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Original article

Atherogen lipid profile in HIV-1-infected patients with lipodystrophy syndrome

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Abstract

Background: Cases of lipodystrophy syndrome and metabolic disorders have been described since the onset of highly active antiretroviral therapy in HIV-infected patients. The aim of our study was to estimate the prevalence of lipodystrophy (LD) and to define the associated lipid profile of these patients. *Methods:* The following were determined for each patient: lipid profile (cholesterol and its subfractions, atherogenicity ratios, and triglycerides), blood glucose, and immunovirological markers ($CD4^+$ cell count and plasma viral load). Patients were classified into two groups on the basis of whether or not they presented with clinical signs of LD. *Results:* Among 233 HIV-infected patients included in the study, 61 cases (26.1%) of lipodystrophy (LD) were noted. Compared with non-LD patients (NLD), LD patients were older men ($P<10^{-4}$) with a lower $CD4^+$ lymphocyte cell count ($P<0.007$) and more often at the AIDS stage ($P<10^{-3}$) (OR=3.2 (95% CI: 1.47–6.2)). Multivariate analysis showed a correlation between LD cases and age (10 years older) (OR=1.78 (95% CI: 1.23–2.57), $P<0.002$) and the decrease in $CD4^+$ cell count (100 $CD4^+/mm^3$ lower) (OR=1.31 (95% CI: 1.09–1.58), $P<0.004$). An analysis of lipid subfractions and atherogenicity ratios clearly indicated a proatherogenic lipid profile for the LD patients. *Conclusions:* The underlying physiopathological mechanism of LD is still unknown. However, the lipid profile of HIV-1-infected patients with a LD syndrome appears to place these patients at an increased risk of progression of atherosclerosis.

Keywords: Atherosclerosis; Cholesterol; Dyslipidemia; HIV-1; Lipodystrophy; Protease inhibitor

1. Introduction

Abnormalities in fat distribution have been amply described since 1997 among patients on highly active antiretroviral therapy (HAART) with protease inhibitors (PI) [1–7]. Lipodystrophy syndrome (LD), which associates various degrees of fat wasting and central adiposity, was initially described as a pseudo-Cushing's syndrome [1]. Fat wasting is accompanied by a reduction in subcutaneous fat, causing facial emaciation (atrophy of buccal fat pads), accentuation of facial bone structure, hollowing of the buttocks, and a pitted appearance of the lower and/or upper limbs [3–6]. Fat accumulation usually occurs in various regions (mesenteric and/or retroperitoneal, abdominal subcutaneous, cervical, supraclavicular, and mammary) [1–9]. Cases of LD have been described more frequently since the introduction of HAART that includes protease inhibitors (PI) and less often without PI [10–12]. In addition, PI give rise to disturbances in lipid metabolism [8] and glucose tolerance [9]. These metabolic distur-

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bances may be a risk factor in the development of atherosclerosis.

The principal objective of our study was to define and analyze the prevalence of LD and disturbances in glucose and lipid metabolism in a single-center cohort of HIV-1-infected patients. We compared the lipid profiles of LD and non-lipodystrophic (NLD) patients.

2. Patients and method

2.1. Patients

We studied 233 consecutive HIV-infected patients who were monitored regularly in our infectious diseases unit. They had a median age of 40.4 years (range, 19–77 years) and 69.1% were male. The inclusion period lasted 60 days (September through October 1998). All patients included in the study had been infected with HIV-1, were regularly monitored by one of the physicians in the department, and were over 18 years of age at the time of inclusion. At the end of the study, two groups were formed, i.e. one group of LD patients and one group of NLD patients, according to the criteria defined below. The final statistical analysis included all of the results collected. Each patient gave his/her informed consent to participate in the 'Aquitaine Cohort' before entering the study [13]. The Aquitaine Cohort is a hospital-based surveillance system of HIV-1-infected patients followed in participating clinical wards in southwestern France.

2.2. Method

2.2.1. Anthropometric data

The patient's weight was obtained using two mechanical balances with a difference in measurement of less than 500 g. Height was ascertained during anamnesis, and body mass index (BMI) was calculated as weight divided by squared height.

