55]. Laboratory tests show lactic acidaemia and metabolic acidosis, as well as increased Tg and free fatty acids. These accumulate as intracellular fat, leading to steatosis and liver dysfunction[56,57]. As a result, multi-organic failure and refractory arrhythmias can occur. The severity

Table 3. *Classification of lactic acidaemia*.*

Grade	Venous lactate (mmol/l)	Acidosis	Symptoms
Normal	<2	No	No
Mild	2-5	No	No
Moderate	5-10	Rare	Possible
Severe	>10	Often	Yes

*A. Carr. State-of-the-art summary and discussion issues in metabolic complications: controversy or consensus. 8th CROI, Chicago 2001.

of this condition requires prompt diagnosis and treatment to prevent the patient from fatal outcome.

Finally, the psychological impact of body-shape changes, which might preclude proper treatment adherence, should be taken into account when treating these individuals. They constitute, in many cases, the principal reason for concern in both patients and physicians.

Lipodystrophy management

As the etiology of LD remains obscure, and several pathogenic hypotheses are in discussion, no clear guidelines for its prevention or treatment have been established. The current available strategies directed against the specific clinical or metabolic entities related to LD are summarized in table 4.

It is obvious that delaying, as far as possible, the start of antiretroviral treatment represents the first measure to avoid the development of LD disturbances. With regard to PI use, if they are the major determinants of LD, they should be excluded in patients with a good immunological status. The reversibility of morphological alterations is another matter of concern. Many studies have evaluated the impact in LD improvement when replacing PI by NNRTI or abacavir (switch therapy). In this respect, although normalization in lipids is not always achieved, a reduction is frequently observed, being more pronounced when switching to nevirapine or abacavir than to efavirenz[58-61]. Similarly, the switch strategy appears to improve insulin resistance[58,60,62], although not in all studies[63]. With respect to body-shape changes, these can partially revert, particularly abdominal fat accumulation[58,60,64], but not in all instances[64-66]. Therefore, a change of drugs is only justified if there is no counter-indication based on virological and immunological criteria. It should be kept in mind that nevirapine has a lower genetic barrier than PI and efavirenz[67], so patients switched to this drug are at higher risk for virological failure. In addition, there is broad cross-resistance between abacavir and other NRTI, so that any simplified regimen containing abacavir should be designed taking into account the pharmacological history of the patient[68]. These factors and the intrinsic immunological benefit associated to PI use[69] make it advisable for switch-therapy to be restricted to patients with long term virus suppression and good immunological status.

Structured treatment interruptions[70,71] or simpler combinations (e.g. ddI+hydroxyurea)[72] constitute therapeutic alternatives able to induce less toxicity, including LD. However, the rebound of viraemia occurring in most patients following any of these options, is a major risk factor for immune deterioration and resistant virus selection. This fact represents a common limitation for the wide use of these strategies, which should be considered only in the context of clinical trials.

Switch-therapy, as well as structured treatment interruptions and ddI+hydroxyurea, should be indicated only in patients with early-stage disease on a very stable combination for a long period of time. Subjects mildly affected by LD with advanced HIV disease on a salvage regimen would not warrant any of these interventions, as they are at far greater risk for HIV related complications.

Finally, the use of cyclic antiretroviral therapies, alternating different drug regimens with diverse toxicities[73], might be of benefit in order to prevent the development of LD disturbances associated with certain drugs.

Together with the control of virus replication and immune restoration, the diagnosis and treatment of cardiovascular risk factors is also important in order to prevent related morbidity and mortality in the future. Its high prevalence in HIV+ subjects under HAART, as well as the increasing incidence of atherosclerotic and ischemic heart disease in this population, warrants an adequate management of these problems. In this context, patients deserve intervention for LD metabolic

Table 4. *Management of lipodystrophy.*

Body-shape changes
Fat accumulation
– physical exercise
– recombinant human growth hormone
– liposuction
Lipoatrophy
– implants: fat, collagen, polilactic acid

Metabolic alterations
Hyperlipidaemia
– diet
– physical exercise
– hypercholesterolaemia: statins (pravastatin)
– hypertriglyceridaemia: fibrates (gemfibrozil, fenofibrate)
Hyperglicaemia
– diet
– oral hypoglicaemic agents: metformin, others
– insulin
Lactic acidaemia
– lactate > 5-10 mmol/l: nucleoside analogues withdrawal
– abacavir, regimens without nucleoside analogues
Lactic acidosis
– nucleoside analogues withdrawal
– treatment of metabolic acidosis
– cofactors (thiamine, riboflavin, L-carnitine)
– antioxidants (vitamins C and E, co-enzyme Q10)

