SERUM LIPID PROFILE AND TRANSAMINASES LEVELS IN HIV PATIENTS ON HAART WITH ADIPOSE TISSUE ALTERATIONS

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ABSTRACT

BACKGROUND

HIV patients receiving highly active Anti-Retroviral Therapy (HAART) usually suffer from side effects like hepatitis, neurological problems, abnormal fat distribution etc. Among these, the most physical, mental and cosmetically disturbing side effect is adipose tissue alterations (ATA), also called as lipodystrophy, which is abnormal fat deposition (Lipohypertrophy) and/or fat atrophy (Lipoatrophy).

AIM

Several studies have shown dyslipidemia in patients on HAART, but there are very few studies on the lipid profile changes in patients on ART with ATA. Hence a study was conducted to assess the serum lipid profile and transaminases activity in patients on ART with ATA and also to evaluate whether lipid profile parameters can predict ATA changes in HIV patients on HAART.

METHOD

Randomly selected HIV positive patients, who were attending ART centre, were included in the study. Twenty five of these patients in whom HAART was yet to be started were considered as Control group, 25 patients on HAART for more than 12 months but without ATA as ART group and 23 patients on HAART with ATA as ATA group. Lipid profile and serum transaminases in all the groups were assayed by standard methods.

RESULTS

Serum cholesterol and LDL were significantly increased in ART group and ATA group when compared to control group, but there was no significant difference in lipid profile parameters between ART group and ATA group. Serum AST and ALT levels were significantly increased ($p<0.02$) in ATA group when compared to ART group. Buffalo hump was seen only in females in our study. Lipoatrophy (facial and limbs) and central obesity was seen in males.

CONCLUSION

There was no significant change in lipid profile parameters in ATA group when compared with ART group. Hence lipid profile parameters are not good predictors of ATA changes in HIV patients on HAART. Significant increase in transaminase levels suggests increased hepatotoxity in ATA patients due to HAART drugs. There is a need for further evaluation on the role of hormones, environmental or genetic factors in different clinical presentations of ATA in male and female patients.

KEYWORDS

Adipose tissue alterations, HAART, HIV, lipid profile, Buffalo hump.

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INTRODUCTION: Highly Active Antiretroviral therapy (HAART) refers to the use of pharmacologic agents that have specific inhibitory effects on HIV replication.[1]The development of combined antiretroviral therapy has shifted the perception of HIV/AIDS from a fatal to a chronic and potentially manageable disease.[2] Increase in the use of HAART drugs has made the management of toxicities of these drugs an important component of HIV care in developing countries. The spectrum of adverse effects of HAART drugs in developing countries may differ from that in

developed countries because of other associated conditions like anaemia, malnutrition, tuberculosis etc. and also as a result of host genetics.[3]

Among the various side effects of HAART, adipose tissue alterations (ATA) [also known as lipodystrophy syndrome] is one of the common and the most important, from the perspective point of HIV patients. ATA is a combination of peripheral and subcutaneous lipoatrophy with a lesser degree of relative fat accumulation in the abdomen, breasts, and upper trunk. This condition is cosmetically distressing and stigmatizing for many persons, and it is also associated with reduced adherence to ART.[4] Furthermore, it is associated with lipid and glycemic abnormalities, such as higher levels of total cholesterol and triglycerides, lower levels of high-density lipoprotein cholesterol, and insulin resistance and type 2 diabetes mellitus. These abnormalities are strongly linked to an increased risk for myocardial infarction and other atherosclerotic disease.[5]

ATA or Lipodystrophy is classified as fat accumulation (in three regions: abdomen, dorsocervical region and breasts in women) or fat wasting (in four regions: face, arms, buttocks and legs).[6] Lipoatrophy is the loss of subcutaneous fat in the face (malar or temporal wasting), arms, shoulders, thighs, and buttocks (peripheral wasting), often accompanied by prominent superficial veins, which produces an emaciated appearance. It is differentiated from HIV wasting in that lean body mass shows little or no decline in lipoatrophy. Lipohypertrophy is fat accumulation that appears as abdominal visceral fat (Crix belly or protease paunch), dorsocervical fat (buffalo hump), increased neck circumference, breast hypertrophy, or lipomas. Risk factors associated with development of lipohypertrophy include increasing age, female sex, increase in BMI, Protease Inhibitors (PI) use, and duration of ART.[7]

