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Original Research Article

A Study of Metabolic Syndrome in HIV patients treated with NNRTI based Antiretroviral Therapy

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Abstract: Several chronic infections like HIV have reported an increased prevalence of metabolic syndrome. With the advent of highly active antiretroviral therapy (HAART), the prognosis of HIV patients have improved dramatically. However, multiple unforeseen complications have been seen in HIV patients on long-term HAART including metabolic syndrome. As multiple drugs are used for HAART with different backbones, the incidence of metabolic syndrome has been shown to vary with different regimes of antiretroviral therapy (ART), though the role of NNRTI-based ART has not been clearly implicated in the genesis of metabolic syndrome in treated HIV patients. The present study aims to study the effects of NNRTI on different components of metabolic syndrome in HIV patients. In this cross-sectional study, 70 HIV patients treated with ART (aged 20-50 years) and 64 ART-naive patients were included as control group. Metabolic syndrome prevalence was examined using the US Metabolic syndrome prevalence was examined using the US National Cholesterol Education Program Adult Treatment Panel III (ATP III) (NHLBI updated definition 2005) criteria. All patients received NNRTI-based ART (either Efavirenz or Nevirapine, in the recommended doses) for a mean period of 14 months. Statistical testing was conducted with the statistical package for the social science system version SPSS 17 and Graph PadInStat. Statistical significance was set at $p< 0.05$. There was no significant difference in the prevalence of metabolic syndrome in NNRTI based ART treated and ART naïve patients. (41.4% vs. 26.6%). The mean weight in kg(45.19 ± 9.39vs.49.57±10.97, p=0.015); and BMI was higher in ART treated patients than ART naïve (18.19 ± 3.05Kg/mt^{2}vs.19.61 ± 3.70Kg/mt2, p=0.017). ART treated patients had higher median serum Cholesterol level (135.75 mg/dl (IQR- 92.10 - 166.40) vs. 106.53 mg/dl, (IQR- 85.17 - 129.35) respectively, p=0.022) and higher serum HDL-C level [26.65mg/dl (18.15-34.00) vs. 18.85 mg/dl (15.02-28.20), p=0.002] than ART naïve patients. HIV disease duration was significantly more in ART-treated patients than ART naïve. (18 months vs. 1 month).Most common components of metabolic syndrome in ART-treated and ART naïve patients were reduced HDL (96.87% & 85.17% respectively) and elevated Triglycerides (56.25% vs. 61.42% respectively). Prevalence of reduced HDL was more in ART naïve as compared to ART-treated patients (96.87% vs. 85.17%, p=0.033). Efavirenz-based ART-treated patient had more prevalence of metabolic syndrome than Nevirapine-based ART-treated patients (64.7% vs. 34%, p=0.025). Elevated FBS prevalence was more in Efavirenz-based ART-treated patients than Nevirapine-based ART-treated patients. (32.1% vs. 58.87%, p=0.049). ART-treated and ART naïve HIV patients had increased prevalence of metabolic syndrome. Elevated Triglycerides and reduced HDL were the major components of metabolic syndrome in both the groups. Efavirenz-based ART had higher prevalence of metabolic syndrome than Nevirapine-based ART.
Keywords: Metabolic syndrome (MeTS), HIV, CD4 count, WHO stage, HAART

INTRODUCTION

As of today, 25 different Anti-retroviral medications from 6 different classes have been approved for treatment of HIV patients which are administered in combination. All approved ART regimens consist of two NRTIs plus one non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs) or an integrase strand transfer inhibitors (INSTIs). The response of these combinations in decreasing HIV RNA load and increasing CD4 along with clinical improvement have been proved in multiple clinical trials around the world and the choice of the initial

regime depend on the national guidelines of individual countries. The success of these regimes has dramatically changed the prognosis of HIV patients converting an once fatal infection to a chronic one albeit with some restrictions in life activity and undesirable side effects not predicted earlier.

