Original Article

Profile of glucose intolerance in HIV-positive patients on 1st line and 2nd line antiretroviral therapy

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ABSTRACT

Background and Aims: Human Immunodeficiency Virus infections have developed into a global pandemic with cases reported from virtually every country. Manipur has also shown an increase in the incidence of HIV/AIDS since the past decade. Thus far, very little data is available in this part of the country about the effect of 1st and 2nd line antiretroviral therapy (ART) on the glycemic status of the patients. Hence, this study was undertaken to assess and compare the effect of 1st line and 2nd line ART on glycemic status of HIV patients. **Subjects and Methods:** The study was carried out in the ART centre in Regional Institute of Medical Sciences, Imphal. It was a cross-sectional comparative observational study carried out from October 2010 to September 2012. A total of 292 patients were included in the study, of which 211 patients were receiving ART 1st line and 81 patients receiving ART 2nd line. HIV patients receiving ART were investigated for fasting, 2 hours post-prandial glucose, CD4 cell count, total cholesterol, and serum triglyceride levels. Chi-square and Student's t tests were used to find the significance between the two groups. Pearson's correlation between clinical variable and sugar and lipid parameters was performed to find the effect of relationship. **Results:** The difference between the two groups was statistically significant in Random Blood Sugar (RBS), Fasting Blood Sugar (FBS) and Post Prandial Blood sugar (PPBS) values ($P = 0.022$; $P = 0.004$ and $P < 0.001$ respectively). Patients in Group II had significantly higher values of TC and TG compared to Group I patients with a P value of <0.001. **Conclusions:** The glucose and lipid parameters were significantly high receiving ART 2nd line patients in comparison with ART 1st line patients.

Key words: Antiretroviral therapy (ART) 1 and 2, glucose profile, lipid profile

INTRODUCTION

Acquired Immune Deficiency Syndrome (AIDS) was first recognized in United States in 1981. At the end of 2007, 33.2 million individuals were living with HIV infection (range: 30.6-36.1 million) according to the Joint United Nations Programme on HIV/AIDS (UNAIDS).[1] India already has the second highest number of people estimated to be living with HIV/AIDS in the world (5.1 million).[2] Manipur has also shown an increase in the incidence of HIV/AIDS since the past decade. The Ukhrul district has the highest seropositivity (4%) among the Antinatal Clinic (ANC) attendees. HIV prevalence among intra uterine devices (IDUs) is very high, more than 15% HIV prevalence, with Churachandpur having the highest percentage (24%).[3] Treatment with highly active antiretroviral therapy (HAART) has improved the prognosis of patients with AIDS but it has also increased the incidence of various metabolic disorders, in particular insulin resistance accompanied by dyslipidemia, hyperglycemia, and lipodystrophy.

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This is often accompanied by frank Type 2 diabetes and increased mortality from cardiovascular diseases. It is important to understand the mechanistic basis for these side-effects as the incidence of these side-effects is likely to increase with the rollout of antiretroviral drugs.[4] Cross-sectional studies have reported 16% HIV-infected patients having impaired glucose tolerance[5] and an additional prevalence of diabetes of 2-7% among HIV-infected patients receiving protease inhibitors (PIs).[6-8] A more recent analysis conducted in the Multicenter AIDS Cohort Study places the incidence of diabetes in HIV-infected men with HAART exposure at four times greater than that of HIV-seronegative men.[9] Recent data suggest that insulin resistance may also be associated with HIV infection in patients not receiving PI therapy. The mortality of these AIDS cases may further be increased because of the associated metabolic complications like glucose intolerance and dyslipidemia. Thus far, very little data is available in this part of the country about the effect of 1st and 2nd line ART on the glycemic status of the patients. Therefore, this study was undertaken to compare the effect of the 1st line and 2nd line ART on the glycemic state of HIV patients and the correlation of glucose levels with CD4 count.

SUBJECTS AND METHODS

This was a cross-sectional observational study carried out from October 2010 to September 2012. The study protocol was approved from Institutional Ethics Committee. All patients registered in ART centre of Department of Medicine, aged >18 years, documented HIV positive and on ART for minimum of six months were recruited after obtaining written informed consent. Patients with diabetes mellitus, other endocrinal disorders, and pancreatitis were excluded. Pregnant and lactating mothers were not included in the study. This was a time-bound study. A total of 292 patients who fulfilled the inclusion and exclusion criteria were included in the study; out of these, 211 patients were receiving ART 1st line and 81 patients receiving ART 2nd line.

