Original Article

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Effect of Antiretroviral Therapy on Circulating Lipid Levels in Human Immunodeficiency Virus Infected Patients: A Cross-sectional Study

Biochemistry Section

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ABSTRACT

Introduction: The antiretroviral drugs have improved the quality and extent of life of Human Immunodeficiency Virus (HIV) infected patients, yet like any other long-term medication, these are known to cause several adverse effects. One such adverse effect is on the lipid metabolism in individuals on Antiretroviral Therapy (ART).

Aim: To analyse the effect of ART on the circulating lipid levels in HIV patients. The secondary aim was to compare the lipid changes in patients treated with ZLN (Zidovudine+Lamivudine +Nevirapine) drug regimen against those, with TLE (Tenofovir+ Lamivudine+Efavirenz).

Materials and Methods: This cross-sectional study was conducted from December 2019 to March 2021 at the District Hospital, Chamarajanagar Karnataka, India. A total of 200 HIV positive patients between 18-55 years of age with no associated co-morbidities and who have been on ART were recruited into this study. Of the total 91 patients were on TLE (Tenofovir+ Lamivudine+ Efavirenz) and 109 were on ZLN (Zidovudine+ Lamivudine+Nevirapine) regimen. Blood samples were collected from all the patients and lipid profile analysis was done.

Results: Statistically significant increase was observed in all lipid parameters in the ZLN group compared to TLE group. Serum Total Cholesterol (TC) {ZLN 190.92±43.57 vs 164.23±40.7 in TLE group (p-value <0.0001)} serum Low Density Lipoprotein Cholesterol (LDL-C) {ZLN 120.44±35.46 vs 100.81±26.84 in TLE group (p-value <0.0001)}, Triglyceride (TG) {ZLN 245.68±132.42 vs 171.56±77.30 in TLE group (p-value <0.0001)} and High Density Lipoprotein Cholesterol (HDL-C) {ZLN 60.71±17.51 vs 53.31±13.8 in TLE group (p-value=0.0012)}. Also the non HDL-C levels {ZLN 130.2±39.51 vs 110.91±36.87 in TLE group (p-value <0.0005)} were higher in patients receiving ZLN drug regimen than those who were on TLE. Of the 200 HIV patients, 53 were taking ART for less than five years (mean 2.51±1.12 years), 109 were receiving ART between 5-10 years (mean 7.78±1.50 years), 38 patients were on ART treatment for more than 10 years (mean 11.73±0.76 years). A positive significant association between lipid derangement and disease/ ART duration was observed.

Conclusion: Lipid abnormalities were more in HIV patients on ZLN drug regimen, than those on TLE regimen. The longer course of disease/ART is associated with imminent lipoprotein derangement. Periodic monitoring of lipid levels are recommended in these patients.

Keywords: Dyslipidaemia, Lipid metabolism, Nucleoside reverse transcriptase inhibitor

INTRODUCTION

Human Immunodeficiency Virus (HIV) is a retrovirus that infects cells of the human immune system, mainly CD4 cells and destroys or impairs their function [1]. Acquired Immunodeficiency Syndrome (AIDS) describes the collection of symptoms and infections associated with acquired deficiency of the immune system. Infection with HIV has been established as the underlying cause of AIDS [2]. The Joint United Nations Programme on HIV/AIDS (UNAIDS) has reported that 38.4 million people are living with HIV infection in the world and 1.5 million newly got infected with HIV in the year 2021 [3]. In India, The National AIDS Control Organisation (NACO) report of 2019 states that, there are 23.48 lakh people living with HIV infection in India among which 2.69 lakh people are from Karnataka state [4].

Lipid derangement is one of the commonly encountered adverse effects of ART [5]. Individuals infected with HIV are vulnerable to lipid derangement, both due the infection and the drugs with which they are treated [6]. Though the intense ART has established a triumph of transforming the fatal HIV infection into a chronic manageable disease, the associated dyslipidaemia in these patients make them prone to cardiovascular disease. Cardiovascular disease is the second (after malignancy) non infection related cause of death in HIV infected patients in the world [7]. Thus, the benefits of ART may be sabotaged by the untoward consequence of associated side-effects.