However, HIV patients have been found to have increased incidence of Metabolic Syndrome (MeTS). Metabolic syndrome is a complex of interrelated risk factors for Cardiovascular Disease (CVD) and diabetes. These factors include dysglycemia, raised blood pressure, elevated triglyceride levels, low high-density lipoprotein cholesterol levels, and obesity (particularly central adiposity). Though MeTS have been reported all around the globe across several countries, the pathogenesis of MeTS is still unclear. The initial event is believed to be development of abdominal obesity, which is now known to cause insulin resistance and release of multiple cytokines like Free Fatty Acids (FFA), proinflammatory mediators (Tumor Necrosis Factor Alpha (TNFα) and Interleukin-6 (IL-6), Plasminogen Activator Inhibitor-1 (PAI-1), and C-Reactive Protein.

Of late, multiple studies have linked MeTS to several chronic viral infections like HIV, HBV and HCV infections. Chronic low-grade infections as seen in these disease conditions lead to increase levels of the cytokines which in some way lead to development of the components of MeTS. HIV-infected patients present are doubly susceptible as regards MeTS. It has been described in treatment naive HIV patients [1] as well as those who have responded to different HAART regimens. Most of the studies concluding the role of ART in the pathogenesis of MeTS have been on PI based ART. A search of literature implicating NNRTI-based ART in the pathogenesis of MeTS has yielded only a handful of studies.

Meta-analysis of studies on HIV patients have found higher incidence of MeTS in patients treated with PI-based ART as compared to those with NNRTI-based ART. However, the number of such studies are few [2]. This study intends to analyse the prevalence of metabolic syndrome in patients receiving first-line ART which includes 2 NRTIs with either Efavirenz or Nevirapine as NNRTI backbone.

SUBJECTS AND METHODS

This was a cross-sectional evaluation of metabolic syndrome in HIV patients conducted at the Medicine Department of Silchar Medical College, Silchar between the period of Jan 2013 to June 2014 which included both outpatients as well as hospitalized patients.

The study was conducted on HIV patients > 18 years of age, attending outpatient and inpatient departments of Medicine of Silchar Medical College. Inclusion criteria were 1) confirmed HIV infection done at Integrated Counseling and Testing Centre (ICTC), Laboratory of Silchar Medical College where tests were done as per National Aids Control Organization (NACO) guidelines[3]. 2) Men and women > 18 years of age. Participation was voluntary and all patients who gave formal consent were included in the study. These patients were divided into two groups 1)Patients treated with first-line ART for minimum duration of 12 months and 2) Patients who were ART naïve acting as control Exclusion criteria included 1) Patients who were seriously ill or had associated chronic inflammatory conditions like Hepatitis B and C, 2) Chronic diseases like Rheumatoid arthritis, SLE 3) Diseases associated with lipid abnormalities like hypothyroidism, familial dyslipidemia 4) pregnant and lactating women, 5) metabolic diseases like chronic kidney disease, cholestatic liver disease 6) patients on drugs that affect lipid and carbohydrate metabolism 7) patient who had a change of ART regime.

The ultimate study group consisted of 64 ART naïve acting as controls and 70 HIV patients on NNRTI based ART. All patients received either Nevirapine or Efavirenz in the recommended doses. A comprehensive physical examination was performed in all patients included in the study with special attention to anthropological features, blood pressure measurement and HIV-related opportunistic diseases. All patients were given a set of questionnaire for information regarding age, sex, family history, substance abuse, characteristics related to HIV infection and use of medications. Patients who were illiterate and unable to answer the questionnaires were helped by departmental staff.

The study was approved by the ethics committee of the College.