Patients with HIV receiving ART had to undergo a fasting, and 2-h post-prandial glucose was collected as in normal diabetes patient care. They were categorized according to the line of HAART they were receiving (ART 1st line and ART 2nd line). The CD4 cell count, total cholesterol, and serum triglyceride values of the patients were also recorded simultaneously with FBS and PPBS. Patients who had deranged blood sugar were asked to undergo HBA1C testing. CD4 cell count was calculated by using automated analyser, Fluorescence Activated Cell Sorter (FACS). Patient's age, gender, duration of HIV, duration of ART, and the present regimen he/she is on, was recorded, and their influences on the glycemic status of the patient were studied. Risk factors of patients, probable mode of transmission, co-infections (HBV and HCV), opportunistic infections, and habits of the patients were noted.

Statistical analysis: The data collected was then analyzed by using Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA) Windows based version 16.0. Results on continuous measurements are presented on Mean ±SD and results on categorical measurements are presented in Number (%). Significance was assessed at 5% level of significance.

Student's t test (two tailed, independent) was used to find the significance of study parameters on continuous scale between two groups on metric parameters. Chi-square or Fisher's exact test was used to find the significance of study parameters on categorical scale between two or more groups. Pearson's correlation between clinical variable and sugar and lipid parameters was performed to find the effect of relationship.

RESULTS

A total of 292 patients receiving ART from ART centre, Regional Institute of Medical Sciences were enrolled in the study. Group I comprised 211 patients receiving ART 1st line treatment, of which 139 (65.8%) were male and 72 (34.1%) were female; Group II had 81 patients, of which 53 (65.4%) were male and 28 (34.5%) were female. Samples were gender matched with $P = 1.000$. Mean age of Group I was 42.22 ± 8.05 years while that of Group II was 43.24 ± 8.37 years. Samples are age matched with $P = 0.337$. Out of the 211 patients in Group I, 71% were married, 16.1% were single, and 17.5% were widows. In Group II, 59.2% patients were married, 13.5% were single, and 27.1% were widows. Widows were significantly more in number in Group II with $P = 0.013$. In Group I, out of 211 patients, 119 (56.3%) had HIV-positive spouses while in Group II, out of 81 patients (69.1%) had seropositive spouses. HIV positive status was significantly higher in Group II with $P = 0.062$. Duration of HIV infection was significantly longer in Group II (96.11 months) when compared to Group I (61.98 months) with $P < 0.001$. Mean duration of ART is significantly longer in Group II (84.77 months) when compared to Group I (57.73) with $P < 0.001$. Present regimen of Group I patients (Z: Zidovudine, L: Lamivudine, S: Stavudine, N: Nevirapine, E: Efavirenz): 14.2% patients were on ZLN, 11.8% were on ZLE, 47.3% were on SLN, and 26.5% were on SLE regimen. These patients were on respective regimen for 6 or more months. Both Group I and Group II HIV patients had more HCV co-infection.

Table 1 shows the CD4 count in Group I and Group II patients.

Table 2 shows the comparison of the glucose parameters between Group I and Group II patients.

Table 3 shows the comparison between the mean values of Total cholesterol and Triglycerides between Group I and Group II.

Table 4 shows the correlation between the CD4 values and the glucose and lipid parameters of Group I and Group II.

