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Original Article

Internal Medicine Section

Lipodystrophy in Human Immunodeficiency Virus (HIV) Patients on Highly Active Antiretroviral Therapy (HAART)

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ABSTRACT

Background: In recent years, abnormal lipid deposition (both lipoatrophy and fat redistribution) and its related complications have changed from an anecdotal issue into a major problem for HIV (Human Immunodeficiency Virus) infected patients on HAART (Highly Active Anti-Retroviral Therapy). Lipoatrophy and fat redistribution are potentially stigmatizing complications of HAART and leads to poor adherence among patients. Hence we conducted this study to determine the pattern and to assess various risk factors for maldeposition of lipids in HIV patients.

Materials and Methods: A cross-sectional case series study was conducted in ART PLUS centre, Bellary over a period of 8 months from January to August 2014 in HIV patients on ART to determine risk factors associated with and epidemiological pattern of fat redistribution or atrophy.

Results: A total of 50 patients with LD {lipodystrophy} (26 with fat redestribution and 24 with lipoatrophy {LA} were diagnosed in this period. Most of them belonged to younger age and was commonly seen in females (76%). Patients with LA had a significantly lower BMI (18.73 ± 7.4), {the p-value being 0.19} compared to LH group (21.54 ± 7.62). The duration of disease was comparable among both groups (6.96 years in LH and 5.79 years in LA group) {p-value is 0.29}. There was a relatively good immunity among these patients with mean CD4 count was 509.23 in LH and 545.91 in LA group {single CD4 count was taken and the p-value was 0.001}. Most of the patients were in TLN (Tenofovir, Lamivudine, Nevirapine) regimen (58%). The duration that patient was on ART before commencement of study varied from patient to patient, but the mean duration was approximately five years in fat redistribution group and 4.5 years in LA group. There were no derangements in lipid and sugar levels among them.

Conclusion: This study shows the need to identify and impact of LD with respect to treatment adherence in young patients especially female patients. Early community based screening for LD by social workers and targeted annual screening might help early detection and awareness about LD. Also adopting the least toxic regimen is one of the main aspects of LD management.

Keywords: Fat redistribution, Lipoatrophy, Lipohypertrophy, Treatment adherance

INTRODUCTION

Highly Active Anti-Retroviral Therapy (HAART) has markedly improved the morbidity and mortality of persons with Human Immunodeficiency Virus (HIV) infection. Meanwhile with prolonged use, the duration of HAART toxicities is becoming more evident.HIV associated Lipodystrophy (LD) is one such problem characterized by selective damage of adipose tissue resulting from antiretroviral drugs and also HIV disease per se. LD is a term used to embrace peripheral LA, localized fat accumulation (visceral, back of neck and lipomata), hyperlipidaemia, insulin resistance and hyperglycaemia [1]. But later on it was discovered that “HIV associated lipodystrophy” was not a single syndrome and consisted of atrophy, fat redistribution and a mixed picture. Therefore these 3 entities are considered separately [2,3]. The prevalence rate of Lipid distribution abnormalities in patients on HAART is reported to be up to 40% [1,4]. Milinkovic and Martinez in 2005 provided an excellent review in this journal on the definition, measurement and management of LD. 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 [5].

LD also has a profound influence on health related quality of life by decreasing patients social functioning and dissatisfaction about body image and disease per se. Also, facial LA can significantly affect a patient’s “relation- ship” with his or her regimen, potentially resulting in poor adherence or termination of therapy altogether, even if the regimen is achieving a desired effect on viral load and CD4+ cell counts [6]. Additionally, patient’s subsequent dysphoria about their body changes could significantly decrease their level of adherence and promote development of drug resistance [7-9].

Apart from cosmetic reason, LD has become a peripheral marker of HIV in community, through which individuals are identified. This poses an alarming ethical issue since it separates these patients from others.

Although LH and LA can occur together, both presentations are thought to occur independently from each other and to have different risk factors. Disease-related factors include HIV infection as well as inflammation, immune activation, and immune depletion. The pathogenesis of LA is linked to severe mitochondrial dysfunction, oxidative stress and inflammation, while LH is related to mild mitochondrial dysfunction and cortisol activation, promoted by inflammation [10]. Accompanying complications may include hypertension, proteinuric kidney disease acanthosisnigricans, and polycystic ovary syndrome.The risk of development of lipoatrophy or fat redistribution is mainly related to nucleoside reverse transcriptase inhibitors (NRTIs) and protease inhibitors (PIs) [11].

While not typically life-threatening, it can lead to comorbidities and is associated with a variety of adverse outcomes including accelerated cardiovascular disease and aging. It is important to determine the cause and also to rule out other causes like Cushing’s syndrome and obesity which can co-exist with HIV disease. Epidemiological data show an increased risk of HIV-associated LD in women, older patients, lower CD4 cell count, lower body mass index and/or AIDS diagnosis, as well as opportunistic infections [12]. Hence, we conducted this observational case series study to determine the pattern and to assess various risk factors for LD in HIV patients in our ART-PLUS centre attached to Vijayanagara Institute of Medical Sciences (VIMS), Bellary, India.

