Original Article

Relevance of Hepatic Enzymes in People Living with HIV on Antiretroviral Therapy

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ABSTRACT

Introduction: Human Immunodeficiency Virus is a non-curable but manageable chronic disease. As HIV-infected patients live longer, non-AIDS illnesses are becoming imperative causes of morbidity and mortality in the HIV-infected population. In particular, liver-related diseases seem to be major in HIV-infected patients. This study was aimed to know the relevance of hepatic enzymes in people living with HIV on anti-retroviral therapy at different stages of infection based on CD4 count.

Methodology: A case-controlled study conducted on 200 subjects. They were divided into two groups. Group one of seropositive 150 HIV patients on antiretroviral therapy and other group of control having 50 HIV seronegative. The HIV group was further categorized into three stages of HIV based on CD4 Count as per CDC classification. The estimation of serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) was carried out on autoanalyzer. The values of CD4 count were noted from patient's record. Statistical analysis was prepared by SPSS Software version 20.0 with appropriate statistical tests.

Results: In our study we observed statistically increased mean activity of enzymes AST and ALT in HIV group as compared to control group ($P<0.05$). Further, it was noted that AST and ALT levels statistically increased from stage I to stage III ($P<0.05$).Serum AST showed significant increase ($P<0.05$) when compared stage I to stage III . Serum ALT showed significant increase ($P<0.05$) when compared stage I to stage III.

Conclusion: Serum ALT and AST are routine biochemical assay used in developing countries with limited-resource settings. Incessant monitoring of hepatic enzymes with larger prospective studies is needed to be carried out to assess effects of antiretroviral therapy drugs and other factors on liver at different stages of HIV infection.

Keywords: Aspartate aminotransferase, alanine aminotransferase, HIV, hepatic enzymes.

INTRODUCTION

Human immunodeficiency virus is a retrovirus that attacks human immune cells, particularly CD4 T cells, which then can cause the worsening of body's immune system. HIV can also straightway impair body's tissues and organs through an inflammatory process. This further leads to organ dysfunction and mortality. Therefore, HIV/AIDS has been becoming a global health problem with a high mortality rate and increasing number of infected people every year.[1] HIV infection later on grounds systemic disease with many complications ahead of acquired immunodeficiency syndrome (AIDS) illnesses that may not yet be recognized.

Liver is a most important part of the reticulo-endothelial system. It is a site of HIV replication and organ for several opportunistic infections. Hepatobiliary system diseases are the main health issues worldwide in HIV infected patients. There have been various studies conducted to intensify the understanding of the characteristics and predictor factors of HIV-infected. Liver function in HIV infected patients may be altered either direct or indirect mechanisms, so enzymes could be used as markers for hepatic injury. Liver diseases in HIV-positive patients may be caused by the virus itself, antiretroviral therapy, or the presence of co morbidities.[2-5] However there is scant attention towards enzymatic relevance at different stages of infection based on CD4 Count. The aim of the present study was to evaluate the relevance of liver enzymes such as aspartate aminotransferase (AST) and alanine aminotransferase (ALT) in HIV patients on antiretroviral therapy at different stages of HIV infection.

MATERIALS AND METHODS

The study was carried out at Government Grant Medical College and Sir JJ Group of Hospitals Mumbai with approval from the Institutional Ethical Committee and National AIDS Control Organization New Delhi. It is a case controlled study.

Inclusion criteria-The patients attending centre of excellence ART centre Sir JJ Group of Hospitals Mumbai were included in the study. The subjects enrolled were of both sexes having age ranging from 16 to 50 years and belonging to different socio-economic status.

Exclusion criteria- The patients with recent history of pre renal dysfunction and burn.

Withdrawal criteria- The patient with insufficient blood sample, rejection of sample on board.