Laboratory Analysis

All HIV patients included in the study were investigated as per the protocol developed by NACO, which is the apex body formulating care of HIV patients in India. Blood glucose and lipid profiles were estimated in every patient as per standard methods.CD4 count was done at diagnosis in every patient. Depending on the presenting features, investigations were also done to diagnose any co-existing opportunistic infections and other associated diseases. Laboratory Analysis

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Diagnosis of Metabolic Syndrome

Though several criteria exist for diagnosis of MeTS, the present study adopted the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III (2001) (NHLBI updated metabolic syndrome definition, 2005) [4] for defining metabolic syndrome in the study group. Metabolic syndrome was said to be present if patient fulfill any three or more of the following criteria:

• Elevated waist circumference- ≥102 cm (≥40 inches) in men and ≥88 cm (≥35 inches) in women.
• Elevated triglycerides ≥150 mg/dl (1.7 mol/L) Or On drug treatment for elevated triglycerides
• Reduced HDL-C- ≤40 mg/dl (≤1.03 mol/L) in men and ≤50 mg/dl (≤1.3 mmol/L) in women or on drug treatment for reduced HDL-C
• Elevated blood pressure- ≥130 mm Hg systolic blood pressure or ≥85 mm Hg diastolic blood pressure or On antihypertensive drug treatment in a patient with a history of hypertension
• Elevated fasting glucose ≥100 mg/dl or on drug treatment for elevated glucose.

STATISTICAL METHODS

Statistical testing was conducted with the statistical package for the social science system version SPSS 17.0 and GraphPadInStat. Continuous variables were presented as mean ± SD, and categorical variables were presented as absolute numbers and percentage. The comparison of normally distributed continuous variables between the groups was performed using Student's t-test; otherwise Mann-Whitney U test was used. Nominal categorical data between the groups were compared using Chi-squared test or Fisher's exact test as appropriate. For all statistical tests, a P value less than 0.05 was considered statistically significant.

RESULTS

Characteristics of the study participants

Both groups had no statistical difference regarding sex distribution. The ART-treated group included 12 females (17.1%) and 58 male patients (82.9%), whereas the ART-naive group included 14 females (21.9%) and 50 male patients (79.1%). It was seen that highest number of patients in both the groups were present in 31-40 age group. There wasn't any significant difference in relation to age in both the groups.

The number of ART naïve HIV patients with a history of smoking and drinking was 48.4% (n=31) and 48.4% (n=31) while the corresponding figures in the ART-treated group were 48.6 %(n=34) and 45.7% (n= 32). The differences were not statistically significant. p=0.988 and p=0.752 respectively.

HIV patients on ART had higher weight than ART-naive HIV patients. Mean body weight in ART-treated patients was 49.57 ± 10.97 Kg and it was 9.39 Kg in ART-naive patients. p=0.015. HIV patients on ART tended to have significantly higher BMI than their ART-naive counterparts. (19.61±3.7 vs. 18.19±3.5; p= <0.05). ART-treated patients had higher incidence of elevated waist circumference than ART-naive, (p=0.069). Prevalence of elevated blood pressure was 29.68 % in ART-naive and 37.14 % in ART treated patients (p=0.361).

HIV patients who were ART-Naive had lower waist circumference than HIV patients who were treated with ART. However, the difference could not reach statistical significance. p=0.144. There was no significant difference between the height, waist-hip ratio, systolic and diastolic blood pressure of ART-treated and ART-naive patients.

Table-1: Demographic profile of the study group

	ART naïve	**ART treated**	
Total	64	70	
Age			
Mean	34 ± 7.5	35.8 ± 7	p=0.21
21-30	23 (35.93%)	18 (25.71%)	p=0.12
31-40	28 (43.75%)	31 (44.28%)	
41-50	13 (20.31%)	21 (30%)	
Sex			
Female	14 (21.90%)	12 (17.10%)	p=0.489
Male	50 (78.10%)	58 (82.90%)	
Smoking	31 (48.4%)	34 (48.6%)	p=0.988
Alcohol	31 (48.4%)	32 (45.7%)	p=0.752
Anthropometric Parameters			
Weight (Kg)	45.19 ± 9.39	49.57±10.97	**0.015**
Height (cm)	157.22±6.99	158.67±6.66	0.22
BMI (Kg/m2)	18.19 ± 3.05	19.61 ± 3.70	**0.017**
Waist Circumference (cm)	75.36 ± 10.54	78.27 ± 12.24	0.144
Waist hip ratio	0.91 ± 0.04	0.92 ± 0.05	0.158
SBP (mm Hg)	115.84 ± 13.76	118.31 ± 16.72	0.355
DBP (mm of Hg)	75.47 ± 9.73	77.69 ± 10.60	0.211

