Prevalence of Metabolic Syndrome among HIV Positive Patients with or without HAART

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ABSTRACT

Introduction: HIV/HAART-induced metabolic imbalances overlap to some extent the components of Metabolic Syndrome (MetS) and its high rates in the HIV population place infected individuals in an elevated CVD risk category. Of all the nucleoside reverse transcriptase inhibitors (NRTI's), Stavudine is most commonly cited antiretroviral agent that is being associated with MetS and HIV related fat accumulation. Aims: To estimate the Prevalence of Metabolic Syndrome among HIV positive patients with or without HAART. Settings and Design: This cross sectional study was conducted in Department of Medicine in collaboration with ART Centre, Rajindra Hospital, Patiala

Material and methods: Anthropometric and Laboratory data from 100 patients was collected and results were statistically analysed. Statistical Analysis used: Results were tabulated and subjected to statistical analysis using SPSS.

Results and Conclusions: In our study most of the patients were on ART i.e 80% while 20 % were not on ART. Association of ART use with metabolic syndrome did not yield significance on statistical analysis (p value=0.90). In our study, 47% patients were on ZLN based ART, 29% on TLE while 2% each on TLN and ZLE and 20% were not on any ART treatment.

Keywords: Metabolic Syndrome, HIV Positive Patients, with or without HAART

INTRODUCTION

Acquired Immunodeficiency syndrome (AIDS) was first recognized in the United States in the summer of 1981, when the Center for Disease Control and Prevention (CDC) reported.[1]

Human immunodeficiency virus (HIV) is a lentivirus (a member of the retrovirus family) that causes acquired immunodeficiency syndrome (AIDS), a condition in humans in which progressive failure of the immune system allows life-threatening opportunistic infections and cancers to thrive.[2-3]

The HIV/AIDS in India came into public view in 1986 with detection of cases of HIV in Chennai, Tamilnadu and in Mumbai in 1987. There were about 2.40 million people living with HIV in India as per sentinel surveillance complemented by population-based surveys like National Family Health Survey. Male to female prevalence ratio was 3:2 as per survey, however more and more women are being infected.[4]

Adult HIV prevalence in Punjab was 0.19% as per 2016 Punjab AIDS control society report. HIV prevalence in males was reported to be 0.32% and females 0.22% throughout India. In Punjab, total HIV positive cases registered for HIV care (Pre ART) till April 2016 were 34819 and total number of patients on ART were 15575.[5]

HIV infects vital cells in the human immune system such as helper T cells (specifically CD4+T cells), macrophages and dendritic cells. HIV infection leads to low levels of CD4+T cells through three main mechanisms: First, direct viral killing of infected cells; second, increased rates of apoptosis in infected cells; and third, killing of infected CD4+T cells by CD8 cytotoxic lymphocytes that recognize infected cells.[6]

Metabolic syndrome (MetS) or insulin resistance syndrome is a distinctive constellation of risk factors for the development of type 2 Diabetes Mellitus and Cardiovascular diseases. The syndrome's hallmarks are glucose intolerance, hyperinsulinemia, a characteristic dyslipidemia (high triglycerides, low high-density lipoprotein cholesterol and small, dense low-density lipoprotein cholesterol), obesity, hypertension, and increased prothrombotic and antifibrinolytic factors.[7]

Other names for MetS are Hypertriglyceridemic waist, Insulin Resistance Syndrome, Deadly Quartet and Syndrome X.[8]

Metabolic Syndrome is a significant predictor of incident cardiovascular disease events and diabetes mellitus.[9] Fasting glucose level is the highest predicting factor for cardiovascular diseases in patients with metabolic syndrome.[10]

Apart from cardiovascular disease and type 2 Diabetes, individuals with metabolic syndrome are susceptible to other conditions, notably polycystic ovarian syndrome, fatty liver, cholesterol gall stones, asthma, sleep disturbances and some forms of cancers.[11]