2.2.2. Clinical definition of LD

Fat wasting was defined as facial emaciation due to atrophy of buccal fat pads, accentuation of facial bone structure, a decrease in fat on the lower and/or upper limbs, a network of veins apparent on the limbs, and a loss of adipose tissue on the buttocks, while central adiposity was defined as buffalo hump, filling in of supraclavicular hollows, accumulation of subcutaneous abdominal fat, and enlarged breasts. Patients were classified in the LD group if a sign of overt LD was present, if these abnormalities in fat distribution were confirmed by the patient, and if they were not associated with any of the metabolic abnormalities defined below. Clinical and biological criteria were identical to those described in the literature [14,15]. LD syndrome was established on the basis of clinical criteria previously drawn up by clinicians in our treatment unit and necessarily confirmed by the patient and a second physician. Six practitioners who had defined the LD criteria together monitored the 233 patients. Clinical and laboratory data were collected at the same time and checked by two clinicians (including one who had not taken part in patient recruitment) using a standardized form.

2.2.3. Virology and immunological data

$CD4^+$ lymphocyte cell count (per mm^3, measured by flow cytometry) and HIV-1 virus load (in copies/ml, Chiron Quantiplex RNA HIV-1, Emeryville, CA, USA) were measured. Blood samples were collected on the day LD was diagnosed and sent to the virology laboratory within 2 h.

2.2.4. Biochemical data

The glucose–lipid profile of the fasting patients included determinations of blood glucose, total cholesterol (TC), triglycerides (TG), HDL- and LDL-cholesterol, lipoprotein (a) (Lp(a)) and two indexes of atherogenicity: total cholesterol/HDL-cholesterol (TC/HDL) and apolipoproteins A_1/apolipoprotein B ($apoA_1$/apoB) ratios. Samples of venous blood were collected from the antecubital fossa from overnight fasting patients.

Normal and impaired glucose levels were defined according to the 1998 American Diabetes Association guidelines [15]. Hypertriglyceridemia was defined as concentrations above 2.0 mmol/l, on the basis of reports of increased risk of cardiac disease with fasting values above 1.6–2.3 mmol/l [16–21]. Hypercholesterolemia was defined as concentrations above 5.5 mmol/l [19], and a low HDL-cholesterol concentration as less than 0.9 mmol/l [16–19,21,22]. The atherogenicity ratios were considered abnormal when the TC/HDL-cholesterol ratio was above 5 and the $apoA_1$/apoB ratio below 1.22. The Lp(a) level was normal for values below 300 mg/l.

2.3. Statistical analysis

Student's t-test was used in comparing the observed means of quantitative variables (results from laboratory tests) and the frequency with the Pearson χ^2-test. The homogeneity of variance was confirmed by means of Bartlett's test. Multivariate analysis used a logistic regression test with LD as the dependent variable and sex, age, BMI, AIDS stage, and $CD4^+$ cell count as independent variables. A P value below 0.05 was regarded as statistically significant.

3. Results

The mean BMI of all patients studied was within the normal limits and, in terms of immunovirological markers, the $CD4^+$ lymphocyte count was below 200/mm^3 in

Table 1
Anthropometric and immunovirological data of the 233 HIV-1-infected patients[a]

Total (n=233)	Age (years)	Weight (kg)	Height (cm)	BMI (kg/m^2)	CD4$^+$ (mm^3)	%VL<500 (copies/ml)	% AIDS stage
Mean (S.D.) or %	40.4 (9.7)	66.1 (10.7)	170.9 (7.9)	22.6 (3)	475.3 (271.3)	64.4	22.8

[a] S.D., standard deviation; VL, HIV-1 virus load; BMI, body mass index.

18.2% of cases and the virus load was below the limit of detection of 500 copies/ml in 64.4% of cases (Table 1). At the time of evaluation, of the 216 (92.7%) patients in therapy, 140 (64.8%) were receiving a protease inhibitor. We calculated the theoretical duration of exposure to antiretroviral drugs of all our patients since the first day of treatment and found no difference between patients with and without LD. These data were previously published [23].