There was no statistical difference between the group as regards smoking and alcohol consumption. It was also seen that median duration of disease was significantly higher in ART treated (18 months) than ART naïve patients. (1 month). p< 0.001

Table-2: Components of Metabolic syndrome

		HIV not on ART (n=64)	HIV on ART (n=70)	P value
Metabolic syndrome		17 (26.6%)	29 (41.4%)	0.07
Elevated WC		1 (1.5%)	6 (8.5%)	0.069
Elevated TG		36 (56.25%)	43 (61.42%)	0.543
Reduced HDL		62 (96.87%)	60 (85.71%)	**0.033**
Elevated BP		19 (29.68%)	26 (37.14%)	0.361
Elevated FBS			27 (38.57%)	0.1
Total Cholesterol (mg/dl)	Median IQR	106.55 85.17 - 129.35	135.75 92.10 - 166.40	**0.022**
Triglycerides (mg/dl)	**Median**	158.5	170	**0.44**
	IQR	119.25 - 198.75	117 - 228.75	
HDL (mg/dl)	Median	18.85	26.65	**0.002**
	IQR	15.02 - 28.20	18.15 - 34.00	
LDL (mg/dl)	Median	50.5	60.5	0.249
	IQR	40 - 70.75	33.75 - 103.75	

The incidence of MeTS was similar in both the treated as well as treatment naïve groups. Median cholesterol in HIV patients was higher in ART treated patients than ART naive patients. (135.75 mg/d LVs 106.55mg/dL, p= 0.022). ART treated patients had significantly higher median serum HDL cholesterol than ART naive patients. (26.65 mg/dl vs. 18.85mg/dL p=0.002). There was no significant difference in the median values of serum triglyceride, serum LDL and serum uric acid level in both groups. ART treated patients had slightly higher median fasting serum glucose level than ART.

Table-3: HIV status of the study population

CDC stage		HIV not on ART (64)	HIV on ART (70)	P value
		Frequency (%)	Frequency (%)	**0.01**
1		6 (9.4%)	0 (0%)	
2		4 (6.2%)	11 (15.7%)	
3		54 (84.4%)	59 (84.3%)	
CD4		ART treated	ART naïve	0.284
	IQR	90.25 - 321.25	87.50 - 188.75	
0-100		26	20	0.0882
101-200		28	26	
201-300		5	2	
301-400		4	3	
401-500		7	4	
>500		0	9	
Duration of disease	**Median**	1	14	<0.001
	IQR	1 – 2	5.75 - 39.00	

In both the group majority of the patients were in the CDC stage 3. However 9.4% patients were in the CDC stage 1, no patients from ART treated group was in CDC stage 1. In both group maximum number of patients had their CD4 count less than 200/ul. There was no significant difference between median CD4 counts of both groups. It was also seen that median duration of disease was significantly higher in ART treated (14 months) than ART naïve patients. (1 month). p< 0.001

CD4 Count and Metabolic syndrome in patients on ART

Table-4: Mean CD4 and Metabolic Syndrome in NNRTI based ART treated patients

	Metabolic Syndrome (29)	No Metabolic Syndrome (41)	
CD4 count	187.18 +/- 131.37	159.26 +/- 110.65	P value 0.3409.
0-100	12	14	
101-200	9	19	
201-300	2	3	
301-400	1	3	
401-500	4	3	
CD4 less than 300	23	36	P=0.7447
CD4 more than 300	6	5	

The Difference between the mean is not significant as two-tailed P value equals 0.3409. The CD4 count was higher among the HIV patients on ART who developed MeTS. However, it was not statistically significant. CD4 count less than 300/mcl was associated with higher incidence of MeTS in both the groups.

