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Original Research Paper

General Medicine

A STUDY TO EVALUATE THE IMPORTANCE OF FASTING LIPID PROFILE ESTIMATION AS THE PART OF INITIAL EVALUATION OF HIV POSITIVE PATIENTS BEFORE STARTING HAART

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ABSTRACT

BACKGROUND:-There is evidence that ART is associated with lipodystrophy syndrome, a disturbance of lipid metabolism characterised by insulin resistance, dyslipidaemia, and fat maldistribution, metabolic bone disease (osteopenia and/or osteoporosis), and lactic acidosis. ART- associated dyslipidaemia is characterized by elevated serum concentrations of total cholesterol, triglycerides, low density lipoprotein 2(LDL-c), very low-density lipoprotein (VLDL), and Apo lipoprotein B (apoB) and low levels of high density lipoprotein (HDL-c) constituting an atherogenic lipid profile[1]. **MATERIAL AND METHODS:-**In this study 143 young patients who were attending the Antiretroviral Therapy Plus Centre & Medicine Wards, ACSR GMC NELLORE were included randomly. **Sample preparation and Biochemical assay :-**5ml of venous blood sample was collected by venipuncture from 12 hours overnight fast and centrifuged at 3000 cycles per minute and serum was separated for lipid profile measurement within one hour of blood collection. The serum levels of TC, HDL-C, LDL-C, VLDL and TG were measured using AU480 BECKMANS random access fully automated auto analyzer at Biochemistry laboratory, ACSR GMC, NELLORE. **RESULTS;-**TC, LDL and TC/HDL lipid profiles are significant. F-Significant values are <0.05, reject null hypothesis. It means that the difference among the lipid profiles of TC, LDL and TC/HDL in the study group is statistically significant with respect to regimen groups. HDL, TG and VLDL lipid profiles are not significant. F-Significant values are >0.05, no evidence to reject null hypothesis. It means that the no significant difference among the lipid profiles of HDL, TG, and VLDL in the study group is not statistically significant with respect to regimen groups. **CONCLUSIONS:-**Significant metabolic and morphological alterations occur in HIV infected patients especially in patients on HAART. The patients on HAART had an elevated Castelli Index I, indicating an increased risk for atherosclerotic cardiovascular disease in this population. There is need to assess lipid profiles at baseline before initiation of HAART treatment and lipid profile monitoring during therapy to monitor any rising trends. New medications with more lipid friendly profiles within existing drugs such as darunavir (PI), etravirine (NNRTI), new classes of drugs such as integrase inhibitors (raltegravir) and CCR5 inhibitors (maraviroc) can be used to avoid dyslipidaemia.

KEYWORDS : NACO - National AIDS Control Organisation NCEP-ATP III - National Cholesterol Education Program, Adult Treatment Panel III SREBPI - Sterol Regulatory Enhancer-Binding Protein- CETP- Cholesterol Ester Transfer Protein

INTRODUCTION:-

Dyslipidaemia has also been associated with the use of HAART.Protease inhibitors have been mostly implicated but other class of drugs nucleoside reverse transcriptase inhibitors also were found to alter lipid profile.

Protease inhibitors interfere with cholesterol synthesis, by inhibition of the proteasome, which regulates Apo lipoprotein B production. It also inhibits sterol regulatory enhancer-binding protein-1 (SREBPI) causing increased hepatic lipid production[2].

The activity of cholesterol ester transfer protein (CETP), which transfers cholesterol esters from HDL-C to Apo lipoprotein-B containing proteins is elevated in HIV infection and its activity correlates inversely with serum HDL concentrations[3].Protease inhibitor and efavirenz induce lipoatrophy by inhibiting SREBP1 (Sterol regulatory enhancer binding protein) which mediates activation of Retnoid X receptor, PPARÝ coactivator1. Except Atazanavir, all protease inhibitors cause lipodystrophy and dyslipidemia.