Lipodystrophy syndrome was diagnosed in 61 patients (26.1%). Table 2 gives details of the abnormalities in fat distribution. Atrophy of buccal fat pads was noted in 91.8% of cases. Fat wasting was more common on the lower limbs than on the upper limbs (55.7 vs. 37.7%). Fat accumulation was noted in 49.2% of the cases. A comparison of clinical and viro-immunological characteristics showed some differences between the LD and NLD patients (Table 3). LD patients were older than NLD patients (38.8 vs. 44.8 years, $P<10^{-4}$). The mean BMI values differed only slightly between the LD and NLD groups. The mean CD4$^+$ lymphocyte cell count was significantly lower in the LD group than in the NLD group (395 vs. 503 cells/mm^3, $P<0.007$). Patients in the LD group were more often at the AIDS stage than those in the NLD group (38.8 vs. 17.7%, $P<10^{-3}$). Almost two-thirds of the patients had a virus load below the limit of detection of 500 copies/ml. Among those with a detectable virus load, no difference in mean virus load was observed (Table 3). Multivariate analysis (Table 4) showed a significant increased relative risk occurring with age in LD patients (10 years older, $P=0.002$) and CD4$^+$ level (100/mm^3 lower, $P=0.004$).

Table 2
Prevalence and topography of the lipodystrophy syndrome among 61 patients with lipodystrophy[a]

LD	Topography	n	%
LA	Buccal fat pads	56	91.8
	Lower limbs	34	55.7
	Upper limbs	23	37.7
FA	Abdominal adiposity	22	36.1
	Buffalo neck	8	13.1

[a] LA, lipoatrophy; FA, fat accumulation; LD, lipodystrophy.

Table 3
Univariate analysis of anthropometric and immunovirological data comparing 61 LD and 172 NLD HIV-1-infected patients[a]

Characteristics (mean (S.D.) or %)	LD patients	NLD patients	P value
Male (%)	68.9	69.2	>0.05
Age (years)	44.8 (10.2)	38.8 (9)	0.00004
BMI (kg/m^2)	21.9 (2.54)	22.8 (3.1)	0.03
CD4$^+$ (mm^3)	395 (259)	503 (270)	0.007
VL<500 (%)	67.2	72.7	>0.05
AIDS stage (%)	38.3	17.1	0.0007

[a] VL, HIV-1 virus load (copies/ml); AIDS stage, defined as per CDC 1993 classification; LD, lipodystrophic patients; NLD, non-lipodystrophic patients; BMI, body mass index.

Glucose and lipid metabolic abnormalities were common in the 233 patients studied (Table 5): hyperglycemia in 13.4%, hypercholesterolemia in 15.9%, hypertriglyceridemia in 61.1%, an elevation in Lp(a) in 19.6%, an elevation in the total cholesterol/HDL-cholesterol ratio in 48.5%, and an elevation in the apoA$_1$/apoB ratio in 66.1% of cases. Of the 61 LD patients, 48 (78.1%) had metabolic abnormalities: 10 (16.4%) had hyperglycemia, 38 (62.3%) hypercholesterolemia, and/or 35 (57.4%) hypertriglyceridemia. Metabolic abnormalities according to the type of LD were also studied. Results are summarized in Table 6.

In our study, the mean TC level (5.62, standard deviation (S.D.)=1.45 mmol/l) was greater than the cut-off value of 5.5 mmol/l. That was the direct consequence of the increased TC level in LD patients (6.01, S.D.=1.39 mmol/l). The mean TC level in NLD patients was below the limit of 5.5 mmol/l (5.48, S.D.=1.44 mmol/l). The mean TG level in the entire patient population was high (2.37, S.D.=1.85 mmol/l); it was 3.10 vs. 2.11 mmol/l in the LD and NLD groups, respectively ($P<0.0003$).

Although the mean TC level was not higher than normal in the NLD patients, the difference between LD and NLD patients was significant ($P=0.014$). Mean blood glucose values were normal in both groups. Results show that HDL-cholesterol levels was lower, and LDL-cholesterol higher, in LD patients than in NLD patients. The TC/HDL ratio was greater than 5 in the total patient population (particularly in LD patients) and the apoA$_1$/apoB ratio was

Table 4
Multivariate analysis (logistic regression) of anthropometric, virological and immunovirological parameters in LD and NLD HIV-1-infected patients[a]

Variable	OR	95% CI	P value
Age (10 years older)	1.78	1.23–2.57	0.002
CD4$^+$ (100/mm^3 lower)	1.31	1.09–1.58	0.004

[a] CI, confidence interval.