Aims and objectives

To study the clinical spectrum of lipoatrophy and fat redistribution among HIV patients in south India who are on HAART treatment and its possible effect on compliance with HAART treatment.

MATERIALS AND METHODS

This is a cross-sectional case series study conducted in ART PLUS centre attached to VIMS, Bellary, India, over a period of 8 months from January 2014 till August 2014. All patients coming for follow-up to ART–PLUS centre, outpatient and admitted patients in Medicine department are screened clinically for LA and fat-redistribution and following parameters are studied. Clinical assessment for LA was done by measuring the triceps skin fold thickness. If it was found to be less than 10th percentile of normal (according to National Health and Nutrition Examination Survey for sex and age) then the patient was said to have LA. For fat redistribution assessment waist – hip ratio (>0.95 for men and >0.85 for women), abdominal circumference (>102 for men and >88 for women) and "pinchable" fat at waistline were the criterias used. Clinical and demographic data including duration of disease (a mean of 5 years for fat redistribution and 4.5 for LA group), presence of co-morbidities and opportunistic infections, and relation with CD4 count were studied. An institutional ethical clearance was taken and a preformed consent is taken from the patient before including into the study. Patients who are critically ill, associated liver and renal diseases, hypothyroidism, other chronic diseases and patients taking steroids were excluded from the study. Patients with HIV not taking ART were also excluded.

RESULTS

A total of 50 patients on HAART with clinically diagnosed LD were included in the study. Among them, 26 had fat redistribution and 24 with LA. Percentages among fat redistribution, abdominal obesity and hump in back were the predominant pattern and in LA, loss of buccal pad of fat, loss of fat in buttocks, thigh and arms were the major presentations [13]. Females were the predominant group among them with 76% and males constituted 24%.

Fat redistribution was commonly seen in younger group of patients. Age <45 years represented 46% among males and 30% among females. Mean age of patients was 23 {p-value is 0.06}. Also, most of patients with both LA and fat redistribution were illiterates [14] {p-value is 0.04} and had studied till primary school, representing the patients with minimal knowledge on LD or its metabolic complications.

Patients with LA had a significantly lower BMI (18.73 ±7.4) compared to LH group (21.54 ± 7.62). The associated co-morbidities and opportunistic infections along with other clinical and demographic data are represented in [Table/Fig-1]. The duration of disease was comparable among both groups (6.96 years in LH and 5.79 years in LA group). There was a relatively good immunity among these patients with mean CD4 count was 509.23 in LH and 545.91 in LA group and none of them were in second line treatment.

The fasting lipid profile, FBS and PPBS was comparable in both groups and are represented in [Table/Fig-2]. There were no derangements in fasting lipid profile or sugar levels in LD patients. Also, it was well controlled in 5 of the Diabetic patients who were on oral hypoglycemic drugs. Most of the patients were in TLN (Tenofovir, Lamivudine, Nevirapine) regimen (58%) followed by ZLN (Zidovudine, Lamivudine, Nevirapine {26%}), SLN (Stavudine, Lamivudine, Nevirapine {12%}) and ARLT (Atazanavir, Ritonavir, Lamivudine, Nevirapine {2%}) regimen.

DISCUSSION

As in other studies, this study considered presence of fat redistribution and LA in HIV patients on the basis of physical evaluation by the study doctors which may be subjective. The study was observational study and relied on a subjective clinical definition along with BMI, waist hip ratio; abdominal circumference and triceps skin fold thickness.

Parameters		Lipohypertrophy (n=26)	Lipoatrophy (n=24)
Gender (in numbers)	male	6	6
	female	20	18
Age (in years)-	- <45	23	15
	->45	3	9
Literacy- illiterate		8	14
-primary school		11	9
- secondary education		7	1
Co-morbidities- Anemia		8	6
-Diabetes mellitus		3	2
Duration of HIV (in years)		6.96 ± 4.06	5.79 ± 3.68
Body Mass Index (BMI)		21.54 ± 7.62	18.73 ± 7.4
Presence of Opportunistic infections			
1. Candidiasis		6	5
2. Tuberculosis		3	4
3. Cryptococosis		1	-
Mean CD4 count (in cells/microliter)		509.23	545.9
Haart Regimen			
1.TLN		14	15
2.ZLN		7	6
3.SLN		4	2
4.ARLT		1	-

[Table/Fig-1]: Represention of demographic data and clinical parameters in HIV patients with Lipodystrophy
T- Tenofovir; L- Lamivudine; N- Nevirapine; Z- Zidovudine; S- Stavudine; A- Atazanavir; R- Ritonavir

