

Lipodystrophy in a cohort of HIV infected antiretroviral treated and naive Indian patients: prevalence and associated factors

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ABSTRACT

Introduction: Body-shape abnormalities are common among HIV-infected patients whether or not they are receiving antiretroviral therapy. No studies from India have profiled their prevalence.

Objectives: We studied the prevalence of body-shape abnormalities among a cohort of HIV infected patients attending the Immunodeficiency Clinic at our Institute.

Material & Methods: Seventy seven patients were administered a standard questionnaire, that enquired about altered fat distribution in the face, neck, arms, breasts, abdomen, buttocks, and legs and prominence of the veins of the extremities. Changes were classified as being "mild" or "severe". "Peripheral fat loss" was represented by any decrease in fat in the face, arms, or legs or prominent veins in the arms or legs. "Central fat gain" was defined by increased fat in the abdomen, neck, or breasts.

Results: Of the 77 patients, 34 were not receiving any antiretroviral medication, 23 were receiving a combination of stavudine, lamivudine and nevirapine, and 20 were being administered a combination of zidovudine, lamivudine and efavirenz. Their median CD4 counts were 135.5. There were no body-shape abnormalities in 44 (57.1%) individuals while as it was peripheral in 11, central in 5 and mixed in 17 subjects.

Conclusions: Body-shape abnormalities occurred in a significant percentage of patients with HIV infection, including those who had not received antiretroviral therapy. This could compromise regular adherence to antiretroviral therapy. [IJEM 2007;11(1&2:19-22)]

Key words: Antiretroviral therapy, AIDS, fat redistribution, HIV, lipodystrophy

INTRODUCTION

Metabolic and morphologic abnormalities complicating the management of human immunodeficiency virus (HIV) infection include dyslipidemia, insulin resistance, peripheral fat wasting, central fat accumulation, lactic acidemia and acidosis, reduced bone mineral density, and avascular necrosis of hip and shoulder. Large cohort studies from the West have shown that lipodystrophy is common among HIV-infected patients who receive treatment with antiretroviral drugs(1-4). Several studies have indicated that lipodystrophy is less common among

nonwhites than it is among whites(3,4). The interrelationship between these problems and role of specific antiretroviral agents and HIV infection itself in their pathogenesis have been a matter of debate(5).

Physical changes were reported soon after protease inhibitors became available and a link was suggested by the increased frequency of these changes with these agents(6-10). Recently, nucleoside reverse transcriptase inhibitors and increased viral replication have been implicated as possible causes(11-12). The prevalence of lipodystrophy is extremely variable because of the absence of a uniformly accepted definition, variability in diagnostic techniques, short duration of follow-up and largely underpowered studies. The figure ranges from 5-83% among patients receiving protease inhibitors(7-9,13). Few studies have documented the prevalence of fat

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abnormalities among patients receiving nucleoside reverse transcriptase inhibitors(14).

Most HIV infected patients seen in our clinic have more advanced HIV disease as compared to those in the West. They are more likely to be more wasted, when first seen. The prevalence of body-shape abnormalities in Indian subjects has not been studied prospectively. In this study we analyzed the prevalence of body-shape abnormalities in a subset of our patients.

PATIENTS AND METHODS

Seventy seven successive patients attending the Immunodeficiency Clinic at the Postgraduate Institute of Medical Education and Research, Chandigarh, India were included in the study. All patients had tested positive on a panel of three ELISA tests and were more than 18 years of age. A standard questionnaire was administered to all patients. It enquired about increases or decreases in the amount of fat in the face, neck, arms, breasts, abdomen, buttocks, and legs. It also asked whether the patients had noticed increased prominence of the veins of the arms or legs. Patients rated the changes as "mild" (i.e., similar to the appearance of the body part at sometime in the past) or "severe" (i.e., the body part had never had this appearance before). Patients were also asked about details of weight loss, notably in the face, front of neck, back of neck, breasts, legs, buttocks, thighs and the presence of fat lumps. In addition note was made of the height, weight and body mass index (BMI) of these patients, current CD4 count and treatment and acute phase response in the form of erythrocyte sedimentation rate.

