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Research Article

Clinical study of lipid abnormalities in anti-retroviral treatment-naive HIV patients

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ABSTRACT

Background: HIV infection has reached pandemic proportions ever since the first case was reported in 1981. Now, it continues to be the most important communicable disease in India with its associated high morbidity, mortality and treatment costs. With the introduction of highly active antiretroviral therapy, people with HIV infection now live longer. And the major contributors to morbidity and mortality are drug toxicities and metabolic derangements due to HAART, not the opportunistic infections. Dyslipidemia is one such metabolic derangement which occurs either as an adverse effect of ART drugs or due to HIV infection per se. This study was undertaken to address the second issue, as the data from India is limited.

Methods: 80 newly detected HIV patients who were naïve to antiretroviral drugs and who did not have exclusion criteria like prior diabetes mellitus, thyroid disease, hepatitis, pregnancy etc. were selected randomly and enrolled into the study over a year. A baseline complete hemogram with CD4 cell count and all necessary biochemical tests were done. The patients were grouped according to WHO staging. 80 age and sex matched healthy controls were also enrolled during the same period and they were also subjected to similar investigations. The various lipid parameters were analysed and compared between two groups as well as among patients with different WHO stages and CD4 lymphocyte counts.

Results: 80 cases and 80 controls who were age and sex matched were enrolled. Mean BMI was significantly less in cases. Among cases, 72 patients (90%) had CD4 count <200 cells/mm^3 and 59 of them had an opportunistic infection. The mean triglyceride (TG) was significantly higher in the HIV-infected patients than in the controls, 176.125 mg/dL vs. 119.225 mg/dL with a P value = 0.02. The HIV-infected patients also had significantly lower mean HDL-C 33.58 mg/dL vs. 48.38 mg/dL with a P value = 0.04. On subgroup analysis in the HIV-infected patients, the mean serum triglyceride and VLDL levels were significantly higher in those with CD4+ cell count <200 cells/mm^3 compared to those with CD4+ cell count of 200 to ≥500 cells/mm^3, with a P value of 0.04 & 0.003 respectively. Similarly, the same lipid parameters showed a rising trend in serum values as the stage of HIV infection advanced.

Conclusions: It can be concluded from the study that dyslipidemia manifesting as significant hypertriglyceridemia and low HDL cholesterol is common among treatment naïve HIV infected patients and it worsens with advanced stages of illness with decreasing CD4 cell count. Hence, a baseline lipid profile should be obtained in all HIV infected patients before initiating HAART.

Keywords: ART naïve HIV, Lipid profile, Dyslipidemia

INTRODUCTION

Incidence of human immunodeficiency virus (HIV) infection has grown to pandemic proportions soon after early cases of acquired immunodeficiency syndrome (AIDS) were reported in 1981. Over 33 million people are now living with HIV in the world and in 2007 there were 2.7 million new HIV infections and 2 million HIV-related deaths world-wide.[1] The estimated number of people living with HIV in India has increased from just over 16000 in 1990 to over 2.39 million in 2007 with more than a quarter (28 per cent) unaware of their infection.[2] HIV continues to be one of the most important communicable diseases in India. It is an infection associated with serious morbidity and high mortality, high costs of treatment and care.

Introduction of highly active antiretroviral therapy (HAART) has transformed HIV infection into a chronic manageable infectious disease. Now people with HIV infection live longer and considerable morbidity and mortality they experience now is not from AIDS related illness, but from adverse effects of ART drugs and other metabolic derangements that affects the population in general. Dyslipidemia is one such metabolic derangement that can occur either as an adverse effect of ART drugs or due to HIV infection parse even before initiation of HAART, and contributes significantly to cardiovascular morbidity and mortality.

In the early 1990s a number of investigators described the lipid abnormalities associated with HIV infection even before advent of HAART. A consistent finding from available few studies in developing countries was, that patients with advanced HIV infection or AIDS had high levels of circulating triglycerides, low levels of HDL cholesterol and a predominance of small, dense LDL particles when compared with the HIV negative individuals.[3-6] This justifies for routine assessment of the lipid profile of patients with HIV infection even before commencement of HAART, and to examine the independent effect of HIV itself on CVD risk and to inform the patient about choice of subsequent antiretroviral therapy (ART).

In this study, which was undertaken in an urban HIV care and treatment centre, we assessed the prevalence of dyslipidemia and associated cardiovascular risk factors in HIV-infected patients at the time of enrollment, prior to ART initiation.

METHODS

Newly detected HIV positive patients who were attending out-patient clinics and also those who were admitted to medicine wards at the Bangalore Medical College & Research Institute teaching hospital from October 2013 to October 2014 were the subject material for this study. Among these, patients with diabetes mellitus, serological evidence of hepatitis B/C infection, thyroid disease, pregnancy, hypertension, obesity and kidney disease were excluded.

