Evolving perspectives on HIV-associated lipodystrophy syndrome: moving from lipodystrophy to non-infectious HIV co-morbidities

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This article will provide insight into the evolving perspectives on HIV-related lipodystrophy syndrome: recent changes in epidemiology, a shifting focus from individual component assessment towards a more comprehensive risk evaluation for organ dysfunction and disease, the impact of patient-related outcomes in health-related quality of life and the integration of this syndrome into a wider scenario of a premature ageing process in HIV-infected people will be discussed. The time has come to proceed beyond lipodystrophy studies based on blood concentrations of lipids and glucose and body fat evaluation. Surrogate markers of organ disease associated with lipodystrophy better identify patients vulnerable to non-infectious co-morbidities (NICMs) rather than statistical risk algorithms. In this evolving perspective NICMs take the place of lipodystrophy in the description of the clinical spectrum of HIV disease and allow integration of this syndrome into the wider scenario of a premature ageing process in HIV-infected people. Management of NICMs needs to be considered as part of a multi-disciplinary holistic approach that accommodates the increasing number of factors influencing non-infectious HIV-related outcomes.

Keywords: LD syndrome, lipodystrophy, HIV

Introduction

Almost 11 years have passed since lipodystrophy was first reported in HIV-infected patients, mitigating the enormous enthusiasm about highly active antiretroviral therapy (ART), which had just become available at that time.1 This syndrome includes peripheral fat loss (lipoatrophy; LA), central fat accumulation (lipohypertrophy; LH) separately present or in combination in the same individual (mixed forms), usually, but not invariably, associated with alterations of lipid metabolism and derangement of insulin sensitivity and diabetes mellitus.1,2

Milinkovic and Martinez3 in 2005 provided an excellent review in this journal on the definition, measurement and management of lipodystrophy. However, a case definition applicable in the clinical setting is still missing, we still lack wide scale routine access to objective measurement of body fat changes and, last but not least, management and prevention strategies have not significantly changed. What is new then?

In this article we will provide insight into the evolving perspectives on HIV-related lipodystrophy syndrome. We will discuss the recent changes in lipodystrophy epidemiology, the shifting focus from individual lipodystrophy component assessment towards a more comprehensive risk evaluation for organ dysfunction and disease, and the impact of patient-related outcomes on health-related quality of life (QoL).

In this evolving perspective non-infectious co-morbidities (NICMs) take the place of lipodystrophy in the description of the clinical spectrum of HIV disease and allow integration of this syndrome into the wider scenario of a premature ageing process in HIV-infected people.

Is lipodystrophy over?

The absence of a clear-cut definition unavoidably has led to uncertainty about changes in prevalence and incidence of lipodystrophy over time.2 Decreasing thymidine analogue (TA) use, the leading risk factor for LA development2 and, moreover, the availability of new drugs and drug classes that allow treatment scenarios where a TA-based backbone and ritonavir boosting of protease
inhibitor (PI) paradigms are over, as well as the effort for earlier
detection and treatment of HIV infection\textsuperscript{6} make it reasonable to
hypothesize a decrease in the prevalence of lipodystrophy in the
coming years.

Few epidemiological data exist to verify this so far. A Swiss
HIV Cohort Study recently reported a reduced likelihood, by
life-table Kaplan–Meier analysis, of lipodystrophy development in
patients who started ART between 2003 and 2006 compared with those who started ART between 2000 and 2002, coinciding with decreased rates of TA use, mainly stavudine. Unluckily the study did not provide any objective assessment of body fat changes.\textsuperscript{7}

In the same time period, epidemiological data from the
southern hemisphere demonstrated an opposite trend towards an
emerging epidemic of lipodystrophy in those countries. In a study from Rwanda, lipodystrophy was observed in 34% of sub-
jects, with prevalence increasing to 69.6% in those receiving
ART for $\geq$72 weeks. Peripheral LA combined with abdominal
LH was observed in 72% of lipodystrophy subjects.\textsuperscript{8} In a more
recent case–control study from Senegal, the prevalence of moderate–severe lipodystrophy was 31.1%, with 13.3%, 14.5%
and 3.3% for LA, LH and mixed forms, respectively. The
overall prevalence of lipodystrophy was 65.0% and stavudine
was the only independent risk factor.\textsuperscript{9}

In both these studies, lipodystrophy was clinically assessed
only, and body fat changes not unexpectedly coexisted with
abnormalities of glucose and lipid metabolism.

Finally, very few prospective studies have evaluated the
natural history of lipodystrophy.\textsuperscript{10} New phenotypes are still
being described, with bilateral retroauricular and pubic lipomas
being the most recent examples.\textsuperscript{11,12} The latter appeared to
be associated with shorter duration of HIV infection, somehow
suggesting that this phenotype was not present in previous
years.\textsuperscript{12}

Moving from individual lipodystrophy component
assessment to risk evaluation for organ disease

From the very first description of lipodystrophy it became
apparent that its individual components significantly overlapped
with diagnostic criteria of the metabolic syndrome (MS), a con-
stellation of abnormalities that lead to an increased risk of
cardiovascular disease and diabetes in the general population.
This was the first warning for HIV-treating physicians not to
concentrate solely on HIV viral management but also to take
into account the potential age- and lifestyle-related conditions
likely to influence long-term morbidity and ultimately survival
of their patients. Cardiovascular, bone, kidney and liver disease
risk evaluations are now suggested as the standard of care by
international guidelines.\textsuperscript{13} What makes risk prediction difficult
in HIV-infected individuals, is the presence of additional—
besides the traditional ones—potentially contributing factors,
represented by HIV-associated immunodeficiency and immune
activation, chronic inflammation as well as drug toxicities.

