Metabolic abnormalities in human immunodeficiency virus patients with protease inhibitor-based therapy

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Abstract

Context: Several studies have reported metabolic abnormalities in patients taking protease inhibitor (PI) based therapy from several parts of the world. But there is no prospective study in India after switching from PI sparing regimen to PI based regimen. Aims: To assess whether North-East Indian Human Immunodeficiency Virus (HIV) patients also develop similar metabolic abnormalities to PI. Settings and Design: This prospective study was conducted in Anti-retroviral therapy (ART) Centre of Excellence, at a tertiary care Medical Institute. Materials and Methods: Fifty-five patients taking PI based ART were taken for the study. These patients were started on Ritonavir based therapy, after treatment with first line drugs had failed according to National AIDS Control Organization (NACO) guidelines 2008. Glucose and lipid profiles were evaluated. American Diabetes Association (ADA) and NCEP ATP III criteria were used to categorize glucose and lipid abnormalities. International Diabetes Federation (IDF) 2006 cut-off was used for waist circumference and blood pressure. Statistical Analysis Used: Paired t-test was done whenever applicable. Results: There was a significant increase in waist circumference after 6 months of 2nd line ART from 78.0 cm to 80.2 cm (P value < 0.001). There was significant increase in both systolic and diastolic blood pressure after 6 months. In 29.8% of patients blood pressure rose to hypertensive level after 6 months. Total cholesterol, triglyceride and low density lipoprotein cholesterol also rose significantly after 6 months but not high density lipoprotein cholesterol. Conclusions: Our study showed that North-Eastern Indian patients also develop metabolic abnormalities to protease inhibitors similar to people of other races.

Key words: Blood pressure, dyslipidemia, impaired glucose tolerance, waist circumference

INTRODUCTION

The wide availability of highly active anti-retroviral therapy (HAART) has made human immunodeficiency virus (HIV) a chronic manageable disease.[1] As patients continue to live longer metabolic complications such as dyslipidemia, changes in body composition, insulin resistance and glucose intolerance have emerged.[2] It is uncertain whether these complications are related to both protease inhibitors (PI) and nucleoside-reverse transcriptase inhibitors (NRTI) or exclusively related to PI.[3] Galli et al. have reported metabolic abnormalities with PI sparing regimens.[4] Although there are studies reporting metabolic abnormalities in HIV patients taking PI based ART from several parts of the world, there is no prospective study in India after switching from PI sparing regimen to PI based regimen. This study was conducted to study whether North-East Indian HIV patients behave differently to PI in terms of lipid and glucose abnormalities.

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MATERIALS AND METHODS

This prospective study was conducted at center of excellence, ART center, Regional Institute of Medical Sciences, Imphal, Manipur, India after obtaining approval from Institutional Ethical Committee. The patients were provided free ART by the center through the National AIDS Control Organization (NACO) program. Triple drug therapy containing 2 NRTI + 1 non-NRTI (NNRTI) are used as first-line ART in India according to NACO guidelines. A total of 55 patients taking 2nd line (PI based) ART were taken for the study. These patients were started on Ritonavir based therapy, after treatment with first line drugs have failed according to NACO guidelines 2008.[5] Out of these 55 cases, 4 cases were lost to follow-up, 2 expired and 2 transferred out to other ART center. Patients with previously diagnosed diabetes mellitus and hypertension were excluded from the study. Detailed clinical history was taken, and physical examination was performed. Routine clinical investigations including fasting and postprandial blood glucose, lipid profile, liver and kidney function test were performed. Plasma glucose was estimated using glucose oxidase method using GLUC-PAP manufactured by Randox Laboratories Limited, 55 Diamond Road, Crumlin, County Antrim, BT29 4QY, United Kingdom. Lipid profile was estimated by enzymatic method using Vitros chemistry, Ortholand Diagnostics Inc., Rochester, NY, USA. CD4 count was done using fluorescence activated cell sorter counter manufactured by BD BioSciences, 2350, Qume Drive, San Jose, CA 95131-1807, USA. Glucose abnormalities were defined according to American Diabetes Association (ADA) guideline.[6] Lipid abnormalities were defined according to International Diabetes Federation (IDF) 2006 and third report of the National Cholesterol Education Program expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment Panel III) guidelines.[7,8] The patients were evaluated before initiation of 2nd line ART and 6 months after.

Data were recorded on a predesigned proforma, and statistical analysis was done using SPSS-16.0 manufactured by SPSS Inc., 233 South Wacker Drive, 11th Floor, Chicago, USA. Paired t-test was done whenever applicable. Statistical significance was assumed at a P < 0.05.

RESULTS

Out of the 47 patients finally included in the analysis of this study, 30 (63.8%) were males, and 17 (36.2%) were females. The mean age of the patients was 40.15 years (range: 21-60 years).