There have been various studies in the recent past which have shown the adverse influence of ART on lipid levels in individuals taking these medications. Ombeni W and Kamuhabwa AR, have observed varied prevalence of dyslipidaemia in HIV patients on ART [8]. A research project undertaken by Ceccato MGB et al., reports lipid derangement in HIV individuals taking ART [9]. Singh J et al., have made a revelation after conducting their study that HIV infection alone causes alterations in lipid levels [10].

The researches reporting these findings are extremely limited from Chamarajanagar, the southern-most district of Karnataka, India. The aim of the study was to analyse the effect of ART drugs on the circulating lipid levels in HIV patients in this region. The second objective was to compare the lipid changes in HIV patients treated with ZLN drug regimen against those with TLE. The study also aimed to examine the association of duration of the disease/ART with lipid levels in these patients.

MATERIALS AND METHODS

The cross-sectional study was conducted from December 2019 to March 2021 at the Antiretroviral Centre of the District Hospital, Chamarajanagar, which is also the Teaching Hospital, associated to Chamarajanagar Institute of Medical Sciences, Chamarajanagar, Karnataka, India. The approval from Institutional Ethics Committee (IEC) was obtained (Letter no. CIMS/IEC-01/2018-2019, dated 06/09/2019). An informed consent was taken from all 200 HIV

patients who were included into the study. The patients were ensured confidentiality about their identity.

Inclusion criteria: HIV patients on ART between 18 and 55 years of age with no acute infections.

Exclusion criteria: HIV patients with other medical or surgical co-morbidities, defaulters and pregnant ladies.

Sample size calculation: The sample size was calculated based on the HIV patient turnover at the study centre. On an average was 190 patients visited the centre in a month. Based on the Yamane equation, $n=N/1+Ne^2$.

n=Sample size

N-Known Population

e-Margin of error (for 95% confidence level, Margin of error=0.05). The calculation made by using the above formula, a sample size of 200 HIV patients was estimated and incorporated in the study.

Among 200 HIV patients, 109 were on ZLN (Zidovudine+Lamivudine +Nevirapine) and 91 were on TLE (Tenofovir+Lamivudine+Efavirenz) regimen. They were assigned as ZLN and TLE groups respectively.

Study Procedure

A random blood sample was drawn from all 200 patients and Biochemical parameters were estimated on fully automated Chemistry analyser, ERBA XL-640. Though the lipid profile test is processed ideally on a fasting blood sample, to encourage the participants, who were hesitant to undergo blood investigation, relaxation of the clause of giving a fasting blood sample to a random sample was made which encouraged them to enroll into the research project. Recent studies prophases that serum TC, HDL and LDL-c estimation do not require fasting status for analysis and if TG are estimated in a random blood sample, then by extending its normal reference range to <175 mg/dL, the TG levels can be interpreted [11]. In the current study, these guidelines are incorporated to assess the lipid parameters analysed on a random sample.

The random blood glucose was estimated by glucose oxidase peroxidase method. Serum creatinine (by Jaffe's method) and Blood urea (Urease/Glutamate Dehydrogenase method) levels were measured in these patients, to rule out possible kidney dysfunction and only those whose levels were within in the normal reference range were included in the study. The serum TC was measured by Cholesterol Oxidase-phenol 4-aminoantipyrine peroxidase method. Serum High Density Lipoprotein cholesterol (HDL-c) and Low Density Lipoprotein cholesterol (LDL-c) assays were done by direct methods.

Serum TG was analysed by Glycerol-3-phosphate Oxidase-Peroxidase method. The rest are the calculated parameters. Very Low Density Lipoprotein (VLDL) is calculated as TGL/5. Non HDL-c=TC:HDL-c.

STATISTICAL ANALYSIS

The results were compiled and tabulated on Microsoft Excel software. Following descriptive statistics were employed in the present study-Mean, standard deviation, frequency and percent. For inferential statistical analysis, Chi-square test procedure which tabulates a variable into categories and computed Chi-square statistic was used. Fisher's-Exact significance values were considered, when cell entries were less.

RESULTS

The mean age of the participants was 39.66 years, gender distribution is shown in [Table/Fig-1]. [Table/Fig-2] shows comparison of Mean±SD of lipid parameters between HIV patients taking ZLN with TLE regimen.

Gender	n	Mean	Std. Error
Male	87	41.7356±7.33811	0.78673
Female	113	38.0789±8.51770	0.79776
Total	200	39.6617±8.21249	0.57926

[Table/Fig-1]: Gender distribution.