HAART and Lipid Metabolism: Before the advent of ART, abnormalities of lipid metabolism were noted in HIV infection, including hypertriglyceridemia in AIDS patients, with reductions in total cholesterol, HDL cholesterol, and low-density lipoprotein (LDL) cholesterol. These changes were thought to be due to cytokine-enhanced lipogenesis as well as impaired postprandial triglyceride clearance. However, with the use of ART, the pattern of dyslipidaemia changes to an even greater increase in triglycerides, reduced HDL cholesterol, and variable increases in LDL cholesterol and total cholesterol. A cohort study showed that the prevalence of dyslipidaemia in patients on PI based treatment may be as high as 44%. Each class of ART produces different effects on lipid metabolism. For PIs, ritonavir increases triglycerides, total cholesterol, and LDL cholesterol but reduces HDL cholesterol. Atazanavir increases total cholesterol and triglycerides but not as significantly as compared with nelfinavir. In general, non-nucleoside reverse transcriptase inhibitors (NNRTIs) have been associated with elevated HDL cholesterol and total cholesterol. Among the nucleoside reverse transcriptase inhibitors (NRTIs) Stavudine is associated with hypercholesterolemia; didanosine and lamivudine do not have this effect. Also studies suggest that there is impairment of lipoprotein lipase in HIV patients on HAART.[8]

HAART and Hepatotoxicity: Hepato-toxicity is serious complication in patients taking HAART. Mechanisms of hepatotoxicity in patients on HAART are due to Mitochondrial damage, hypersensitivity reactions, steatohepatitis, drug interactions and co-infections with hepatitis B and C.[9] Regular monitoring of transaminases is mandatory when commencing on HAART.

Hence this study was undertaken to assess whether there is any change in lipid profile parameters and serum transaminase levels in HIV patients on HAART with ATA. And also to evaluate whether lipid profile parameters in HIV patients on HAART can predict or indicate ATA changes in these patients.

MATERIALS AND METHODS: Randomly selected 73 HIV positive patients, who were attending ART centre in Bellary, were included in the study.

Grouping: 25 of these patients in whom HAART was yet to be started were considered as Control group, 25 patients on HAART for more than 12 months but 0without ATA as ART group and 23 patients on HAART for more than 12 months with adipose tissue alteration changes as ATA group.

Inclusion Criteria: HIV patients aged more than 25 years, who are taking HAART for more than 12 months and showing obvious signs of Lipohypertrophy and /or lipoatrophy, ie., ATA changes.

Exclusion Criteria: Known cases of Hepatitis, TB, chronic smokers & alcoholics, patients on lipid lowering drugs, diabetes mellitus, cardiovascular diseases, neoplasms, etc were excluded from study. Patients with any active opportunistic infection or neoplasm were excluded from the study.

Consent: Written consent was obtained in all cases after explaining about the study in their own language. All previous and ongoing antiretroviral therapy history, including exposure time to specific drugs, based on cumulative months on therapy was recorded.

HAART Regimen: The first choice for first-line HAART regimen was Zidovudine (AZT) + Lamivudine (3TC) + Nevirapine (NVP) for patients with Hb> 8 g/dl. The second choice of First-line ART regimen was Stavudine (d4T) + Lamivudine (3TC) + Nevirapine (NVP) for patients with Hb< 8g/dl. NVP was substituted with Effavirenz (EFV) for patients with Tuberculosis or toxicity to NVP. The choice of the regimen was based on the complete Blood count before starting HAART.

Ethical Clearance was obtained by Institutional Ethical Committee at VIMS, Bellary.

Laboratory Determination: Blood was drawn from each patient after an overnight fast. Blood samples were centrifuged at room temperature after half an hour of collection. Serum Total cholesterol, Triglycerides (TG) and HDL cholesterol were determined by standard methods using commercial kits (Erba Company) in Fully automated Analyzers. Low-density lipoprotein (LDL) cholesterol was calculated by the Friedewald method, except in patients with TG levels higher than 400 mg/dL (LDL=CHOL-([TG/5]+ HDL).

STATISTICAL ANALYSIS: The obtained results were analysed statistically by Students 't' test.

RESULTS:

The results of the present study are depicted in Table 1-4 and in Pictures a) and b).

