Original Article

Assessment of metabolic syndrome in HIV-infected individuals

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Abstract

Background: Metabolic syndrome (MS) is a cluster of risk factors for cardiovascular disease and Type 2 diabetes mellitus. **Objectives:** The aim is to assess the prevalence of MS in HIV patients receiving highly active antiretroviral therapy (HAART) and to compare it with treatment naïve HIV patients. **Methods:** Cross-sectional study carried out in a teaching hospital in North India. A total of 116 HIV positive patients who were on HAART and those who were treatment naïve were included in the study. Adult Treatment Panel III (ATP III) and International Diabetes Foundation (IDF) definitions were used to define MS. Clinical and laboratory investigations were performed as per requirement and then analyzed using SPSS software. **Results:** A high prevalence of MS was observed in HIV positive patients (ATP III – 19.8% and IDF – 25.9%). The prevalence of MS was higher in the anti-retroviral therapy (ART) group (ATP III – 33.3% and IDF – 36.4%) than ART-naïve group (ATP III – 2% and IDF – 12%). **Conclusions:** A sincere effort should always be made to detect MS in patients on HAART, especially in Indian subcontinent where there is a genetic predisposition to cardiovascular risk.

Key words: Adult Treatment Panel III, highly active antiretroviral therapy, HIV, International Diabetes Foundation, metabolic syndrome

INTRODUCTION

Metabolic syndrome (MS) is a cluster of risk factors for cardiovascular disease (CVD) and Type 2 diabetes mellitus (DM). Several definitions exists to identify those at "risk," but the most widely promulgated being the definition in the third report of National Cholesterol Education Program Expert Panel (NCEP) on detection, evaluation, and treatment of high cholesterol (Adult Treatment Panel III [ATP III]) and International Diabetes Foundation (IDF).[1,2]

Highly active antiretroviral therapy (HAART) has transformed infection with HIV from a rapidly progressive and uniformly fatal disease into a chronic manageable condition. However, the remarkable decrease in morbidity and mortality, and increase in life expectancy (>35 years following diagnosis) has come at the cost of a spectrum of metabolic complications.[3] These findings were first described by Carr *et al*. in 1998.[4] The clustering of these morphological and metabolic abnormalities have striking similarities with the MS.

The importance of finding an association of HIV/HAART with MS lies in the fact that many studies have shown that patients diagnosed with MS have more prevalent CVD and are at increased risk

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of developing them.[5] Thus, a better understanding would allow for more effective clinical management of these patients.

METHODS

The study was a cross-sectional study carried out at an anti-retroviral therapy (ART) Center at a teaching hospital in North India over 1 year. After ethical approval consenting patients who satisfied inclusion criteria (HIV positive patients on ART for ≥12 months and HIV positive patients who are treatment naïve) were enrolled. Patients withdrawn of ART/with the evidence of clinical signs of active AIDS in the past 3 months before entry because of possible impact on anthropometric and laboratory parameters/pregnancy/age <18 years were excluded from the study.

MS was diagnosed by NCEP-ATP III or IDF criteria as shown in Tables 1 and 2.

Detailed history and clinical examination were carried out and an 8 h fasting venous blood sample was collected for enzyme-linked immunosorbent assay for HIV, CD_4 T-cell count, fasting blood glucose (FBS), serum cholesterol, high-density lipoprotein (HDL) cholesterol, serum triglycerides, and serum insulin in all the study patients.

Insulin resistance (IR) was calculated using the homeostatic model assessment (HOMA) and 1.93 was taken as cut-off value.[6]

The data analysis was performed using SPSS software version 17.0 (IBM corporation, Chicago, USA).

Table 1: National Cholesterol Education Program Expert Panel-Adult treatment Panel III criteria for metabolic syndrome

Risk factors (Any 3 of the 5)	Defining level
Abdominal obesity	waist circumference (cms)
Men	>102
Women	>88
Triglycerides (mg/dl)	≥150*
HDL cholesterol (mg/dl)	
Men	<40*
Women	<50*
Blood pressure (mm Hg)	
Systolic	≥130*
Diastolic	≥85*
Fasting plasma glucose (mg/dl)	≥100*