Friis-Møller N et al[4]. reporting the results of a large cross-sectional study noted that hypercholesterolemia(more than 240 mg /dl) in 27% of subjects receiving combination therapy that included a protease inhibitor, 23% receiving non nucleoside reverse-transcriptase inhibitor and 10% receiving only nucleoside reverse-transcriptase inhibitors. In the Swiss HIV Cohort, triglycerides tend to decrease in those treated with nevirapine but increase with efavirenz.

Use of the NRTI stavudine has been associated with a worse lipid profile than the nucleotide reverse transcriptase inhibitor (NtRTI) tenofovir, with significantly larger increase in total cholesterol, LDL-C and triglycerides.

MATERIALS AND METHODS:-

In this study 143 young patients who were attending the ART Plus Centre & Medicine Wards ACSR GMC, NELLORE were included randomly.

Inclusion Criteria:-

1. Patients selected in random attending ART plus centre.
2. Age group 20 – 49 years.
3. HIV infection confirmed by Triple ELISA testing according to NACO guidelines.
4. Patients on HAART treatment groups for more than 2 years.

Exclusion Criteria:-

1. Diabetic patients,
2. Tuberculosis positive and on ATT
3. Nephrotic range proteinuria.
4. Overt Hypothyroidism.
5. Patients on Antihyperlipidemic drugs, Thiazides, Steroids, Beta blockers.
6. HIV patients on HAART for less than 2 years.

Patients included in the study were divided into 4 regimen groups.

1) TEL (Tenofovir, Efavirenz, Lamivudine)
2) TLAR (Tenofovir, Lamivudine, Atazanavir, Ritonavir)
3) ZLE (Zidovudine, Lamivudine, Efavirenz)
4) ZLN (Zidovudine, Lamivudine,Nevirapine)

Sample preparation and Biochemical assay :-

5ml of venous blood sample was collected by venipuncture from 12 hours overnight fast and centrifuged at 3000 cycles per minute and serum was separated for lipid profile measurement within one hour of blood collection. The serum levels of TC, HDL-C, LDL-C, VLDL and TG were measured using AU480 BECKMANS random access fully automated auto analyzer at Biochemistry laboratory, ACSR GMC, NELLORE . TG and total TC were evaluated with enzymatic method and HDL-C and LDL-C were analyzed by enzymatic method when triglycerides> 400 mg/dL. Low-density lipoprotein cholesterol (LDL-C) was calculated using Friedewald's formula in individuals with triglycerides < 400 mg/dL. To assess cardiovascular risk, Castelli's Index I was calculated using the ratio: TC/HDL-C; a Castelli Index I > 5.1 for men and > 4.4 for women were considered indicative of an elevated risk. In accordance with the US National Cholesterol Education Program, Adult Treatment Panel III guidelines[5], abnormal lipid profile was defined as TC ≥ 200 mg/dL, HDL-c < 40 mg/dL, LDL-c ≥ 130 mg/dL, TG ≥ 150 mg/dL and TC/HDL-c ratio ≥ 5.