Physical Characteristics: In our study Buffalo hump (BH) was seen only in females (Refer pictures a and b). Lipoatrophy (facial and limbs) and central obesity was commonly seen in males. During our study period we came across 23 ART patients with ATA. Twenty one of these were on SLN regimen and two on ZLN regimen. Out of 23 lipodystrophy patients, 11 were females and 12 were males. Among 11 female patients, 5 showed Buffalo hump and remaining showed abdominal and buccal fat deposition. Among 12 male patients, 4 patients showed severe buccal fat atrophy and others showed moderate buccal fat atrophy with abdominal fat deposition. The duration of NRTI therapy in the present study was 25.3+13.17 months in ART group.

Lipid Profile Parameters Like: 1. Cholesterol was significantly increased (p <0.001) in ART group (range:134.83-221.93mg/dl) and ATA group (range: 155.78-234.40mg/dl) when compared to control group (range:122.17-180.99mg/dl). 2. LDL cholesterol was significantly increased (p <0.001) in ART group (range:77.65-148.31mg/dl) and ATA group (range:92.89-162.49mg/dl) when compared to control group (range: 68.59-115.23mg/dl). But there was no significant difference seen in other lipid profile parameters, between all the 3 groups.

Serum Transaminases: Serum AST and ALT levels were significantly increased (p< 0.001) in ART group (range: AST 19.04-32.84IU/L & ALT 17.93-24.81IU/L) when compared to control group (range: AST 17.67-24.55IU/L & ALT 16.28-20.40IU/L). Further significant increase was seen in ATA group (range: AST 23.61-36.01IU/L & ALT 20.72-26.5IU/L) when compared to ART group.

Parameter	Control group (n=25)	ART group (n=25)	p Value
Serum total cholesterol (mg/dl)	151.58+29.41	178.38+43.55*	p (<0.02) significant
HDL cholesterol (mg/dl)	33.28+7.78	36.52+9.42	<0.10 not significant
LDL cholesterol (mg/dl)	91.91+23.32	112.98+35.33*	p (<0.02) significant
VLDL cholesterol (mg/dl)	26.60+7.73	29.8+8.54	<0.10 not significant
Triglycerides (mg/dl)	133.78+38.73	147.95+42.85	<0.10 not significant
Cholesterol/HDL ratio	4.65+0.80	5.09+1.53	<0.10 not significant
Cholesterol/TG ratio	1.13+0.18	1.25+0.29	<0.10 not significant
TG/HDL ratio	4.02+0.97	4.37+1.90	<0.10 not significant

Table 1: Lipid profile parameters in Control group and ART group patients

Note: *=p (<0.02) **=p (<0.001)

Parameter	ART group (n=25)	ATA group (n=23)	p Value
Serum total cholesterol (mg/dl)	178.38+43.55	195.09+39.31	<0.10 not significant
HDL cholesterol (mg/dl)	36.52+9.42	34.45+6.80	<0.10 not significant
LDL cholesterol (mg/dl)	112.98+35.33	127.69+34.8	<0.10 not significant
VLDL cholesterol (mg/dl)	29.8+8.54	32.92+10.00	<0.10 not significant
Triglycerides (mg/dl)	147.95+42.85	165.54+50.56	<0.10 not significant
Cholesterol /HDL ratio	5.09+1.53	5.8+1.55	<0.10 not significant
Cholesterol /TG ratio	1.25+0.29	1.25+0.33	<0.10 not significant
TG/HDL ratio	4.37+1.90	5.01+1.92	<0.10 not significant

Table 2: Lipid profile parameters in ART group and ATA patients

Note: *=p (<0.02) **=p (<0.001)

Parameter	Control group (n=25)	ART group (n=25)	p Value
Serum AST (IU/L)	21.11+3.44	25.94+6.90**	<0.001 significant
Serum ALT (IU/L)	18.34+2.06	21.37+3.44**	<0.001 significant

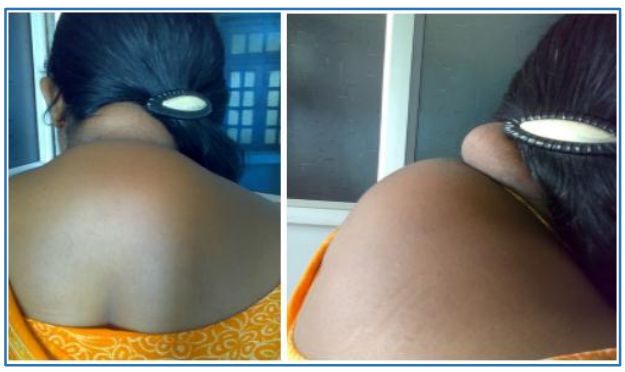
Table 3: Serum transaminases in Control group and ART group patients