Investigations	Lipohypertrophy	Lipoatrophy
FBS	146.21	121.62
PPBS	176.14	160.54
Total Cholesterol	242.62	228.31
Triglyceride	184.22	189.63
Hdl Cholesterol	34.6	28.7
Ldl Cholesterol	181.1	154.3

[Table/Fig-2]: Demonstration of haematological parameters in patients with lipodystrophy at the time of interview

Drug	LA	LH	Dyslipidaemia	Insulin resistance
Stavudine (d4T)	+++	++	++	++
Zidovudine (AZT)	++	+	+	++
Didanosine (DDI)	+/-	+/-	+	+
Lamivudine (3TC)	0	0	+	0
Abacavir (ABC)	0	0	+	0
Tenofovir (TDF)	0	0	0	0
Emtricitabine (FTC)	0	0	0	0
Efavirenz (EFV)	+/-	+/-	HDL<++	+
Nevirapine (NVP)	0	0	HDL<+	0
Ritonavir (RTV)	+/-	+	+++	++
Indinavir (IDV)	+/-	+	+	+++
Lopinavir (LPV)	+/-	+	++	++
Saquinavir (SQV)	+/-	+	+/-	+/-
Atazanavir (ATV)	0	++	+/-	0
Darunavir (DRV)	0	+	+/-	+/-
Enfuvirtide (INN)	Insufficient data	Insufficient data	0	0
Maraviroc (MVC)	Insufficient data	Insufficient data	0	0
Raltegravir (RAL)	Insufficient data	Insufficient data	0	0

[Table/Fig-3]: The effects of different ART drugs on fat and metabolism [10]

[Table/Fig-4]: Lipohypertophy of cervicodorsal region in a patient

In our study, fat redistribution was commonly seen in younger group of patients. Age <45 years (n = 38) represented 76 % of the study population.The mean age of overall study was 46 years (for <45 years mean age was 30 years and > 45 years mean age was 56 years).Overall, females were the predominant group in our study with 76% and males constituted 24% {p-value is 0.87}. Many studies have shown a higher prevalence of LD among patients with HIV. An observational study from Madurai showed a prevalence of 28% [11]. A study conducted in Thailand consisting of 166 men (60%) and 112 women (40%) had a prevalence of 21%. In that study, LD was found more frequently in men (19%) than in women (12.5%) and the mean age of LD patients was 43.59 [15].

The education level among these patients was very low showing the importance of awareness of disease and complications among them. Most of them believed LD to be a part of disease process itself and not the side effect of ART.Mean BMI were in normal range in both the groups. This is comparable with the study done in Madurai [16]. The mean duration of disease in our study was comparable with the mean duration of HIV infection and of antiretroviral therapy was 59.93 + 23.73 and 43.39 + 17.38 months respectively in the Thailand study [15].

There was a relatively good immunity among these patients with mean CD4 count was 509.23 in LH and 545.91 in LA group (statistically significant) and none of them were in second line treatment. This is in contrast to other studies done outside India where patients with LD had lower CD4 count when compared to NON-LD HIV patients [17,18]. Although our study did not show correlation between cholesterol levels with LD, hypertriglyceridemia was significantly seen in study conducted by Mauss et al., [17]. In the study by Puttawong et al, elevated total cholesterol (56%), elevated triglyceride (67%), and decreased high density lipoprotein cholesterol (37%) were seen [15]. Also, Glucose abnormalities were categorized as impaired fasting glucose (12%), impaired glucose tolerance (21%), hyperinsulinemia (27%), insulin resistance (30%) and diabetes mellitus (27%) [12] {Stavudine and zidovudine are significantly associated with diabetes in HIV patients on HAART after adjustment for risk factors for diabetes and lipids. presence or absence of lipodystrophy did not modify the relationship, suggesting that the two drugs probably directly contribute to insulin resistance, potentially through mitochondrial toxicity. Probably because in our study majority of the patients were on TLN regimen presence of drug induced diabetes was absent} [19].

Most of the patients in our study were in TLN regimen (58%) followed by ZLN (26%), SLN (12%) and ARLT (2%). Data on the effect of ART on LD exist for the NRTIs and unboostedPIs, but seem to be conflicting for the non-nucleoside reverse transcriptase inhibitors (NNRTIs) and newer PIs, and are mostly unavailable for the new drug classes. Many studies have implicated stavudine and zidovudinein the development of LD and this is generally uncontested. Abacavir and Tenofovir have been shown to have minimal effect [20]. The effects of different ART drugs on fat and metabolism are shown in [Table/Fig-3].