Table 5
Comparison of glucose level and lipid profile between LD and NLD patients[a]

Biological parameters	Total (n=233)	LD patients (n=61)	NLD patients (n=172)	P value[b]
Glucose (mmol/l)	5.25±1.38	5.41±1.70	5.19±1.23	>0.05
Total cholesterol (mmol/l)	5.62±1.45	6.01±1.39	5.48±1.44	0.014
Triglycerides (mmol/l)	2.37±1.85	3.10±2.19	2.11±1.64	0.0003
HDL cholesterol (mmol/l)	1.18±0.38	1.05±0.34	1.22±0.39	0.0036
LDL cholesterol (mmol/l)	3.54±1.30	3.85±1.41	3.43±1.24	0.034
TC/chol HDL	5.23±1.94	6.07±2.15	4.93±1.78	0.0002
$ApoA_1$/ApoB	1.40±0.65	1.21±0.63	1.47±0.65	0.008
Lp(a) (mg/l)	225.3±285.2	255.1±302	214.2±279	>0.05
Hemoglobin (g/dl)	14.1±1.35	14.3±1.42	14±1.3	>0.05

[a] Results are indicated as mean±S.D. TC, total cholesterol; $ApoA_1$, apolipoprotein A_1; ApoB, apolipoprotein B; Lp(a), lipoprotein (a).
[b] Comparison between LD and NLD patients.

below 1.22 only in LD patients. The Lp(a) level was identical in the two groups.

4. Discussion

In HIV-1-infected patients, HAART including a protease inhibitor has resulted in a significant reduction in virus load and restoration of immune response, leading to decreased morbidity and mortality associated with HIV-1 infection [24–26]. Since they first came into use, PI have been held responsible for causing disturbances in glucose and lipid metabolism, as well as abnormalities in the distribution of adipose tissue [27]. Abnormalities in fat distribution during the course of HIV infection remain unexplained.

Recently, Carr et al. proposed a case definition for protease inhibitor-related LD syndrome associating one or more clinical and biological data [14]. Our clinical classification was identical, but only 78.1% of our LD patients had metabolic disorders (fast insulinemia and C-peptide levels were not measured in our study). On the basis of our classification criteria, it appears that our LD patients were older, were more frequently at the AIDS stage, and had a lower $CD4^+$ cell count than NLD patients. Although the repercussions of chronic viral replication have yet to be evaluated, a single determination of plasma virus load does not appear to be correlated with the occurrence of LD. The prevalence of LD cases in our study was low (26.1%) and may have been the result of rigorously selecting advanced cases which, relying on confirmation by the patient, reduced the subjective component of a purely clinical syndrome. However, in our longitudinal study, preliminary results show an increased prevalence of LD cases in the course of time, namely, 36% at 6 months and 45% at 12 months (data analysis in progress). The etiology of LD syndrome remains unknown. Certain antiretroviral molecules seem to be implicated in the unexpected LD syndrome and metabolic disorders, particularly the combined antiretroviral therapy including PI. Nevertheless, these clinical and biological abnormalities are probably the result of demographic, clinical, immunological, virological, and pharmacological factors that affect HIV-1 patients [28,29].

The concept of atherogenicity in HIV-infected patients had already been mentioned in the early 1990s [30,31]. The recent description of cases of cardiovascular complications during the administration of more active therapy raises the problem of potential vascular risks in HIV patients [32], but it is not a true reflection of the cardiovascular risk in HIV-1-infected patients. Although these complications do not pose an immediate public health problem, the long-term vascular risks related to such clinical and laboratory abnormalities need to be defined. PI also give rise to glucose and lipid disorders without LD. Moreover, if LD is responsible for metabolic disturbances (insulin resistance, hypertriglyceridemia, and hypercholesterolemia), an accumulation of several vascular risk factors (antiretroviral therapy and mobilization of adipose tissue) may induce acceleration in the progression of atherosclerosis. Hence, LD patients should be monitored if they have an atherogenic lipid profile.