Note: *=p (<0.02) **=p (<0.001)

Parameter	ART group (n=25)	ATA group (n=23)	p Value
Serum AST (IU/L)	25.94+6.90	29.81+6.20 *	<0.02 significant
Serum ALT (IU/L)	21.37+3.44	23.61+2.89 *	<0.02 significant

Table 4: Serum transaminases in ART group and ATA group patients

Note: *=p (<0.02) **=p (<0.001)



Pictures showing "buffalo hump" in a woman on ART drugs a) Back view & b) side view

DISCUSSION: ATA is a term used to describe body fat changes (lipoatrophy and lipohypertrophy) and metabolic abnormalities (dyslipidaemia, insulin resistance and hyperglycaemia, hyperlactatemia, lactic acidosis) sometimes seen in patients infected with HIV, particularly those on HAART. In addition to medications, factors including a person's age, gender, weight, genetic predisposition, length of time he or she has been HIV-positive, and severity of the disease may be linked to the development of lipodystrophy.[7] Facial fat wasting is one of the early signs of lipodystrophy that was observed in lipodystrophic patients in the present study. This was obvious when we compared the patients' faces before and after they started antiretroviral therapy, with their identity card provided by the ART centre, Bellary. Accumulation of fat over the dorsocervical spine, or "buffalo hump" (BH), is reported in 2% to 13% of HIV-infected patients.[10] In our study we found BH in the female patients only and; limb and facial lipoatrophy with central obesity mainly in male ATA patients. This gender difference in ATA presentation might be due to hormones[11,12] along with differences in drug transport and metabolizing enzymes.[13]

The HIV-associated ATA was first described in 1998, shortly after the introduction of PIs.[14] It is well known that PIs induce derangements of lipid profile during ART.[15-17] It is now clear that HIV lipodystrophy can also develop in patients who have never been treated with PIs[7]. The use of NRTI's Stavudine (d4T) in particular has been linked specifically to the development of the lipoatrophic component of HIV-associated ATA.[14] There was no significant change seen in lipid profile in patients on ART with ATA when compared to ART patients without ATA. This is similar to the findings of Patrick WG et al.[10]

A number of studies have found that Stavudine was more involved in the occurrence of lipid derangements as compared with other NRTI's.[18,19] A prospective multicentre study by the recover study group found that HIV-positive patients who replaced Stavudine with TDF (Tenofovir Disoproxil Fumarate) had significant decrease in triglycerides and cholesterol levels. This suggests, at least partly, a Stavudine (d4T)-associated dyslipidaemia.[14] Our previous study[20] showed no difference in lipid profiles when participants on SLN regimen (Stavudine+Lamivudine+ Nevirapine) were compared to those on ZLN regimen (Zidovudine+Lamivudine+Nevirapine). These findings are similar to the findings of Buchaczet al in Uganda,[21] Pujari et al in Western India[22] and PefuraYone et al in Cameroon.[23] There is now strong evidence that NRTI-induced mitochondrial toxicity plays a major role in the development of the lipoatrophic component of HIV-associated ATA.[24] Many studies have shown significant increased triglyceride levels in patients with ATA.[4,8] But our study did not show any significant changes in triglyceride levels. This might be due to variations in genetic and dietary habits of the study subjects.

Anti-retroviral drugs are known to cause hepatotoxicity.[9] In our study, 23 HIV patients with ATA show statistically significant increase in serum transaminase levels when compared to HIV patients without ATA. But this increase in serum transaminase levels, are not clinically significant. But it suggests that mild hepatotoxicity may exist in these patients.

CONCLUSION: Our study shows lipid profile parameters are altered in HIV patients taking HAART, but there is no significant difference in lipid profile in patients with ATA compared to patients without ATA. Serum transaminase levels in patients with ATA are significantly increased, when compared to patients without ATA, suggestive of increased hepatotoxicity. There might be different mechanisms (may be hormonal, environmental, genetic) that is causing different presentations of adipose tissue alterations in male and female HIV patients on HAART.

Hence it can be concluded from our study that, lipid profile parameters are not good predictors of ATA changes in HIV patients on HAART. There is a need for further evaluation on the role of hormones, environmental or genetic factors in different clinical presentations of ATA in male and female patients.

LIMITATIONS: The study was conducted in small group of 30 patients. The study does not define ATA while selecting patients and the study group was chosen by observations of obvious signs of LA and LH. The study did not look for the other metabolic syndrome parameters altered in ATA in the study group.

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