*or receiving specific treatment for this abnormality or diagnosed diabetes

Table 2: International Diabetes Foundation criteria for metabolic syndrome

Central obesity
Waist circumference: Men ≥90 cm; Women ≥80 cm (South Asian)
Plus any two of the following
Plasma triglycerides >150 mg/dl*
HDL-cholesterol <40 mg/dl in men*/<50 mg/dl in women*
Blood pressure ≥130/85 mm Hg*
Fasting plasma glucose ≥100 mg/dl*

*or receiving specific treatment for this abnormality or diagnosed diabetes

RESULTS

There were 116 patients in the study group. The majority were men (n = 71) and the mode of transmission in the majority was heterosexual transmission (n = 106). 66 patients were on ART and 50 were ART-naïve. 15 were smokers of whom 10 were in the ART group. Increased waist circumference was found in 22 patients (men = 3/women = 19) by ATP III criteria and in 53 patients (men = 23/women = 30) by IDF criteria. Hypertriglyceridemia was present in 53% (n = 61). A low HDL cholesterol was present in 74% (n = 86), whereas 23% (n = 27) had hypertension and 8% (n = 9) had increased FBS levels.

The ART and ART-naïve groups did not differ with regards to body mass index (BMI). The mean duration of infection was higher (5.1 ± 2.3 years vs. 3 ± 1.5 years) in the ART group. The mean CD_4 count were much higher in the ART group (476 ± 221/mm^3 vs. 382 ± 95/mm^3). Mean weight (59.6 ± 11 kg vs. 56.7 ± 10.3 kg) and waist circumference (87 ± 8 cm vs. 83 ± 8 cm) measurements were higher in the ART group. The mean HDL cholesterol was higher in ART group (44.4 ± 13.4 mg/dl vs. 37.4 ± 19.6 mg/dl).

The prevalence of MS by ATP III criteria was 19.8% (n = 23; men = 12; women = 11) whereas 25.9% by IDF criteria (n = 30; men = 14; women = 16). One component of the MS was present in 94% (n = 109) and 56% (n = 65) had at least two components.

MS related factors in the univariate analysis are shown in Table 3. Patients with MS were significantly older (41 ± 8 years vs. 35 ± 9 years; P = 0.002). Among the patients with MS by ATP III definition, 52% were men and 48% were women (P = 0.321). Patients with MS had a longer duration of HIV infection (5 ± 3 years vs. 4 ± 2 years; P = 0.007) and majority of them were on HAART (22 vs. 1; P < 0.001). The mean

Table 3: Statistical correlation of various parameters with metabolic syndrome

	Metabolic Syndrome by ATP III			Metabolic Syndrome by IDF		
	Patients with MS (*n*=23)	Patients without MS (*n*=93)	*P*	Patients with MS (*n*=30)	Patients without MS (*n*=86)	*P*
Age (years)	41±8	35±9	0.002	40±9	35±8	0.002
Male Sex	12(52.2%)	59(63.4%)	0.321	14(46.7%)	57(66.3%)	0.058
Smokers	1(4.3%)	14(15.1%)	0.245	5(16.7%)	10(11.6%)	0.25
Transmission Group						
IV	0	0		0	0	
Heterosexual	19	87		28	78	
Homosexual	0	0		0	0	
Others	4	6		2	8	
Duration of infection (years)	5±3	4±2	0.007	5.4±3	3.8±2	0.005
CD4 count/mm^3	556±250	405±150	0.001	514±251	408±145	0.006
ART exposure (no's)	22(95.7%)	44(47.3%)	<0.001	24(80%)	42(48.8%)	0.003
Weight (in kg)	65±11	57±10	0.001	65±11	56±10	<0.001
Height (in cms)	163±12	162±10	0.67	163±12	162±10	0.64
Waist (in cms)	92±7	84±8	<0.001	92±6	83±8	<0.001
BMI (kg/m^2)	24.3±3.8	21.6±3.3	0.001	24.3±3.31	21.4±3.4	<0.001
Systolic BP (mm Hg)	126±15	108±13	<0.001	116±19	111±13	0.12
Diastolic BP (mm Hg)	86±11	74±9	<0.001	77±13	76±9	0.58
Total Cholesterol (mg/dl)	191.6±34.8	167.3±56	0.05	195.3±45.2	164.1±53.6	0.005
HDL cholesterol (mg/dl)	39.3±8	41.8±18.1	0.51	39.5±9.6	42±18.5	0.49
LDL cholesterol (mg/dl)	91.7±28.4	94±39	0.8	97.3±29.7	92.2±39.5	0.53
Triglycerides (mg/dl)	324.7±221.2	171.6±134.7	<0.001	291.5±199.2	171.8±141.6	<0.001
FBS (mg/dl)	106.4±29.7	86.7±11.2	<0.001	100.8±28.4	87±11.1	<0.001
Insulin (mU/l)	15.3±15	6.02±5.9	<0.001	12.8±14.7	6.14±6.1	0.001
HOMA	4.4±5.3	1.3±1.5	<0.001	3.6±4.9	1.4±1.5	<0.001
Insulin resistance	14(60.9%)	16(17.2%)	<0.001	13(43.3%)	17(19.8%)	0.011