Lipid parameters	Normal reference rage	Mean±SD ZLN group n=109	Mean±SD TLE group n=91	p-value
Total cholesterol (mg/dL)	150-200	190.92±43.57	164.23±40.7	0.0001
High density lipoprotein (mg/dL)	40-60	60.71±17.51	53.31±13.8	0.0012
Low density lipoprotein (mg/dL)	<100	120.44±35.46	100.81±26.84	0.0001
Triglycerides (mg/dL)	<175	245.68±132.42	171.56±77.30	0.0001
Very low density lipoprotein (mg/dL)	10-50	49.12±26.35	34.21±15.59	0.0001
Non HDL cholesterol (mg/dL)	<130	130.2±39.51	110.91±36.87	0.0005

[Table/Fig-2]: Comparison of lipid parameters.

There was a statistically significant elevation in the lipid parameters in those with the disease and on ART between five and 10 years as against to those for less than five years. However no significant change in lipid levels was observed between those with disease and on ART duration of 5-10 years and those who were for more than 10 years [Table/Fig-3].

The levels of HDL-c, LDL-c, TC were significantly increased as the disease/ART duration increased [Table/Fig-4].

Lipid parameters	<5 years n=53	5 to 10 years n=109	p-value	5 to 10 years n=109	>10 years n=38	p-value
Total cholesterol (mg/dL)	162.79±37.8	184.16±47.12	0.004	184.16±47.12	185.63±39.14	0.86
High density lipoprotein (mg/dL)	51.14±14.10	58.52±14.96	0.003	58.52±14.96	62.62±20.33	0.18
Low density lipoprotein (mg/dL)	101.3±25.27	115.48±35.85	0.01	115.48±35.85	114.3±32.97	0.85
Triglycerides (mg/dL)	179.75±95.11	224.80±123.1	0.02	224.80±123.1	220.03±118.74	0.83
Very low density lipoprotein (mg/dL)	37.07±18.97	44.65±24.82	0.05	44.65±24.82	42.95±23.57	0.71
Non HDL cholesterol	111.65±35.22	125.64±42.83	0.02	125.64±42.83	123.0±32.76	0.72

[Table/Fig-3]: Comparison of lipid parameters between patients cohort distributed based on disease/ART duration.

Parameters	Value	df	Asymp. Sig. (2-sided)
Total cholesterol (mg/dL)	13.074	4	0.011
High density lipoprotein (mg/dL)	11.644	2	0.003
Low density lipoprotein (mg/dL)	12.184	2	0.002
Triglycerides (mg/dL)	2.086	2	0.352
Very low density lipoprotein (mg/dL)	6.177	2	0.046
Non HDL cholesterol	2.364	2	0.307

[Table/Fig-4]: Pearson's Chi-square association between lipid parameters and duration of the disease/ART.

DISCUSSION

The mean serum TC, HDL-c, and Non-HDl-c were within the normal reference ranges for the entire group. Zhou DT et al., also reported that the lipid levels were within reference range in their study [12]. Serum LDL-c, and TG levels were however elevated in the current

study populace. The same was observed and reported Wafai N et al., in their study on HIV patients [13]. In a study conducted in Ethopia on HIV patients on first line ART, Tadewos A et al., have reported hypertriglyceridaemia [14]. Increase in TG levels in HIV positives was also observed by Dave JA et al., in a project done in South Africa [15].

The HIV patients in the present study largely constituted patients prescribed with combination regimen of Zidovudine (300 mg)+ Lamivudine(150 mg)+Nevirapine (200 mg) twice daily regimen and Tenofovir (300 mg)+Lamivudine (300 mg)+Efavirenz (600 mg) once daily regimen. In the ZLN combination, Zidovudine and Lamivudine are drugs belonging to Nucleoside Reverse Transcriptase Inhibitors (NRTI), Nevirapine is a Non Nucleoside Reverse Transcriptase Inhibitor (NNRTI). Similarly, among TLE drugs Tenofovir is a Nucleotide Reverse transcriptase inhibitor (NtRTI) and Efavirenz is non Nucleoside Reverse transcriptase inhibitor. After analysing and comparing lipids components of patients between the groups, the lipid dysfunction appears to be more in the group prescribed with ZLN regimen. All the lipid particles, TC, TG, LDL-c were significantly elevated in patients on ZLN therapy compared to TLE. This was in accordance with findings by Gurav N et al., who have reported hypertriglyceridaemia and hypercholesterolaemia in HIV patients on ZLN compared to patients, who were on TLE [16]. Apart from this, the current study reports a significant increase in HDL-c levels in patients on ZLN than in TLE group. Study by Van Leth F et al., have compared Nevirapine (NVP) and Efavirenz (EFV) with regard to lipid response they elicit in HIV patients and have found that NVP-containing ART shows larger increases in HDL-c and decreases in TC:HDL-c ratio than an EFV-containing regimen [17].