A total of 200 subjects with written consent were part of this study. They were divided into two groups. Group one of seropositive 150 HIV patients on antiretroviral therapy and other group of control having 50 HIV seronegative. The HIV group was further categorized into three stages of HIV based on CD4 Count ie Stage I CD4 count >500(cells/µl), Stage II CD4 count 201 –500 (cells/µl) and Stage III CD4 count ≤200 (cells/µl). The estimation of serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) was carried out on AU400 fully automated chemistry analyzer. The values of CD4 count were recorded from patient's data. Statistical analysis was prepared by SPSS Software version 20.0 with appropriate statistical tests, ANOVA and post Hoc test Tukey.

RESULTS AND DISCUSSION

Table 1: Serum AST/ALT levels from Control and HIV group

Tests	HIV Group		Control Group		Independent T test	P-value	Sig. at 5% level
	n	Mean±SD	n	Mean±SD			
AST(IU/L)	150	28.939±7.477	50	25.020±7.523	3.205*	0.002	Yes
ALT(IU/L)	150	31.021±10.515	50	26.200±3.907	3.166*	0.002	Yes

*Statistically Significant at 5% level i.e. P<0.05.

Table 2: Serum AST and ALT Levels at different stages of HIV based on CD4 Count

Level of CD4	HIV Group		F test (ANOVA)	P-value	Sig. at 5% level
	N	Mean±SD			
AST(IU/L)					
CD4count≤200 (cells/µl)stage III	50	31.396±4.473	5.246*	0.006	Yes
CD4count201–500 (cells/µl)stage II	50	28.720±8.320			
CD4count>500 (cells/µl) stage I	50	26.700±8.333			
AST(IU/L)					
Post-Hoc Test; Tukey HSD ; If F test -Sig	CD4 Level	Mean diff	P-Value	95% CI	
(I)	(J)				
CD4count≤200 cells/µl) stage III	201 – 500 II	2.6760	0.160	-0.7679	6.1199
CD4count≤200 (cells/µl) stage-III	>500 I	4.6960*	0.004	1.2521	8.1399
CD4count201–500 (cells/µl) stage - II	>500 I	2.0200	0.349	-1.4239	5.4639
ALT (IU/L)					
CD4 count ≤200 (cells/µl) stage-III	50	33.724±4.227	3.851*	0.023	Yes
CD4 count 201–500 (cells/µl) stage- II	50	31.320±12.74			
CD4 count >500 (cells/µl)stage- I	50	28.020±11.80			
ALT(IU/L)					
Post-Hoc Test; Tukey HSD ; If F test -Sig	CD4 Level	Mean diff	P-Value	95% CI	
(I)	(J)	(I-J)			
CD4 count ≤200 (cells/µl) stage- III	201 – 500 II	2.4040	0.476	-2.4826	7.2906
CD4 count ≤200 (cells/µl) stage- III	>500 I	5.7040*	0.018	0.8174	10.5906
CD4 count 201–500 (cells/µl) stage- II	>500 I	3.3000	0.249	-1.5866	8.1866

*Statistically Significant at 5% level i.e. P<0.05.

Table 3: Correlation Coefficient: CD_4 Count with serum enzymes in progression of HIV infection.

		Count CD4 (cells/µl)
Count CD4(cells/µl)	Pearson Correlation	1.000
	Sig. (2-tailed)	-
	N	150
AST/SGOT (IU/L)	Pearson Correlation	-.265**
	Sig. (2-tailed)	.001
	N	150
ALT/SGPT (IU/L)	Pearson Correlation	-.241**
	Sig. (2-tailed)	.003
	N	150

**. Correlation is significant at the 0.01 level (2-tailed).

Table 4: Correlation Coefficient: CD4 Count with serum enzymes in progression of HIV infection at different stages

		CD4 count ≤ 200 (cells/µl) stage III	CD4 count 201 – 500 (cells/µl) stage II	CD4 count >500 (cells/µl) Stage I
CD4 count (cells/µl)	Pearson Correlation	1.000	1.000	1.000
	Sig. (2-tailed)	-	-	-
	N	50	50	50
SGOT IU/L	Pearson Correlation	-.232	-.156	.569**
	Sig. (2-tailed)	.104	.278	.000
	N	50	50	50
SGPT IU/L	Pearson Correlation	-.215	-.125	.596**
	Sig. (2-tailed)	.134	.389	.000
	N	50	50	50