80 newly detected HIV-positive patients (30 female and 50 male patients), who were naïve to antiretroviral (ARV) drugs, with no exclusion criteria, were randomly selected and enrolled for the study. They were divided into four groups according to their WHO Clinical staging and CD4 lymphocyte count. Patients in group 1 had CD4 counts of up to 50 cells/mm^3 of blood; those in groups 2 and 3 had respectively, CD4 counts of 50-199 and 200-350 cells/mm^3; and those in group 4 had CD4 counts of 350 cells/mm^3.

80 HIV-negative, healthy age and sex matched subjects (40 males and 40 females) were controls. They were recruited during the same period and in the same hospital as the cases.

Data collection

Information obtained from each participant was recorded in a Performa, which included socio-demographic characteristics, history of alcohol consumption and cigarette smoking as well as drug history. Anthropometric measurements (weight, height, and BMI) and cardiovascular system examination were carried out for each subject.

Random blood glucose measurement was done on the spot using a glucometer for each participant to exclude those with undiagnosed diabetes mellitus. After a 12-hour overnight fast, five milliliters of blood samples were collected from each participant by vene-puncture into plain sample tubes. The blood samples were allowed to coagulate and spun at 3,000 rpm for 10 minutes. The serum samples were collected and stored at –4°C and subsequently assayed for Total Cholesterol (TC), High Density Lipoprotein Cholesterol (HDL-C), and triglyceride (TG) within 48 hours of sample collection using an enzymatic UV method.

Presence of a derangement in any of the lipid profile parameters was defined as high total or LDL cholesterol, high triglycerides, or low HDL cholesterol according to the National Cholesterol Education Program (NCEP) adult treatment panel III (ATP III) guidelines.

Statistical analysis

The X^2 test was used to determine the significance of differences in the prevalence of dyslipidaemia in HIV-positive and control groups using SPSS software version 10.1. Student's t-test was used to compare the lipid parameters of HIV-Positive patients and Control Group subjects. Multiple correlation tests were used to determine any associations among lipid parameters, CD4 Count, WHO Clinical staging and the occurrence of Opportunistic Infections using the SPSS software. Results were considered significant only if p value <0.05.

RESULTS

Characteristics of participants

Of the 80 HIV-positive patients, 50 (62.50%) were male and 30 (37.50%) were female, while of the 80 HIV-negative subjects, 40 (50%) were male and 40 (50%) were female. The mean BMI in HIV-infected patients was significantly lower (P <0.0001). There was no statistically significant difference between the HIV-positive patients and controls in terms of proportion of subjects with a positive history of alcohol consumption (P = 0.41) or cigarette smoking (P = 0.31).

As per the WHO Clinical Staging, 20 (25%) belonged to Stage I, 37 (46.25%) of ART Naïve HIV-Positive patients belonged to Stage II, 17 (21.25%) to Stage IV and the rest of 6 (7.50%) to Stage III. 72 of the HIV-positive patients (90%) had CD4 counts<200 cells/mm^3. According to the CDC criteria, Opportunistic Infections were observed in 59 HIV-positive patients while 21 were asymptomatic (Table 1). Fifty nine HIV-positive patients had experienced at least one AIDS event based on the occurrence of Opportunistic Infections (Tuberculosis pulmonary and Extra-Pulmonary variants in 12 cases, pneumocystosis in 6 cases, toxoplasmosis in 4 cases, cryptococcosis in 4 cases, pneumonic consolidation in 4 cases, herpes zoster in 3 cases, cytomegalovirus infection in one case, cerebrovascular accident in one case and myocardial infarction in one case).

Table 1: Showing demographic comparison of study subjects.

	HIV negatives		HIV positives	
	n	%	n	%
Age group				
20-29 years	-	-	13	16.25%
30-39 years	15	18.78%	48	60%
40-49 years	31	38.75%	14	17.5%
50-59 years	15	18.75%	4	5%
60-69 years	19	23.75%	1	1.25%
Sex				
Female	40	50%	30	37.5%
Male	40	50%	50	62.5%
WHO stages				
Stage 1			20	25%
Stage2			37	46.25%
Stage3			6	7.5%
Stage4			17	21.25%
CD4 Count				
0-199/mm^3			72	90%
200-500/mm^3			8	10%

Lipid profile and lipid abnormalities

The mean triglyceride (TG) was significantly higher in the HIV-infected patients than in the controls, 176.125 mg/dL vs. 119.225 mg/dL with a P value = 0.02. The HIV-infected patients also had significantly lower mean HDL-C 33.58 mg/dL vs. 48.38 mg/dL with a P value = 0.04. The mean LDL-C (p value = 0.23) and mean TC (P value = 0.34) were similar in the two groups. A statistical increase in the VLDL values was observed in HIV-Infected patients with a mean of 41.435 mg/dL vs. 26.737 mg/dL with significant p value of 0.004 (Table 2).

Table 2: Showing comparison of mean lipid parameters between two groups.