Table 6
Metabolic abnormalities (%) in the lipodystrophy subgroups[a]

Total LD (n=61)	Glyc>6.1 mmol/l (%)	TC>5.5 mmol/l (%)	TG>2.0 mmol/l (%)	HDLc<0.9 mmol/l (%)	TC/HDLc >5 (%)	$ApoA_1$/ApoB <1.22 (%)	Lp(a)>300 mg/l (%)
LA (n=60)	15.1	23.3	86	60.5	52.3	78.1	25.6
FA (n=30)	10.0	36.7	93.3	60.0	53.3	83.3	20.0
MS (n=29)	10.3	37.9	93.1	62.1	55.2	82.6	17.2

[a] LD, lipodystrophy; LA, lipoatrophy; FA, fat accumulation; MS, mixte syndrome; Glyc, glycemia; TC, total cholesterol; TG, triglyceride; Lp(a), lipoprotein (a).

Hypercholesterolemia is a vascular risk factor for coronary atherogenicity [33,34], quite independent of any other risk factors. Numerous studies carried out in atheromatous patients have clearly demonstrated the protective role of an increase in the plasma HDL-cholesterol level [35,36] and the deleterious role of an elevation in LDL-cholesterol [37,38]. Modified LDL have a direct cytotoxic effect on endothelial cells [39–42]. It has been clearly shown that a high plasma LDL-cholesterol concentration is a major risk factor for the progression of atherosclerosis [22]. In our study, we show that mean total- and LDL-cholesterol levels in LD patients are significantly increased.

There is a close link between hypertriglyceridemia and cardiovascular atheromatous disease [43,44]. In HIV-1-infected patients, hypertriglyceridemia is thought to be the result of insulin resistance, possibly due to the mobilization of subcutaneous adipose tissue. Although increased triglyceride levels were reported before HAART became available [45], PI seem to play a major role in recent reports of hypertriglyceridemia [46].

Lp(a) is similar in structure to the LDLs and its atherogenic potential is acknowledged at plasma concentrations greater than or equal to 300 mg/l. Since the Lp(a) level is 90% genetically determined, it is not surprising that similar Lp(a) levels were noted in both LD and NLD patients in our study.

Viral infection in endothelial cells may be a possible triggering factor in atherogenesis [47]. It has been clearly shown that HIV infection of endothelial cells constitutes a risk factor for the progression of atherosclerosis. The recent increase in life expectancy of HIV-1-infected patients may also be a factor that encourages the progression of atherosclerosis.

At present, the question is whether metabolic disorders associated with LD increase the risk of atheromatosis diseases and to what extent this risk may be affected by the various antiretroviral therapies. Future longitudinal studies will make it possible to accurately define incident cases of LD, lipid profile evolution, and the corresponding associated therapies.

Several recent studies show that coronary heart diseases have not increased [48–50], but exposure to clinical and metabolic abnormalities may be a cause of arterial disease progression in the long run. If LD patients have an evident atherogenic lipid profile compared with NLD patients, it will be necessary to clearly specify monitoring and appropriate management. Arterial non-invasive morphological analysis using carotid intima media thickness by B-mode echography has recently been proposed as a way of predicting atheromatous disease progression in HIV-1-infected patients [51–53].

The classification criteria of LD cases in our study make it possible to select a population at risk for atherosclerosis. The metabolic disorders observed must be monitored and potential therapeutic measures suggested. Although the use of more active antiretroviral therapy for HIV infection seems to be partly responsible for cases of LD, it appears difficult to accurately define the degree of responsibility of individual antiretroviral therapies. Although no evidence is thus far available, the results of our study lead one to suspect virological, immunological, and pharmacological factors of being implicated in LD in HIV-1-infected patients. The lipid profile of HIV-infected patients with a LD syndrome can place them at risk for progression of atherosclerosis. It is, therefore, necessary to use B-mode echography, such as carotid intima media thickness, when examining a large population of HIV-infected patients.

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