The SMART study showed an unexpectedly higher rate of
NICMs in the arm undergoing CD4 cell count-guided treatment
interruption.\textsuperscript{14} The association between all-cause mortality and
HIV infection appeared to be related to activation of coagulation
and systemic inflammation impairing the endothelium. This
observation together with the availability of metabolically
neutral drugs make HIV experts consider that ART without
metabolic effects that effectively suppresses HIV is likely to be
associated with the lowest risk for NICMs.\textsuperscript{15}

Nevertheless a close association between drug exposure and
NICMs is still recognized. Examples include the association
between cumulative exposure to PIs and current or recent
exposure to abacavir and cardiovascular disease;\textsuperscript{16,17} nucleoside
reverse transcriptase inhibitor (NRTI) cumulative exposure and
fatty liver disease;\textsuperscript{18} cumulative exposure to PIs and osteopenia/
osteoporosis\textsuperscript{19} and potentially tenofovir and PI exposure and
kidney disease.\textsuperscript{20} These associations form the basis for the
rationale of switching antiretroviral agents even when virological
control is obtained.

Regular screening helps identify those asymptomatic
HIV-infected individuals who are most at risk of developing
coc-morbidities. Nevertheless we lack validated HIV-specific
algorithm tools for organ disease risk prediction.

With regard to cardiovascular risk scoring systems, the
Framingham score has been evaluated in HIV-infected patients
but, as expected when applied in a relatively young population,
appears to underestimate the risk for myocardial infarction.\textsuperscript{21,22}
Proteinuria and glomerular filtration rate are suggested to screen
for kidney disease.\textsuperscript{13} What is not yet incorporated in general
screening is dual energy X-ray absorptiometry (DEXA) for bone
disease and liver ultrasound for fatty liver disease in hepatitis B
virus- and hepatitis C virus-uninfected patients, notwithstanding
that the prevalence of bone mineral density abnormalities and
fatty liver disease are as high as 67% and 37%, respectively.\textsuperscript{18,19}
Limited access to these tests is related more to organizational
issues than to risks or costs.

Impact of patient-related outcomes on health-related
QoL

Besides organ-related co-morbidities, lipodystrophy can
undoubtedly have a profound influence on health-related QoL
through erosion of self-esteem and decreased social functioning
due to the patient’s perception of bodily changes.\textsuperscript{23} It has been
shown that the impact of lipodystrophy on QoL can be identified
only in patients with a perceived body image alteration of mod-
earate to severe degree notwithstanding the physician-based defi-
nition of lipodystrophy.\textsuperscript{24} Patient dissatisfaction about his/her
body image may lead to anxiety and depression as well as
sexual dysfunction.\textsuperscript{25,26} Additionally, soon after lipodystrophy
was described it was realized that although greater adherence to
ART was related to a higher probability of developing lipody-
 strophy, a patient’s subsequent dysphoria about his/her
physical changes could significantly decrease their level of adherence and
promote development of drug resistance.\textsuperscript{27,28}

Lipodystrophy as a premature ageing process

Atherosclerosis, diabetes mellitus, changes in body fat distribution, 
loss of renal function, osteopenia and non-AIDS-defining cancers have increasingly been described as occurring prematurely in several HIV observational cohorts. Rather than occurring merely as a consequence of extended survival among ART recipients, it has been suggested that the increased rate of these morbidities may
result from accelerated biological ageing imposed by HIV itself and/or antiretroviral therapies. Several hypotheses have been formulated in an attempt to provide a justification for the premature ageing. They include an accelerated immune senescence secondary to the exhaustion of immunological resources, ART toxicity (mitochondrial dysfunction and oxidative stress induced by TAs) or even the accumulation of abnormal lamin A associated with PI use. The saquinavir family of HIV aspartyl PIs, including lopinavir and atazanavir, can affect the physiological maturation of prelamin A to lamin A, a key structural component of the nuclear lamina, at least in part through inhibition of the zinc metalloprotease ZMPSTE24 and possibly through other mechanisms. This may lead to increased oxidative stress and premature cellular senescence in a similar manner to progeroid ageing syndromes, which share several phenotypic characteristics with HIV-related lipodystrophy (both LA and LH).

This concept may justify an accelerated frailty in HIV-infected people, in comparison with their same-age HIV-uninfected counterparts, and is corroborated by data from a large cohort.

**Future directions**

The time has come to proceed beyond lipodystrophy studies based on blood concentrations of lipids and glucose and body fat evaluation.

In this perspective even the lipodystrophy syndrome diagnosis has become somewhat obsolete and its definition should be replaced with the description of an evolving scenario of NICMs.

Furthermore, given the unexpected premature occurrence of NICM events, HIV has become a model for the identification of a new pathogenetic hypothesis for the general population.

From a clinical point of view research is focusing on new surrogate markers of organ disease to identify patients vulnerable to NICMs. In the HIV scenario, risk prediction algorithms appear to underestimate events in this still relatively young population and clinicians appear to be more interested to know which patients qualify for primary prevention of NICMs rather than who is theoretically at risk. Examples of surrogate markers include coronary calcium scoring or carotid intima-media thickness measurement as markers of global atherosclerosis burden and flow-mediated dilatation testing or pulse wave velocity as markers of endothelial dysfunction.

From this perspective, the evaluation of drug toxicities during the drug development process or research on therapeutic strategies for HIV infection should rather focus on organ damage instead of biochemical abnormalities.

The management of NICMs needs to be considered as part of a multi-disciplinary holistic approach that accommodates the increasing number of factors influencing non-infectious HIV-related outcomes. One possible structured model for HIV care might include initial screening and regular monitoring for HIV-related outcomes. One possible structured model for HIV a multi-disciplinary holistic approach that accommodates the strategies for HIV infection should rather focus on organ damage instead of biochemical abnormalities.

Transparency declarations

None to declare.

**References**