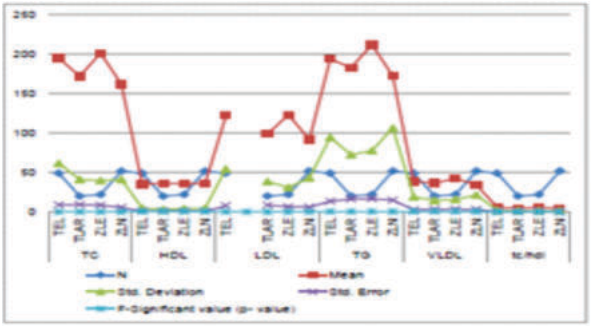
RESULTS:-

TABLE-1 lipid profile in study regimen groups

		N	Mean	Std. Deviation	Std. Error	F-Significant Value (p- value)	Result
TC	TEL	49	195.41	61.697	8.814	0.001	Significant
	TLAR	20	172.15	41.107	9.192		
	ZLE	22	201.64	39.842	8.494		
	ZLN	52	162.10	41.048	5.692		
	Total	143	181.00	51.305	4.290		
HDL	TEL	49	34.96	4.765	.681	0.574	Not Significant
	TLAR	20	36.35	3.345	.748		
	ZLE	22	35.68	4.145	.884		
	ZLN	52	35.98	4.518	.627		
	Total	143	35.64	4.395	.368		
LDL	TEL	49	122.10	54.520	7.789	0.003	Significant
	TLAR	20	99.15	38.486	8.606		
	ZLE	22	123.27	31.035	6.617		
	ZLN	52	91.94	43.219	5.993		
	Total	143	108.10	47.185	3.946		
TG	TEL	49	194.02	94.618	13.517	0.379	Not Significant
	TLAR	20	183.35	72.565	16.226		
	ZLE	22	212.27	77.756	16.578		
	ZLN	52	172.54	106.474	14.765		
	Total	143	187.52	94.290	7.885		
VLDL	TEL	49	38.57	19.012	2.716	0.375	Not Significant
	TLAR	20	36.65	14.597	3.264		
	ZLE	22	42.32	15.616	3.329		
	ZLN	52	34.23	21.529	2.986		
	Total	143	37.30	19.006	1.589		
tc/hdl	TEL	49	5.5714	1.69658	.24223	0.001	Significant
	TLAR	20	4.8000	1.28145	.28654		
	ZLE	22	5.6364	1.13580	.24215		
	ZLN	52	4.5192	1.21253	.16815		
	Total	143	5.0909	1.47232	.12312		

TC, LDL and TC/HDL lipid profiles are significant. F-Significant values are <0.05, reject null hypothesis. It means that the difference among the lipid profiles of TC, LDL and TC/HDL in the study group is statistically significant with respect to regimen groups.HDL, TG and VLDL lipid profiles are not significant. F-Significant values are >0.05, no evidence to reject null hypothesis. It means that the no significant difference among the lipid profiles of HDL, TG, and VLDL in the study group is not statistically significant with respect to regimen groups.

FIGURE-1 lipid profile in study regimen groups



DISCUSSION:-

Lipid profiles should be performed at baseline before commencement of antiretroviral therapy and then periodically through treatment follow-up to monitor any rising trends.

Farhi et al[6]. in 2008 had a cross-sectional study in HIV patients on HAART and found that there is 77.5% prevalence of dyslipidaemia. We found that the prevalence of raised TC in the HAART group was high.

Several studies have found that stavudine was more involved in the occurrence of lipid derangements as compared to other NRTIs. However, instead of stavudine, our participants were either on tenofovir or zidovudine. We found no difference in lipid profiles (TC, LDL-c and HDL-c) when participants on tenofovir were compared to those on zidovudine. This is in line with the findings of Buchacz and colleagues in Uganda and those of Yone and colleagues in Cameroon.

Adewole et al[7]. in 2010 had a cross-sectional study on NNRTI drugs for 12 months and found that nevirapine promoted raised HDL-c and stabilisation of TC and TG.

Lu et al[8]. in 2011 conducted a prospective observational study for 48 weeks on HIV patients taking 2 NRTI drugs and atazanavir or atazanavir and ritonavir and found that atazanavir regimen was well tolerated and resulted in significant improvement in hyperlipidemia.

In contrary to the above study, Agete Tadewos, et al[9]. in 2012, stated that use of antiretroviral therapy regimens that contain Efavirenz and Nevirapine were associated with raised total cholesterol, LDL-cholesterol and triglycerides, an established atherogenic lipid profiles.

In the present study, the raised TC and LDL-c were significantly and positively associated with the use of HAART treatment and the findings are in line with another study conducted in Cameroon. Moreover, NNRTIs have been reported to derange lipid profiles during therapy. However, supportive evidences are very scarce in Sub-Sahara African countries concerning lipid derangements in patients receiving NNRTIs treatment regimens. We found a similar scenario with other cross-sectional studies carried out in resources-constrained settings with reported prevalence of high level of total cholesterol ranging from 23 to 41 % in patients treated with NNRTI based regimens.