Since most patients in our Clinic are unable to afford protease inhibitors, almost all the patients are administered a combination of one non-nucleoside and two nucleoside reverse transcriptase inhibitors. Patients either received a combination of zidovudine, lamivudine and efavirenz (Efavirenz based) or stavudine, lamivudine and nevirapine (Nevirapine based). The former requires an intake of three pills daily and, the latter, two.

Descriptive statistics were used. The results were analyzed using analysis of variance (ANOVA). A *p* value less than 0.05 was considered significant. The study was carried out after obtaining permission from the Institute's Ethics Committee.

RESULTS

Out of a total of 77 patients who were assessed, 33 (42.9%) showed evidence of body-shape abnormalities. The clinical characteristics were similar in the two groups as shown in Table 1. However, individuals with body-shape abnormalities had lower CD4 counts when compared with individuals who did not have these abnormalities. Twenty patients received the efavirenz based combination and 24 received the nevirapine based combination. The mean (+

Table 1: Characteristics of patients with and without body-shape abnormalities

Feature	Patients with no body- shape Abnormalities (n=44)	Patients with body- shape abnormalities (n=33)
Mean Age, years (+SD)	35.3(+9.9)	35.2(+7.9)
Body Mass Index, mean(+SD)	19.3(+5.4)	19.9(+3.8)
Sex ratio (Male: Female)	29:15	25:8
Infection in the past 6 months	15	10
Evidence of current infection	7	5
Current CD4 count, Median*	142.5	120.5
Number of patients receiving ART	26 (59%)	17 (51%)

*CD4 counts among patients with no body shape abnormalities were higher than those with these defects (P 0.03)

SD) duration of follow-up of all the patients was 6.2 (+4.9) months. Patients receiving efavirenz based therapy were followed up for a mean of 6.6 (+4.9) months, while those receiving nevirapine had been followed up for 5.9 (+5.1) months.

The characteristics of individuals who had body-shape abnormalities are shown in Table 2. Eleven patients

Table 2: Characteristics of patients with body-shape abnormalities

Feature	Peripheral (n=11)	Central (n=4)	Both (n=18)
Mean Age, years (+SD)	33.3(+7.4)	49.8(+7.1)	35.3(+9.1)
BMI, mean (+ SD)	19.7(+4.2)	18.6(+1.8)	21.2(+5.1)
Sex ratio (Male: Female)	7:4	2:2	15:3
Infection in the past 6 months	2	2	6
Evidence of current infection	2	1	3
Current CD4 count, median	106	554.5	117
No. of patients on ART	6	2	9
Hemoglobin, mean (+ SD)	11.2(+2.3)	12.2(+0.9)	11.4(+1.4)
ESR (mm/1st hr) (+ SD)*	48.3(+33.1)	55.0(+0.9)	33.5(+17.5)

*Patients with peripheral lipodystrophy had higher ESR than individuals with both peripheral and central lipodystrophy (*p*<0.05). No of patients with central obesity alone was too few for a meaningful comparison with other groups.

had peripheral body-shape abnormality, while four had central body-shape abnormality. Eighteen of the 33 individuals had body-shape abnormality that involved both the central and peripheral pattern. There was no significant difference between the three groups in the major characteristics like past and current opportunistic infections, use of antiretroviral therapy (ART), CD4 count and BMI (*p*>0.05). Patients with peripheral lipodystrophy had a median CD4 count of 106/mm³, while those

with both peripheral and central lipodystrophy had a median CD4 count of 117/mL.