Metabolic syndrome among different types of NNRTI

As the treatment protocols were based on NACO guidelines, most patients who fulfilled the eligibility criteria were receiving five major drugs i.e. Zidovudine, Lamivudine, Nevirapine, Efavirenz and Tenofovir[4]. ART-treated patients were further subdivided into two groups: Nevirapine-based ART and Efavirenz-based ART. 53 (75.71%) patients were receiving Nevirapine-based ART and 17 (24.29%) patients were receiving Efavirenz-based ART.

We found that there was significantly higher incidence of metabolic syndrome in Efavirenz-based ART (64.7%) than the patients with Nevirapine-based ART (34%). It was also seen that patients treated with Efavirenz-based ART were found to have a higher percentage of patients with elevated FBS than Nevirapine-based ART-treated patients. ($p<0.05$). There was no significant difference between both groups with respect to other components of metabolic syndrome.

Table-5: Metabolic syndrome in Efavirenz-based ART and Nevirapine-based ART

	Nevirapine based ART (n=53)		Efavirenz based ART (n=17)		P value
	Frequency	%	Frequency	%	
Elevated Waist Circumference	4	7.5%	2	11.8%	0.628
Elevated TG	30	56.6%	13	76.5%	0.143
Reduced HDL	43	81.1%	17	100.0%	0.104
Elevated BP	19	35.8%	7	41.2%	0.776
Elevated FBS	17	32.1%	10	58.8%	0.049
Metabolic syndrome	18	34.0%	11	64.7%	0.025

DISCUSSION:

The study assessed the prevalence of MeTS in ART naïve and ART-treated group. Our findings show that MetS was seen in higher number of ART patients than in ART naïve patients (34.3% vs. 7.5%), which was not statistically significant (p =0.07). Similar findings were seen in the studies by Dimodi *et al.;* [5] and Idiculla *et al.;* [6] Dimodi *et al.;* in their study found that 36% ART-treated patients had metabolic syndrome, while 23.4% ART naïve patients had metabolic syndrome. However Bonfanti *et al.;* [7] and Mittal *et al.;* [8] reported that there was nonsignificant difference in both the groups. In both these studies the prevalence of metabolic syndrome in ART-treated and ART naïve patients was almost similar.

78.1% ART-treated and 82.9 % ART naïve patients were male in our study. This was consistent with the study done by Idiculla J et al and Jacobson *et al.;* [9]. Idiculla J *et al.;* found that ART-treated patients had higher mean BMI and mean waist circumference than ART naïve patients. Though not statistically significant, our study also reported the similar findings. Mean systolic and diastolic BP in our study was similar in both groups. Similar results were obtained by Estrada *et al.;* [10]. Mean cholesterol in our study was significantly higher in ART-treated patients than ART naïve patients. While ART naïve patients had significantly lower mean serum HDL than that of ART-treated naïve. other biochemical parameters like serum LDL, fasting plasma glucose, serum triglycerides were not shown to be significantly different in both the groups. Idiculla *et al.;* [6] also found similar findings in their study.

Among the components of metabolic syndrome reduced HDL and elevated triglycerides were the two most prevalent components in both ART-treated and

ART naïve groups. Similar observations were made by Bonfanti *et al.*[6]. Reduced HDL was more prevalent in ART naïve patients than ART-treated patients ($p<0.05$) in the present study. This is different from findings by van der Valk *et al.;* [11] who found higher HDL levels with Nevirapine. There was no significant difference in the prevalence of other components of metabolic syndrome in ART-treated and ART naïve patients. In our study Protease inhibitor treated patients were not included which are known to cause more dyslipidemia. There was no significant difference in the prevalence of other components of metabolic syndrome in ART-treated and ART naïve patients.