Molla Abebe,Samuel Kinde, et al[10]. in 2013 had a cross-sectional study on Antiretroviral treatment associated dyslipidemia among HIV infected patients on HAART at Burayu Health Center, Addis Ababa, Ethiopia and concluded that HAART with regimens NRTIs and NNRTIs were associated with potentially atherogenic lipid profile levels in Ethiopian setting.The association between HAART and adverse lipid profile has been largely described for regimens that include PIs, but this is contrary to our findings. This may be due to the small number of patients treated with PIs in our study. In this study, high TC and LDL-c were associated with HAART use.

The mean values for patients on TEL regimen are TC is 195.4 mg%, LDL 122.1 mg%, HDL 34.96 mg%, TG 194.02 mg% and TC/HDL is 5.5714. In patients treated with TLAR regimen the mean values of TC is 172.15 mg%, LDL 99.15 mg%, HDL 36.35 mg%, TG 183.35mg% and TC/HDL is 4.8.

In patients treated with ZLE regimen, TC is 201.64 mg%, LDL 123.27 mg%, HDL 35.68 mg%, TG 212.27 mg% and TC/HDL is 5.6364. In patients treated with ZLN regimen, TC is 162.1 mg%, LDL 91.94 mg%, HDL 35.98 mg%, TG 172.54 mg% and TC/HDL is 4.5192.

In our present study, TC, LDL AND TC/HDL lipid levels are significant. F-significant values are <0.05, reject null hypothesis. The difference among the lipid profiles of TC and LDL in the study group is statistically significant with respect to regimen groups. The HDL, TG and VLDL are not significant. F-significant values are >0.05, no evidence to reject null

hypothesis and there is no significant difference among the lipid profiles of HDL, TG and VLDL in the study group and is not statistically significant with respect to regimen groups.

Similar to our findings, a cross-sectional study from India showed significantly higher prevalence of dyslipidemia in the first line treatment groups. Moreover, according to an another study from India, at baseline and at 12 months, TC was >200 mg/dl for 1% and 26% of patients; LDL-C level was >130 mg/dl for 3% and 23%; HDL-C level was <40 mg/dl for 91% and 23% respectively.

In Canada, among 745 ARV treated patients, 10% and 16% showed increased TG and TC levels respectively. Unlike to the above and in agreement with ours is a study from Cameroon that showed the prevalence of TC ≥200 mg/dl as 37.6% in ART groups. The equivalents for LDL-C ≥130 mg/dl was 46.4%.

In line to our finding, a long term analysis on plasma lipid concentration was performed in patients starting first-line antiretroviral therapy in Netherlands and showed concentrations of TC, LDL-C and TG continued to increase with slight decrease in HDL-C. Similarly, a study from Cameroon showed TC, LDL-C and HDL-C levels increased significantly, but TG remained unaltered with first line ARV therapy for 3 months. This might be due to short treatment period.

Limitations of the study:-

This is a cross-sectional study with no follow up of patients to see the effects of HAART at individual level and inference about causal relationship is not possible. In addition, this does not include all potential confounders of dyslipidaemia such as physical exercise. Comprehensive cardiovascular risk stratifications were not assessed in this study. However, the increased risk of cardiovascular diseases associated with described lipid derangements is well known and long term use of first-line HAART may have an impact on cardiovascular system. Subsequent studies could address the issue of the small number of participants and the lack of HIV untreated and HIV-negative controls that our study could not handle.

CONCLUSION:-

Significant metabolic and morphological alterations occur in HIV infected patients especially in patients on HAART.

There is a statistically significant increase in the total cholesterol and LDL cholesterol. There is statistically insignificant increase in total triglycerides, VLDL and decrease in HDL cholesterol in HIV patients on HAART.

Dyslipidemia is more in the efavirenz based regimens compared to nevirapine, tenofovir, lamivudine, zidovudine and atazanavir containing regimens.

There is need to assess lipid profiles at baseline before initiation of HAART treatment and lipid profile monitoring during therapy to monitor any rising trends.

New medications with more lipid friendly profiles within existing drugs such as darunavir (PI), etravirine (NNRTI), new classes of drugs such as integrase inhibitors (raltegravir) and CCR5 inhibitors (maraviroc) can be used to avoid dyslipidaemia.

The results also recommend implementation of well-controlled cohort studies for the evaluation of long-term effects of HAART treatment on lipid profiles.

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