Patients were analyzed for the presence of body-shape abnormalities depending upon the use of antiretroviral medication (Table 3). Fifty nine percent patients with no

Table 3: Prevalence of body-shape changes according to antiretroviral treatment*

Body-shape change, Location	All (n=77) (%)	Not receiving ART (n=34) (%)	Receiving ART (n=43) (%)
Fat Loss			
Face	38 (49.3)	16 (47.1)	22 (51.2)
Neck	19 (24.6)	9 (26.47)	13 (30.2)
Arms	32 (41.5)	14 (41.1)	18 (41.9)
Breasts	5 (6.5)	1 (2.9)	4 (9.3)
Abdomen	5 (6.5)	2 (5.8)	3 (6.9)
Buttocks	22 (28.6)	10 (29.4)	12 (27.9)
Legs	15 (19.5)	6 (17.6)	9 (20.9)
Prominent veins	3 (3.9)	1 (2.9)	2 (4.7)
Fat gain			
Face	21 (27.2)	13 (38.2)	8 (18.6)
Neck	22 (28.6)	9 (26.4)	13 (30.2)
Arms	10 (12.9)	6 (17.6)	4 (9.3)
Breasts	11 (14.3)	6 (17.6)	5 (11.6)
Abdomen	27 (35.1)	15 (44.1)	17 (39.5)
Buttocks	6 (7.8)	2 (5.8)	4 (9.3)
Legs	10 (13)	4 (11.7)	6 (14)

*None of the parameters were significantly different between those who received ART and those who did not. References

body shape abnormalities were receiving antiretrovirals, while 51% patients receiving them had these abnormalities. The sites of involvement for fat loss, in terms of decreasing order of prevalence, were the face, buttocks, arms and legs and neck. A higher percentage of individuals receiving antiretroviral therapy had fat loss involving the neck, arms and breast, when compared with those who did not receive such medication but this did not reach statistical significance ($p > 0.05$). When fat gain was analyzed, patient's not receiving antiretrovirals had greater fat gain on the face and arms, while those who had received antiretrovirals had more fat gain at the back of the neck, but this, too, did not reach statistical significance ($p > 0.05$).

DISCUSSION

There is a paucity of information regarding body-shape abnormalities among Asian subjects with HIV infection. One study published from Singapore reported peripheral fat loss among 46% of subjects, central fat gain in 32%, and 8% patients overall had a mixed clinical presentation(14). Another study from South India has reported eight patients who had lipodystrophy out of a cohort of 286 patients who were receiving antiretroviral(15).

In the present evaluation of a cohort of unselected

HIV-infected patients seen at a single referral center, self-reported body-shape changes were common; with 42.9% of patients overall and 58.4% of patients receiving an antiretroviral drug reported some body-shape abnormality. Twenty five percent patients receiving nevirapine based regimen, which included stavudine, had body-shape abnormality, while 52.3% patients receiving efavirenz based regimen showed such changes. Comparison of study cohorts is difficult because of differences in the methods of data collection, the definitions of body-shape abnormalities, the patterns of antiretroviral drug use, and the prevalence of other possible risk factors. However, our figures do not differ markedly from those from published studies of large, predominantly white cohorts in which the overall prevalence of lipodystrophy is 38% to 50% in unselected patients(2,3,16).

This study suggests there is a high prevalence of body-shape abnormalities among HIV infected individuals regardless of the treatment administered to them. This is significant as results of studies carried out in the context of body-shape abnormalities have suggested that protease inhibitors are primarily causative(1,2). None of our patients received protease inhibitors. The reason for this is two-fold. First, antiretrovirals have been in use only for a few years in our patients. Second, generic version of drugs, especially a combination of nevirapine, lamivudine and stavudine is available at less than Rs. 50 per day and are the preferred regimens in India.