duration of treatment on current therapy was 4 ± 2 years. The mean CD_4 counts were much higher in those with MS (556 ± 250/mm^3 vs. 405 ± 150/mm^3; P = 0.001). Subjects with MS had significantly higher BMI (24.3 kg/m^2 vs. 21.6 kg/m^2; P = 0.001). Two patients with MS had BMI < 18.5 kg/m^2, 12 had BMI ranging from 18.5 to 24.9 kg/m^2, 9 had BMI > 25 kg/m^2 and 2 were obese. In those with MS, low HDL cholesterol was the most frequent trait seen (96%, n = 22), followed by hypertriglyceridemia (91%, n = 21) followed by high blood pressure (BP) (65%, n = 15), increased waist circumference (56%, n = 13) and high FBS levels (26%, n = 5) [Figure 1].

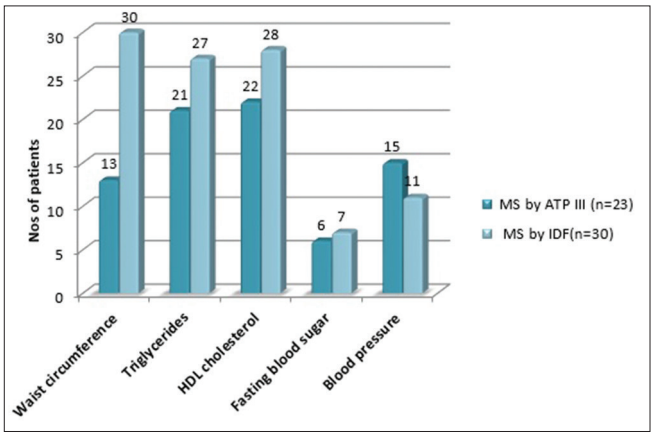

Figure 1: Spectrum of metabolic syndrome

IR was present in 60.9% in those with the MS and 17.2% of those without the MS (P < 0.001). Out of the 30 patients with IR, 22 were on ART and 8 were ART-naïve. Two patients in the ART group were on oral hypoglycemic drugs. Among the ART drugs, only protease inhibitors were significantly associated with the MS.

DISCUSSION

In this study, 116 HIV positive patients were recruited, of which, 66 were on ART, whereas 50 were ART-naïve. The age of the patients ranged from 18 to 60 years with mean being 36 ± 9 years. The duration of HIV infection ranged from 1 to 18 years with mean being 4.1 ± 2.2 years. The duration for which patients had been taking ART ranged from 2 to 11 years, with mean being 4.6 ± 1.6 years. The CD_4 count ranged from 117 to 1148/mm^3 with the mean being 435/mm^3. The majority of the patients were on nonnucleoside reverse transcriptase inhibitor (NNRTI) and nucleoside reverse transcriptase inhibitor (NRTI) combinations, only two of them were on NRTI and

protease inhibitor combinations as they were taking ART from the national program.

The study group was analyzed for the prevalence of MS using the ATP III definition as it has been used in most previous studies, and also by IDF definition as this is the basis of the international consensus group definition for future study.[1,2] MS by ATP III definition showed a prevalence of 19.8% whereas IDF definition revealed a prevalence of 25.9%. The prevalence was much higher in the ART group, that is, 33.3% (IDF = 36.4%) than 2% (IDF = 6%) in the ART-naïve group ($P < 0.001$). Thus, in this study, the overall prevalence of MS appears to be similar to that found in the general Indian population.[7] However, when we compared the prevalence of MS in our patients between the ART and ART-naïve groups we found the prevalence to be significantly higher in the ART group, that is, 22 out of 66 patients (33.33%) compared to just one in the ART-naïve group (2%) ($P < 0.001$) by ATP III definition and by IDF definition it was present in 24 of 66 patients (36.4%) compared to 6 in the ART-naïve group (12%) ($P = 0.003$). A similar study from South India by Idiculla *et al*. found a prevalence of MS in HIV positive patients to be 26.6%; nearly 43.3% in the ART treated group and 10% in the ART-naïve group.[8] This was higher than our study. This difference could be attributed to the higher prevalence of MS in the South Indian population as compared to the North Indian population which comprised our study group.