Among the two different NNRTI – Efavirenz and Nevirapine, higher triglycerides, reduced HDL and higher incidence of MeTS were found more often with Efavirenz than with Nevirapine. Similar findings were found by Frank van Leth, *et al.;* [12]. Observations from ECHO ((Efficacy Comparison in Treatment-Naïve, HIV-Infected Subjects of TMC278 and Efavirenz) and THRIVE (TMC278 against HIV, in a Once-Daily Regimen Versus Efavirenz) also showed that Efavirenz was associated with increase in TC, LDL, Triglycerides and HDL levels [13]. The genesis of hypertriglyceridemia has not been adequately explained. It may be due to decreased clearance of triglycerides and increased synthesis of VLDL [12]. Similar to our study, in a study done by Elgalib *et al.;* [14] an increased use of Efavirenz in HIV patients with metabolic syndrome was observed. Increase in the lipid parameters in Efavirenz treated group was also seen the study done by Squires *et al.;* [15].

Higher blood glucose in patients on Efavirenz observed in this study was also found by Dave *et al.;* and Rosenkranz [16, 17]. The explanation for this finding is not yet known but in vitro assays have found altered adipocyte functions and decreased adiponectin which might have a bearing on insulin actions. In this study, HIV-infected patients on ART had a higher CD4 count than those without therapy. However, patients on ART who had MeTS had higher CD4 count than those without though it did not reach statistical significance Lower prevalence of MeTS in patients with higher CD4 count was also seen in other studies [2].

MetS is a state of chronic low-grade inflammation as a consequence of the complex interplay between genetic and environmental factors. Studies on the central role of inflammation have recently unearthed many rather unexpected nodes of interaction with various infectious diseases like HIV. HIV infection is associated with deregulated inflammatory response. HIV-infected monocytic cells have down regulated expression of the tyrosine kinase RON, a negative regulator of the inflammatory process and HIV transcription as well, via ubiquitin-proteosome degradation. Tat, a key molecule in HIV replication and pathogenesis can affect both mesenchymal stem cells survival and differentiation by down-regulating the expression of VEGF-induced endothelial markers and this might play an instrumental role in vessel damage and in the atherosclerotic lesions observed in HIV infection [17].

The natural course of HIV infection is associated with particular unbalances in lipid levels. The dynamics of HIV infection determine an initial decrease in HDL-C followed by a decrease in LDL-c levels. In more advanced stages, there is an increase in TG and in VLDL levels with a strong correlation between serum IFN-α levels and TG clearance time 24. These declines in TC, LDL-C and HDL-C observed after HIV seroconversion are consistent with a chronic inflammatory state [18].

Limitations:

Physical activity was not considered in the study group. Also though the patients were counseled, adherence to non-smoking and abstinence from alcohol could not be ascertained fully. Considering that the study design was cross-sectional, the temporal relationship of HIV and ART with metabolic syndrome could not be determined. The study period of 18 months may not be sufficient to study the entire spectrum of MeTS as HIV patients are required to take the medicines lifelong. There is need for prospective studies assessing development of metabolic syndrome in HIV-infected patients. Also some of the findings were from a small number of patients for which statistical significance could not be determined. In our study there were no patients treated with protease inhibitors and other second-line ART, which also have important metabolic effects. HIV RNA was not done in this study due to limited resources

CONCLUSIONS:

The study concludes that metabolic syndrome is present in both HIV patients treated with ART and HIV patients who were ART naïve. Most common components of metabolic syndrome in both ART treated and ART naïve patients were reduced-HDL and elevated triglycerides. ART treated HIV patients had higher mean weight, higher mean BMI, higher median HDL, more duration of HIV disease and lesser prevalence of reduced HDL than ART naïve patients.
Metabolic syndrome was more prevalent in Efavirenz based ART than Nevirapine based ART. Elevated FBS was more prevalent in Efavirenz based groups than Nevirapine based group.

Conflict of interest none

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