A recent study carried out in 25 asymptomatic antiretroviral-naïve HIV infected patients and 25 healthy control subjects study showed that HIV-infected patients who had never been treated with antiretrovirals had decreased mitochondrial DNA levels, along with decreased enzyme activity of the mitochondrial respiratory chain complexes and other metabolic pathways, as well as increased oxidative damage of the peripheral blood mononuclear cell membranes(17). This might provide an explanation why patients who have never been treated with antiretrovirals may develop body-shape abnormalities. Additional mechanisms that might hasten the development of lipodystrophy include tumor necrosis factor (TNF)- α gene polymorphism. One study has reported that $_238$ (but not the $_308$) promoter region TNF- α gene polymorphism is a determinant in the development of HIV-related lipodystrophy(18). It is also possible that the virus can infect adipose cells and this might influence replication of these cells. One recent study has suggested that significant increase in Gagp24 production was observed after stimulation of infected adipocytes with pro-inflammatory cytokines, such as TNF- α or interleukin-1- β -, suggesting that HIV-1 does infect human adipose cells in vitro(19).

Our study was based on the patients self-reporting of changes and, it did not include physician assessment.

However, there is a high level of concordance noted previously between subjective patient self-reports and physician-based reports that suggests that the latter may make a relatively small contribution¹. Some self-reported fat changes could be due to normal variation in the pattern of diet and exercise over time, by aging, and by opportunistic infections⁽²⁰⁾. The nonspecific appearance of these changes might make it difficult to distinguish them from lipodystrophy by subjective assessment alone. Although histories of recent opportunistic infection and weight loss that satisfies the criteria of wasting may help to distinguish some cases, the timing and thresholds are arbitrary, and, indeed, the various processes may overlap. Additionally, drug induced lipodystrophy takes months if not years to appear. In this study, a mean follow up of just over 6 months may be inadequate to determine the exact prevalence of fat redistribution as a consequence of drug use.

The major problem that has existed in defining the prevalence of lipodystrophy has been the absence of a uniformly accepted case definition. Shortly after we collected our data, an objective case definition for this disorder appeared that was based on a case-control study⁽²¹⁾. This was based on 1081 consecutive HIV, infected patients. The authors suggested the use of several variables that included demographic (sex, age, duration of HIV disease, and clinical stage), clinical (waist/hip circumference ratio), metabolic (anion gap, HDL cholesterol) and body composition (leg fat, trunk/limb fat ratio, intra-abdominal/subcutaneous abdominal fat ratio) factors. Each of these variables was assigned a score and, on the basis of the net score, different levels of sensitivity and specificity were calculated. As opposed to their cohort, which had 15% females, nearly 30% subjects in our study were women. This is significant as in their study; female sex carried an odds ratio of 9.33, as opposed to men who had the odds ratio of 1. Another significant difference in our study cohort was that our patients had advanced disease. Although not strictly comparable, the mean current CD4 counts in their study was greater than 450/mL in each of their subgroups, while the median current CD4 count in our patients with no body shape abnormalities was 142.5/mL and those with these defects, it was 120.5/mL.

CONCLUSION

The importance of lipodystrophy is not so much in the actual changes in body shape themselves, but in the possible impact of the changes on the patient's quality of life. The adverse effects of treatment on quality of life may potentially decrease motivation and compliance with therapy or may result in stopping therapy.

REFERENCES

1. Carr A, Samaras K, Thorisdottir A, Kaufmann GR, Chisholm DJ, Cooper DA: Diagnosis, prediction, and natural course of HIV-1 protease-inhibitor-associated lipodystrophy, hyperlipidemia, and