Mean lipid values	HIV positives (n=80)	HIV negatives (n=80)	P value
Triglyceride (mg/dl)	176.125	119.225	0.02
Total cholesterol (mg/dl)	134.6	142.38	0.34
HDL-cholesterol (mg/dl)	33.58	48.38	0.04*
LDL-cholesterol (mg/dl)	71.037	75.275	0.23
VLDL-cholesterol (mg/dl)	41.435	26.737	0.004

On subgroup analysis in the HIV-infected patients, the mean triglyceride and serum VLDL levels were significantly higher in those with CD4+ cell count <200 cells/mm^3 compared to those with CD4+ cell count of 200-499 or ≥500 cells/mm^3, with a P value of 0.04 & 0.003 respectively, as depicted in the Table 3. The difference across the CD4+ cell categories was not significant for the TC (P = 0.08), LDL-C (P = 0.23) and HDL-C (P = 0.22).

Table 3: Showing correlation of mean lipid values with CD4 counts in HIV +ve cases.

Mean lipid value (mg/dl)	Low CD4 (mean<200) (n=72)	Normal CD4 (mean200&>) (n=8)	P value
Triglycerides (TG)	177.51	163.62	0.04
Total Cholesterol (TC)	135.84	123.37	0.08
HDL-Cholesterol	33	38.87	0.22
LDL-Cholesterol	71.66	65.37	0.23
VLDL-Cholesterol	42.79	24.25	0.003

Similarly, among the HIV infected patients the mean serum triglycerides and VLDL cholesterol levels were significantly higher in those patients with more advanced clinical disease (Stage 3, Stage 4) compared to those in Stage 1 and Stage 2 disease. Though HDL-C levels decreased and LDL-C levels increased with advancing HIV infection, they were not statistically significant (Table 4).

Table 4: Showing correlation of mean lipid values with WHO stage in HIV +ve cases.

Mean lipid values (mg/dl)	Stage 1 (n=20)	Stage 2 (n=37)	Stage 3 (n=6)	Stage 4 (n=17)	P value
Triglycerides(TG)	121.95	166.51	233.176	254.33	0.002
Total cholesterol (TC)	109.1	131.67	152.16	153.23	0.21
HDL-cholesterol	39.2	34.78	31	25	0.09
LDL-cholesterol	57.35	73.189	81.33	78.82	0.06
VLDL-cholesterol	30.45	40.18	44.83	49.35	0.05*

From the present study, it was found that HIV +ve patients had 92% risk of having high VLDL cholesterol levels (Absolute risk = 92.2%, Relative risk = 13) in the due course of their disease. Overall (i.e., irrespective of the specific lipid abnormality), the HIV-infected group had a significantly higher proportion of patients with dyslipidemia than the controls (P value - 0.001).

DISCUSSION

Our findings show that treatment-naïve HIV-infected patients have significantly higher levels of triglycerides (TG) and lower levels of HDL-C as compared to age- and sex-matched apparently healthy individuals. Hypertriglyceridemia worsened significantly with advancing HIV infection.

Our observations are in agreement with previous studies done in United States and other parts of sub-Saharan Africa and India, that documented significantly higher levels of TG as well as lower levels of total cholesterol (TC) and HDL-C in treatment-naïve HIV-infected individuals.[7-11,13]

The mechanism of lipid disorders observed in ART-naïve HIV-infected patients is thought to be cytokine-mediated / lipid peroxidation.[12] An association between plasma TG levels and circulating interferon (IFN)-α levels has been documented in persons with AIDS. IFN-α is believed to bring about increased TG levels through a decrease in TG clearance as well as an increase in *de novo* hepatic lipogenesis and VLDL synthesis. Although the mechanism of hypo-cholesterolemia is poorly understood, low levels of TC, HDL-C, and LDL-C have been associated with elevated levels of β-2 microglobulin.[4]

The consistent findings of low HDL-C in combination with hyper-triglyceridemia can easily increase the burden of cardiovascular diseases in HIV-infected patients by unwanted proportions. This is because hyper-triglyceridemia and low HDL-C are recognized as independent risk factors for coronary artery disease.[12] The scenario is even more complex considering the fact that ART, especially PI-based therapy, is associated with lipid changes.

Our study was not without limitations. Familial causes of dyslipidaemia were unaccounted for due to lack of facilities for such screening. Considering that the study design was cross-sectional, it is not possible to determine the temporal relationship between acquisition of HIV infection and development of dyslipidaemia. There is need for prospective studies to investigate the evolution of lipid abnormalities in HIV-infected patients.

CONCLUSION

Lipid abnormalities are common in treatment-naïve HIV-infected patients, even in the absence of major host-related risk factors for dyslipidaemia. The combination of hyper-triglyceridemia and low HDL-C is the most consistent abnormality. HIV-infected patients should, therefore, be routinely screened for lipid disorders before commencement of ART, and those found to have dyslipidaemia, should be appropriately treated. Population-based prospective studies are needed to further explore the relationship between lipid profile changes and immunological status of HIV-infected patients.

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