DISCUSSION

Out of 292 patients receiving ART, Group I comprised 211 patients and Group II comprised 81 patients. Age and gender distribution among the two groups were comparable. In Group II, widows were significantly more in number ($P = 0.013$) and HIV-positive status of spouse was higher ($P = 0.062$). The most common risk factor in both groups was heterosexual route. Duration of HIV infection was significantly longer in Group II (96.11 months) compared to Group I (61.98 months) with $P < 0.001$. The co-infections were significantly more in Group I (26%) compared to Group II (12.3%). CD4 count was similar in two groups. All parameters of glycemic status in HIV patients studied showed significant difference between the two groups suggesting that patients exposed to ART 2nd line had more deranged blood sugar values compared to the 1st line ART patients. This shows that ART 2nd line is associated with insulin resistance, glucose intolerance, and overt diabetes compared to ART 1st line. The total cholesterol levels and triglyceride values in Group II were significantly higher compared to Group I. CD4 count showed a trivial positive correlation with RBS, FBS, PPBS, and total cholesterol in Group I, and a trivial negative correlation with HbA1C and Triglyceride values. In Group II, CD4 count showed a trivial negative correlation with all parameters (RBS, FBS, PPBS, HbA1C, total cholesterol, and TG). A study by Carr *et al*.[6] found a 7% incidence of new-onset diabetes as diagnosed by a 2-h blood glucose value > 200 mg/dl after administration of an oral glucose tolerance test (OGTT). A more recent analysis conducted in the Multicenter AIDS Cohort Study[9] places the incidence of diabetes in HIV-infected men with HAART exposure at four times greater than that of HIV-seronegative men. Another study by Castro-Sansores *et al*.[10] on hyperglycemia and glucose intolerance in patients with HIV infection receiving ART found that 44% had hyperlipidemia. Of these, 20% had hypercholesterolemia (HC) and 39% hypertriglyceridemia (HT). Nelfinavir was administered to 13 asymptomatic HIV-infected individuals in a study by Hans J *et al*., which showed deterioration in glucose tolerance in all subjects. Insulin sensitivity was decreased by 40-50% as determined by HOMA and the hyperglycemic clamp technique. Overall pancreatic β-cell function, as assessed by HOMA, and first-phase insulin release, assessed during hyperglycemic clamp experiments, decreased significantly. Second-phase insulin release during the hyperglycemic clamp experiments was not reduced in an absolute sense but with use of the disposition index — an assessment of the appropriateness of β-cell function for a given degree of insulin resistance — it was found to be reduced significantly. Regarding the mechanisms/sites of insulin resistance induced by protease inhibitor treatment, they found a reduction in glucose disposal, whereas glucose production appeared to be appropriately reduced for the prevailing plasma insulin concentration. Under euglycemic-hyperinsulinemic clamp conditions, maximum glucose disposal occurs in skeletal muscle.[11] Indinavir has been shown to inhibit muscle glucose transport.[12]

Table 1: CD4 count of HIV patients studied

CD4 count	Group I		Group II	
	Number of patients	%	Number of patients	%
<100	5	2.3	2	2.4
100-200	34	16.1	15	18.5
200-500	115	54.5	42	51.8
>500	57	27.0	22	27.1
Total	211	100.0	81	100.0
Mean±SD	399.45±210.08		391.25±212.36	

Mean CD4 count is statistically similar in two groups of patients with $P = 0.766$

Table 2: Comparison of glucose parameters of two groups of patients studied

Variables	Group I	Group II	*P* value
RBS (mg/dl)	108.91±29.94	121.77±41.90	0.004
FBS (mg/dl)	90.28±21.37	104.85±34.84	<0.001
PPBS (mg/dl)	127.45±34.61	153.46±67.95	<0.001
HbA1c	6.37±0.76	7.09±1.19	0.021

Table 3: Comparison of lipid parameters of two groups of patients studied

Variables	Group I	Group II	*P* value
Total cholesterol (mg/dl)	137.36±34.54	185.23±53.55	<0.001
Triglycerides (mg/dl)	138.00±43.74	165.43±60.69	<0.001

Table 4: Pearson correlation of CD4 count with sugar and Lipid parameters

Parameters	Group I ($n = 211$)		Group II ($n = 81$)	
	r value	*P* value	*r* value	*P* value
Log CD4 *vs.* RBS	0.013	0.856	−0.063	0.579
Log CD4 *vs.* FBS	0.012	0.862	−0.115	0.309
Log CD4 *vs.* PPBS	0.050	0.470	−0.060	0.576
Log CD4 *vs.* HbA1c	−0.181	0.421	−0.263	0.226
Log CD4 *vs.* Total cholesterol	0.059	0.397	−0.030	0.794
Log CD4 *vs.* TGL	−0.079	0.253	0.136	0.226

The limitations of our study were lack of facilities for investigating HIV/HBV/HCV genotyping and viral load and study the effect of individual drugs in the regimen on glycemic status of patient. Therefore, a larger study with adequate sample size, follow-up, and duration will be required to give us more insight about the effect of anti-retrovirals on the glycemic status of HIV patients.

CONCLUSIONS

We conclude that with the increasing use of the HAART, no doubt there is increase in the immune status of patients,

quality of living, and prevention of opportunistic infections, but it should also be emphasized that, with these benefits, ART also has its own side effects, one of which is deranged glycemic environment of patients receiving ART.

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