- diabetes mellitus: a cohort study. *Lancet* 1999; 353:6:209-39.
2. Currier JS, Havlir DV: Complications of HIV disease and antiretroviral therapy. *Top HIV Med* 2005; 13:16-23.
3. Lichtenstein KA, Ward DJ, Moorman AC, *et al*: Clinical assessment of HIV-associated lipodystrophy in an ambulatory population. *AIDS* 2001; 15:1389-98.
4. Martinez E, Mocroft A, Garcia-Viejo MA, *et al*: Risk of lipodystrophy in HIV-1-infected patients treated with protease inhibitors: a prospective cohort study. *Lancet* 2001; 357:5928.
5. Nolan D, Gaudieri S, John M, Mallal S: Impact of host genetics on HIV disease progression and treatment: new conflicts on an ancient battleground. *AIDS* 2004;18:1231-1240.
6. Sanchez Torres AM, Munoz Muniz R, Madero R, *et al*: Prevalence of fat redistribution and metabolic disorders in human immunodeficiency virus-infected children. *Eur J Pediatr* 2005; 164:271-6.
7. Carr A, Cooper D: Lipodystrophy associated with an HIV-protease inhibitor. *N Engl J Med* 1998; 339:1296.
8. Lipsky JJ: Abdominal fat accumulation in patients with HIV-1 infection. *Lancet*. 1998; 351:847-8.
9. Mishriki YY: Baffling case of bulging belly. Protease punch. *Postgrad Med* 1998;104:45-6.
10. Saint-Marc T, Poizot-Martin I, Partisani M, Fabre J, Touraine JL: A syndrome of lipodystrophy in patients receiving a stable nucleoside-analogue therapy [abstr] in Program and Abstracts of the 6th Conference on Retroviruses and Opportunistic Infections, Chicago: Jan 31-Feb 4, 1999.
11. Gervasoni C, Ridolfo AL, Trifiro G, *et al*: Redistribution of body fat in HIV-infected women undergoing combined antiretroviral therapy. *AIDS* 1999;13:465-71.
12. Kotler DP, Rosenbaum K, Wang J, Pierson R: Studies of body composition and fat distribution in HIV-infected and control subjects. *J AIDS* 1999; 20:228-37.
13. Miller KD, Jones E, Yonavska JA, Shankar R, Feuerstein I, Falloon J: Visceral abdominal fat accumulation associated with use of indinavir. *Lancet* 1998; 351:871-5.
14. Paton NI, Earnest A, Ng YM, Karim F, Aboulhab J: Lipodystrophy in a Cohort of Human Immunodeficiency Virus Infected Asian Patients: Prevalence, Associated Factors, and Psychological Impact. *Clin Infect Dis* 2002; 35:1244-49.
15. Saghayam S, Chaguturu SK, Kumarasamy N, Solomon S, Mayer KH, Wanke C: Lipodystrophy Is the Predominant Presentation of HIV-Associated Lipodystrophy in Southern India. *Clin Infect Dis* 2004;38:16467.
16. Heath KV, Hogg RS, Chan KJ, *et al*: Lipodystrophy-associated morphological, cholesterol and triglyceride abnormalities in a population-based HIV/AIDS treatment database. *AIDS* 2001; 15:2319.
17. Miro O, Lopez S, Martinez E, Pedrol E, Milinkovic A, Deig E, *et al*: Mitochondrial Effects of HIV Infection on the Peripheral Blood Mononuclear Cells of HIV-Infected Patients Who Were Never Treated with Antiretrovirals. *Clin Infect Dis* 2004; 39.
18. Maher B, Alfirevic A, Vilar FJ, *et al*: TNF- α promoter region gene polymorphisms in HIV-positive patients with lipodystrophy. *AIDS* 2002; 16:2013-2018.
19. Maurin T, Saillan-Barreau C, Cousin B: Tumor necrosis factor- α stimulates HIV-1 production in primary culture of human adipocytes. *Experimental Cell Research* 2005; 304: 544-51.
20. Paton NI, Macallan DC, Jebb SA, *et al*: Longitudinal changes in body composition measured with a variety of methods in patients with AIDS. *J Acquir Immune Defic Syndr Hum Retrovirol* 1997; 14:11927.
21. HIV Lipodystrophy Case Definition Study Group. An objective case definition of lipodystrophy in HIV infected adults: a case-control study. *Lancet* 2003; 361: 726-35.

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