Lipoatrophyis defined clinically by the physical findings of any wasting of extremities, face or buttocks along with a triceps skin fold thickness <10th percentile of normal. Fat redistribution is defined fat accumulation in the abdomen and dorsocervical spine [Table/Fig-4] along with an elevated waist hip ratio, increased abdominal girth and absence of “pinchable” fat in the waist line. The leading hypothesis is that ART subsequently leads to depletion of mitochondrial DNA in subcutaneous adipocytes and uncoupling of oxidative phosphorylation resulting in cellular dysfunction and increased fat cell apoptosis. The oxidative stress induced by NRTIs/PIs play a major role in setup of LD [21,22].

Patients with advanced HIV disease clearly benefit from NRTIS and PIs in terms of disease regression, survival and reversal of some opportunistic infections. However, survival advantage in early HIV disease on comparison with the metabolic disturbance that occurs is unproven. Alternative strategies for complete suppression of HIV replication might be appropriate, particularly for those with low viral load. Although, change of regimen was recommended for LD previously, now it has been adviced to continue same regimen in view of increasing resistance and need of second line drugs in future. Furthermore, several patients with LD were mistakenly assumed to have HIV wasting syndrome with its psychological, social and economic consequences.

Longer time follow-up is required to assess whether vascular complications of insulin resistance and hyperlipidaemia will develop and whether there is significant morbidity associated with severe fat depletion, especially if the patient also develops HIV associated wasting. Here, weight loss may be aless important aspect of wasting than the loss of lean body mass. However, measuring triceps skin fold thickness, waist hip ratio and “pinchable” fat in waistline remains much easier on practical basis. Finally, evidence of fat maldistribution during antiretroviral treatment suggests abnormalities of glucose and lipid which are risk factors of coronary heart disease. Also, the changes associated with LD (body fat redistribution, dyslipidemia, and insulin resistance) are associated with cardiovascular disease. Many studies have implicated an increased risk for developing symptomatic cardiovascular disease [23]. Hence, serum lipid and glucose monitoring shall help in early diagnosis of lipodystrophy associated metabolic abnormalities.

It is important to note that the number of patients changing ART regimens because of LD appears to be decreasing over time. The Swiss HIV Cohort Study followed 5777 participants who started ART between 2000 and 2006, and compared rates of LD between 2000 and 2002, and 2003 and 2006. The findings revealed that 4% of patients had changed ART regimens due to LD during 2000-2002, whereas only 1% of patients changed during 2003-2006. This reduction was attributed to the decreased use of Zidovudine (88% v. 64%) and Stavudine (4.2% v. 0.7%) and the increased use of Tenofovir (0% v. 30%) over this time [24].

HIV/HAART-induced LD is a difficult condition to manage. There are well-established treatment modalities, but all have limitations. Treatment of dyslipidemia and alterations in glucose metabolism is the same as in non-HIV-infected individuals. LA is managed by strategic choice of antivirals or by antiviral switching, and in some cases by plastic/reconstructive surgery. The situation in patients with clinically detectable LA is less promising, as drug switching leads to only partial reversal of LA.

LH has been managed mainly by lifestyle modification with a hypocaloric diet and exercise. Although many drugs like metformin, glitazones, statins, Growth hormones (GH) and uridine are studied as potential treatment modalities, their use routinely also has some undesirable effects. Metformin and GH use could be associated with

further limb fat loss, which is unacceptable. GHRH (GH Releasing Hormone analogues) analogues offer benefits without the typical side effects associated with GH. However, both are costly and need to be given parenterally, which may not be tolerable. The efficacy of statins in treating dyslipidaemia is well established, but there is little evidence of their effects on LD. PPAR-gamma agonists are known for increased cardio-vascular events which precludes itsuse. Uridine treatment is beneficial in LA and might be of use to prevent lactic acidosis, which is a serious and life-threatening side effect of NRTIs [25]. At the end, exact treatment options and guidelines are still debatable and should be individual based approach.

CONCLUSION

Our study showed that younger group of patients and females are the most commonly affected group with LD. This is also the group of patients who are more prone to stop drugs with these cosmetically important side effects. Also, educating patients about these LD and adequate life style management shall help in good adherence to HAART, which shall reduce the further challenging resistance to HAART drugs in these patients. Since the duration of disease was more among these patients, regular monitoring and follow up is very important. Although there were no haematological manifestations in our study, regular monitoring of lipid profile and sugar levels will definitely help in identification of metabolic derangements in early course of disease. Last but not the least, a good patient relationship and counseling shall remove the misconception about LD among these patients and also provides opportunity to spread awareness in the community.

The availability of HAART to common man has definitely improved this stigma about the disease and helped him overcome it and lead a normal life. However, few of HAART related side effects should be tackled more legitimately to manage disease and patient as a whole. This is more challenging especially in developing countries like India.We recommend approaching the condition with targeted annual screening. In light of the absence of cost-effective measures to treat LD, prevention remains the best option.

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