**. Correlation is significant at the 0.01 level (2-tailed).

In our study we observed statistically increased mean activity of enzymes AST and ALT in HIV group as compared to control group (P<0.05) (Table-1). Further, Serum AST and ALT Levels at different stages of HIV based on CD4 Count were compared. It was noted that AST and ALT levels statistically increased from stage I to stage III (P<0.05) (Table-2).Serum AST showed significant increase (P<0.05) when compared stage I to stage III and Serum ALT showed significant increase (P<0.05) when compared stage I to stage III with Post-Hoc Test; Tukey HSD.

Later we attempted to find correlation of CD4 Count with serum enzymes and found negative correlation in HIV group. (Table 3) Whereas, in stage wise manner negative correlation was seen in stage II and stage III group and positive correlation in stage I. (Table 4) Most of the studies have findings similar to our results.[6-13] However few studies revealed no statistically significant differences in mean AST and ALT levels in HIV group when compared to Control group.[14-15]

The variation in liver enzymes seems to be multifactorial. Oxidative stress is a process by which free reactive oxygen species cause increased activation of Kupffer cells in the liver. These activated immune cells promote stellate cell activation leading to increased production of proinflammatory and profibrotic cytokines. If left unrestricted, liver damage, fibrosis and cirrhosis may result.[16]

Mitochondrial injury occurs in patients with HIV due to increased stress on the endoplasmic reticulum. This increased endoplasmic reticulum stress may crop up due to triggering enlarged production of inflammatory cytokines, increased macrophage activation and beta-oxidation of accumulated fatty acids within the liver. The older Nucleotide reverse transcriptase inhibitors and protease inhibitors that is also able to directly cause mitochondrial toxicity. Protease inhibitor mediated alteration of adiponectin and resistin levels leads to increased body fat composition and decreased insulin sensitivity, resulting in increased interleukin-6 , hepatic stellate cell activation, and leptin, which in turn up regulates transforming growth factor-beta production and creation of reactive oxygen species. Moreover, antiretroviral drug indinavir could increase activity of hydroxymethylglutaryl coenzyme A (HMG CoA) synthase, which lead to increased cholesterol in cell membranes. It also increases activity of fatty acid

synthase, leading to increase in monounsaturated fatty acids in hepatocytes.[17-18]

The primary immune cells, Kupffer cells triggers local inflammatory responses and hepatocellular repair, whilst Hepatic stellate cells act as the primary drivers of hepatic fibrogenesis and deposition of extracellular matrix proteins. An imbalance among the activities of these two cell lines, viral agents can lead to increased hepatic cell death and fibrosis.[19]

Gut microbial translocation leads to hepatic injury primarily via increased hepatic levels of bacterial lipopolysaccharides causing hepatic inflammation. HIV viral proteins increase production of inflammatory cytokines by gut epithelium, leading to increased apoptosis of epithelial cells and breakdown of tight junctions. Gut microbial translocation has also been recognized as a possible cause of both alcoholic and non-alcoholic liver disease.[20-21]

It is also noted that medications used with larger frequency in people living with HIV, including both HAART components and medications used to take care of opportunistic infections, may direct to accumulation of toxic metabolites.[22-24]

Thus, main etiologic providers to the burden of liver diseases in HIV-infected patients include viral hepatitis co infection, nonalcoholic fatty liver disease, and anti-retroviral therapy induced liver injury and infection related factors.

CONCLUSION

Serum ALT and AST are readily available, inexpensive and routine biochemical assay used in clinical practice, especially in developing countries or limited-resource settings. Continuous monitoring of hepatic enzymes may be beneficial in people living with HIV. Further large prospective studies are needed to be carried out for improvement in recognition, diagnosis and effective management of hepatic damage by several factors. It is also important to assess effects of antiretroviral therapy drug on liver at different stages of HIV infection.

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