Several studies have compared ZLN with TLE drug regimen with respect to change in CD4 count and emergence of opportunistic infections [18]; immunological outcome and effect on liver function [19]; adverse effects [20]; clinical and immunological responses [21]. In all these research projects TLE regimen therapy outcome has emerged better than ZLN. Gallant JE et al., observed that, when tenofovir was compared to zidovudine, there was significantly smaller increase in total cholesterol and LDL-c observed with tenofovir use [22].

The HIV infected patients in the present study were on ART for two years till more than 13 years. The study intruded into explore whether an association with degree of dyslipidaemia and duration of the disease/ART existed. It was noticed that, a positive correlation existed between serum TC, HDL-c ad LDL-c levels and disease/ ART duration. This was in accordance with the findings by Kemal A et al., who also report association between dyslipidaemia and duration of ART, in Ethiopia [23].

There are several in-vitro and in-vivo studies which have demonstrated that HIV infection prompts dyslipidaemia. The retro virus, HIV, stimulates lipogenesis in the liver and alters lipid profile of the host [6]. The virus induces synthesis of enzymes and proteins that promotes fatty acid synthesis and increases the LDL-c, TGL levels in the circulation. It also alters lipid metabolism, transport and stimulates oxidation of circulating lipoproteins [24]. With the initiation of ART, the lipid derangement appears to fall back to baseline [25]. However, the cardioprotective effect of ART wanes away and dyslipidaemia resurfaces with the continued course of the drugs [26]. The pathogenesis of ART-related dyslipidaemia is multifactorial. The ART have direct effect on endothelial and adipocyte cell function. This causes the release of proinflammatory cytokines like interleukin-1, interleukin-6, Tumour necrosis factor-α from these sites. These factors inhibit lipoprotein lipase activity, decrease TGL clearance and promote hepatic VLDL production [10].

There are two NRTIs in the drug regimen of patients of present research. The NRTIs cause dyslipidaemia by decreasing transcription of mitochondrial RNA, which causes upregulation of nuclear genes involved in transcriptional regulation of mitochondrial RNA and oxidation of fatty acids [27]. Efavirenz, belonging to NNRTI class of drug found here. It is also known to be associated with high plasma lipid levels by mechanism similar to that exerted by NRTIs [28]. Nevirapine, another NNRTI found in the present study is associated with a favourable lipoprotein profile, as it increases HDL-cholesterol and apo A1 plasma levels [29]. This explains, the high HDL-c levels in ZLN group of the study, as compared to the TLE group.

The evolution of new ART has paved way to substitute dyslipidaemia, causing medications with more lipid friendly drugs. Over the years, Stavudine has been replaced by Zidovudine. Tenofovir, a NtRTI is more lipid compliant as proven by studies [30] and NACO now recommends, Tenofovir based ART regime, as the first line regimen for newly diagnosed HIV patients [31].

Limitation(s)

The cross-sectional nature of the study, made it difficult to analyse any causality.

CONCLUSION(S)

The current study validates the prevalence of dyslipidaemia in HIV patients on ART, enrolled at the ART centre of Chamarajanagar. The study also ascertains that lipid abnormalities are more in HIV patients on ZLN drug regimen than those on TLE regimen. The longer course of disease/ART is associated imminent lipoprotein derangement in HIV infected individuals. The ART has increased the lifespan of the individuals living with HIV infections. By doing so, the people living with HIV now involve a good percentage of elderly people, who like rest of the population have age related health issues. Dyslipidaemia, is one among them. HIV infected people have to now confront cardiovascular disease risk not only due to their environmental and genetic predisposition but also due to the viral infection and the therapy to fight the infection. This amplifies the CVD risk manifold in these people. The ART should now be designed to address this challenge. This can be achieved by Institution of novel group of ART, which are more lipid compliant. Likewise regular monitoring of their blood lipid parameters and timely intervention by lipid lowering drugs, will further enhance their health status and promote longevity of these individuals.

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