The mean waist circumference (WC) of patients before and after 6 months of 2nd line ART were 77.96 ± 5.90 and 80.21 ± 6.94 (P < 0.001). Abnormal WC according IDF criteria was seen in 29.8% of patients after 6 months of treatment.

The blood pressure rose up in 29.8% of patients reaching the IDF 2006 criteria for high blood pressure after 6 months of 2nd line ART, but 70.2% remained normotensive. The change in mean blood pressure before and after 6 months of 2nd line ART therapy is shown in Table 1.

Changes in lipid profile were analyzed according to ATP III classification. Total cholesterol (TC) rose to borderline high in 19.1% and high in 10.6% after therapy. Triglyceride (TG) rose to borderline high in 36.2%, high in 51.1% and very high in 4.3% of patients. High density lipoprotein cholesterol (HDL) was lowered in 44.7%, increased in 12.8% and 42.6% maintained normal level. Low density lipoprotein cholesterol (LDL) rose to borderline high in 17%, high in 4.3% and very high in 2.1%. Table 2 shows the changes in the mean level of various lipid parameters before and after 6 months of 2nd line ART.

After 6 months of treatment, 19.1% developed IFG, and 17.0% reached the ADA cut-off (fasting) for diabetes mellitus and 19.1% developed impaired glucose tolerance, and 19.1% reached the ADA cut-off (postprandial) for diabetes mellitus. The difference in mean fasting and postprandial blood glucose before and after 2nd line therapy is shown in Table 3.

DISCUSSION

Metabolic abnormalities have been reported from several countries in patients receiving PI. To our knowledge, this is the first North-East Indian study describing glucose and lipid abnormalities in patients on PI, who switched from PI sparing regimen. In a smaller study by Mittal et al., evaluating 27 cases on PI, who switched from PI sparing regimen. In a smaller study by Mittal et al., evaluating 27 cases on PI for at-least 6 months and 13 drug naive patients reported no significant difference among the patients who were on PI based ART and the treatment naive patients with regards to their fasting blood sugar. But a statistically significant difference was seen with respect to the TC and the LDL and HDL cholesterol.[9] Previous other Indian studies reporting metabolic abnormalities were on PI sparing regimens.[10,11] The metabolic changes seen in the present study are over and above metabolic complications induced by NRTI or NNRTI as the patients were switched to PI based therapy after failure of these drugs.
In the present study, 47 patients were evaluated at baseline and after 6 months following initiation of PI based therapy (2nd line ART) following failure with first line drugs according to NACO guidelines 2008.[5]

Serum cholesterol, TG and LDL increased significantly after 6 months of therapy with PI boosted regimen. Martínez et al., found hypertriglyceridemia in 100% of their cases after a median of 12 (6-26) months of PI based ART in Spanish population.[12] In another study by Martínez et al., glucose and HDL levels did not change but TG and TC levels significantly increased after 6 months of ART containing Lopinavir-Ritonavir.[13] In Swiss HIV Cohort Study Young et al., reported that TG levels were higher in those starting PI-based therapy compared with those starting NNRTI-based therapy.[14] In a Thai study there were statistically significant increases in mean serum TC, LDL, TG and TC: HDL ratio with PI therapy. There was a slight increase in mean HDL after taking PI, but the difference was not statistically significant.[15]

In a Nigerian study of 327 patients, prevalence of hypertriglyceridemia was higher under a PI based HAART compared to NNRTI; 74 (79%) versus 108 (54%) and it was similar for hypercholesterolemia; 58 (51%) versus 72 (31%).

Occurrence of post-ART elevated LDL was nonsignificantly higher in the PI group than the NNRTI; (39% vs. 30%, P = 0.8). HDL was elevated to about the same frequency in both groups; 32 (34%) versus 78 (33%) without any significant difference.[16] However, according to Hadigan et al., no differences in levels of glucose, insulin, cholesterol, and HDL were observed by PI treatment status.[17] Furthermore, in the analysis of three randomized clinical trials Indinavir did not further increase mean TG levels in HIV-infected patients treated with NRTIs.[18]

In the present study, the mean serum HDL was insignificantly lowered, in 44.7% of patients. The increased incidence of hypercholesterolemia after HAART may be associated with an increased risk of myocardial infarction. Patients who demonstrate elevated TC and/or TG levels may need to be treated appropriately, in order to prevent the development and progression of atherosclerotic heart disease, stroke, and pancreatitis.

Both the fasting and postprandial blood glucose increased significantly after 6 months of therapy, with 9 (19.1%) developing diabetes mellitus. Brown et al., reported diabetes mellitus in 14% of patients in a cohort of 411 patients after a median follow-up of 2 years.[19] Vigouroux et al., reported 20% of their patients developed diabetes mellitus on PI based ART.[20]

The finding of the present study reconfirms the development of metabolic abnormalities with PI and Indians patients also develop metabolic abnormalities similar to other races. In this study, the metabolic abnormalities developed as early as 6 months indicating that patients on PI treatment need to be monitored for metabolic abnormalities early on.

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