Cardiovascular risk prevention
– treatment of other modifiable risk factors: smoking, obesity, physical inactivity, hypertension

Antiretroviral treatment strategies
– delaying start of treatment
– switch therapy: protease inhibitors → non-nucleoside analogues, abacavir, ddI-hydroxyurea
– structured treatment interruptions
– cyclic therapy

complications given the frequent association with other cardiovascular risk factors such as smoking or a marked family history. Estimates of benefit (delayed progression to AIDS) or harm (myocardial infarction) derived from antiretroviral therapy have been determined[74]. They are based on data from the Multicenter AIDS Cohort Study and the Swiss HIV cohort, as well as the Caerphilly Heart Study (the Welsh equivalent of the Framingham study). There might be circumstances in which the number of PI-treated patients required to precipitate one myocardial infarction might be as few as 10 (e.g. a 50-year old male smoker with PI-induced hypercholesterolaemia and glucose intolerance). In contrast, there are CD4/HIV RNA strata where the number of treated patients to prevent one progressing to clinical AIDS is well above this (e.g. with a CD4 count of 350 and a viral load of 30,000, about 50 patients are treated to prevent one progression to AIDS, and so 49 patients get no gain and potential harm). Thus there are situations in which the risk/benefit ratio of treatment may not be favorable, such as in subjects with high atherosclerotic co-morbidity and high CD4+ cell count or slow disease progression. This analysis, which needs further confirmation in larger cohorts, will help clarify criteria concerning the moment to start antiretroviral therapy, considering potential cardiovascular morbidity.

It would be advisable to recommend antiretroviral agents less prone to induce hiperlipidaemia. Data recently reported from the Atlantic Study show that nevirapine, when combined with ddI and d4T, is associated with a more favorable lipid profile than 3TC or indinavir[75]. This regimen represents a good alternative, both in naive patients and in those in whom a switch strategy is considered.

Regarding metabolic disturbances, in addition to the treatment strategies mentioned above, the advice addressed to the general population should also be beneficial for HIV+ subjects. The AIDS Clinical Trials Group (ACTG) has issued a number of recommendations for the treatment of HAART-related hyperlipidaemia[76], based on the previous guidelines of the National Cholesterol Education Program[77], which have been recently updated[78]. In case of hyperlipidaemia, low fat diet and physical exercise must initially be prescribed. If these measures are not sufficiently effective, gemfibrozil and atorvastatin have been shown to reduce Tg and Chol levels at 6 months by 60 and 30%, respectively[79]. Fibrates (gemfibrozil, fenofibrate) are indicated mainly for Tg reduction, and statins for hypercholesterolaemia[80]. Pravastatin is the drug of choice, since it lacks interactions with antiretrovirals[81,82].

Patients who develop hyperglycaemia or diabetes can be controlled with diet, although they may need oral hypoglycemic agents or insulin[27]. Metformin may contribute to reversing HAART-related insulin resistance and abdominal fat accumulation, although the appearance of lactic acidaemia should be monitored, especially in case of concomitant liver or renal insufficiency, or in subjects receiving NRTI[83]. At low doses, however, levels of lactate and transaminases do not rise[84]. Initial studies with troglitazone showed promising results in glucose control, lipid profile and lipoatrophy in diabetic HIV-negative subjects[85]. Nevertheless, this drug has been dropped by the FDA due to sporadic cases of fatal liver damage. Two other related drugs, pioglitazone and rosiglitazone, are under clinical investigation.

In case of lactic acidaemia, withdrawal of NRTI has been recommended when lactate levels are over 5-10 mmol/l. Their routine determination is not justified, except if symptoms or liver dysfunction appear, and in pregnant women[86]. The treatment of lactic acidosis includes immediate suspension of NRTI, as well as other measures for reversion of metabolic acidosis. The supplementation with diverse co-factors (thiamine, riboflavin, L-carnitine) and antioxidants (vitamins C and E, and co-enzyme Q10) has been demonstrated to be effective in congenital mitochondriopathies, so they could be indicated in patients with mitochondrial dysfunction due to NRTI[87]. Riboflavin seems to normalize lactate levels very rapidly[88].The new antiretroviral combination in these patients should include agents less prone to induce lactic acidaemia, such as abacavir or regimens without NRTI, if possible.

With respect to changes in the body habitus, human recombinant growth hormone (rhGH) increases muscular tissue and improves abdominal fat accumulation, although the later seems to reappear once rhGH is discontinued[89-91]. As expected, physical exercise may reduce centripetal fat deposits[92]. Finally, in selected patients, plastic surgery could be performed for unaesthetic fat deposits removal. In areas of lipoatrophy, adipose tissue, collagen or polilactic acid may be implanted[93].

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