In our study, 69.8% ($n = 81$) subjects did not have MS by both definitions whereas 15.3% ($n = 18$) had MS by both definitions. The observed agreement between the two classifications was moderate ($\kappa = 0.586$, $P < 0.001$). In our study, IDF definition of MS picked up more patients with MS and this could be attributed to the fact that IDF definition requires a much lesser waist circumference (men-102 vs. 88 cm, women-90 vs. 80 cm) as compared to ATP III definition to meet the criteria.

In our study of the whole population 94% ($n = 109$) had one component of MS, 56% ($n = 65$) had two components of MS, 20% ($n = 23$) had three components of MS and 7% ($n = 8$) had four components of MS. Therefore, in our study, 94% of the whole population had at least one component of the MS. Our findings may not be directly comparable to other studies, but these results suggest that unlike in our patients, 31.7% of the patients in the Spanish study did not have any feature of MS, implying that these metabolic derangements may be more prevalent in the Indian population.[8,9]

In our study, low HDL cholesterol and hypertriglyceridemia were the most prevalent parameters present MS, similar to other studies.[8] Although low HDL cholesterol was the most prevalent component in our study group, those patients on ART had an overall higher HDL cholesterol level than those in the ART-naïve group. This could be explained by relatively frequent use of NNRTIs, especially nevirapine which are known to increase HDL cholesterol level.[10]

In this study, among patients with MS who were receiving ART, 6 patients had elevated FBS as compared to none in the ART-naïve group. Of the six patients with hyperglycemia, 3 met the diagnostic criteria for DM and were on oral hypoglycemic agents. As observed in most previous studies, hyperglycemia was the least fulfilled among all the 5 criteria.[9] The use of NRTI as first line drugs in India has been strongly implicated in the development of IR and subsequent DM.[7]

In our study group, excluding the NCEP criteria, traditional risk factors such as old age, increased BMI, increased body weight and increased total cholesterol levels were the strongest predictors of the MS similar to other studies.[8] Apart from these well known risk factors, the duration of HIV infection, ART exposure, and high CD_4 count were significantly associated with the MS similar to other studies.[9] This finding can be attributed to the expected increase of weight, improved nutrition, and immunological status seen with ART.

IR based on HOMA was present in 60.9% of the patients with MS and all of them were on ART, thereby reiterating its pivotal role in the pathogenesis of this condition.[11]

Only 1 out of 23 patients with the MS was ART-naïve. The prevalence of the MS was low in the ART-naïve group because of lower BP, lower triglycerides level and only a few of them had abdominal obesity. As the BMI in our study was similar in ART treated and ART-naïve patients, a possible explanation of greater abdominal obesity in ART treated patients is that ART induced visceral fat accumulation.

Our study found a strong association between ART and MS by both definitions. No association could be found with any particular drug.

CONCLUSIONS

On the basis of our study, we conclude that the prevalence of MS is high among HIV-infected

patients but not higher than the prevalence among HIV-uninfected persons. The prevalence of MS is much higher in the ART treated patients. Apart from the traditional risk factors for MS, the duration of HIV infection, high CD_4 count and ART exposure are significantly associated with MS.

A sincere effort should always be made to detect MS in HIV positive patients particularly those who are on HAART as it is well known that MS is a significant, multifaceted and modifiable risk factor for CVD, especially in Indian subcontinent where there is a genetic predisposition to cardiovascular risk.

Our study is a very small preliminary study and in view of paucity of data pertaining to MS and HIV infection in our Indian population it is felt that these observations are to be further verified by larger studies. Till then, we conclude that total cholesterol level, triglyceride level, and BP should be closely monitored in all ART treated patients.

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Conflicts of interest

There are no conflicts of interest.

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