The mechanism underlying the metabolic syndrome is not fully known. However resistance to insulin stimulated glucose uptake seems to modify biochemical responses in a

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way that predisposes to metabolic risk factors.[12]

A central role has been attributed to the pro-inflammatory cytokines, tumour necrosis factor-alpha (TNF-alpha) and Interleukin 6, supported by the fact that both are produced in substantial amounts by human adipose tissue. TNF-alpha impairs insulin stimulated glucose uptake in a variety of cells and decrease lipoprotein lipase activity. Both cytokines increase hepatic lipogenesis and elicit a systemic acute phase response.[13]

Furthermore, various aspects of the acute phase response, such as fibrinogen and plasminogen activator inhibitor-1 levels, whole blood viscosity and white blood cell count, have recently been found to correlate positively with the metabolic syndrome.[14]

Macrophage and T-cell infiltration is a major feature of atherosclerotic plaques, especially at sites of plaque rupture and epidemiological studies show strong positive associations of systemic markers of inflammation with atherothrombotic disease. Moreover, C-reactive protein (CRP), the classic and exquisitively sensitive acute phase reactant, shows a strong independent association with the risk of coronary heart disease and other atherothrombotic events. CRP levels have also been found to correlate with body mass index.[14-15]

Prevalence of MetS increases with age and is more prevalent in males. Weight control is more vital in earlier stages of life for prevention and management of MetS.[16]

Metabolic syndrome helps in predicting Cardiovascular and coronary heart disease mortality, in fact the presence of even 1 or 2 components of the MetS increases the overall mortality compared with the individual with none.[17]

A 65% excess risk has been determined for cardiovascular disease in individuals with metabolic syndrome.[20] As reviewed recently, worldwide prevalence of MetS ranges from < 10% to as much as 84% depending on age, region, urban/rural environment, ethnicity and the definition of metabolic syndrome used.[21] In the United States, in last decade prevalence of MetS has increased from 23% to 27% along with increase in obesity and physical inactivity.[18]

According to various studies around the world, the prevalence varies from 8% (India) to 24 % (US) in men and from 7% (France) to 46% (India) in women.[23] It is estimated that 20-25% of South Asians have developed Metabolic Syndrome and many more may be prone to it.[19]

In addition, adults with metabolic syndrome are five times more prone to develop Type 2 Diabetes Mellitus.[20] Obesity is associated with an increase in cardiovascular risk factors (also indicators of metabolic syndrome).[21]

Recent observations have suggested that chronic infectious diseases like HIV and chronic hepatitis B and C are associated with MetS. High blood levels of pro-inflammatory cytokines like CRP have been found in these conditions indicating enhanced inflammation. However, the infectious disease which has been conclusively linked with MetS for more than two decades has been HIV infection even if the patient has responded to antiretroviral therapy. The high prevalence of MetS in HIV infection has added entirely new dimensions in the pathogenesis of MetS.[22-24]

The initial description of MetS was made in HIV patients few years after initiation of protease inhibitors chiefly ritonavir plus saquinavir combination based antiretroviral therapy. The unquestionable success of ART has led to a wider availability of the drugs around the globe thereby bringing to notice an unanticipated aspect of drug therapy of HIV. Though the actual numbers of MetS in HIV populations are still debatable, reported prevalence for MetS in the HIV population can be regarded as high, ranging from 11.2% up to 45.4%.[24]

Since its initial description about three decades back, our understanding of HIV has increased exponentially. With effective therapy, the infection has been converted from a disease with profound immune suppression and often terminal, fatal opportunistic infections to a disease associated with disordered lipid metabolism, dysglycemia and high blood pressure with increased proinflammatory cytokines. And as HIV patients live longer, this aspect of HIV infection is now an important global health concern.[24]

The pathogenesis of MetS is not completely understood. The metabolic changes in HIV infections begin early in the course of infection. Due to selective targeting of the immune system by the virus and the consequent progressive deterioration of the immune system, the individual becomes susceptible to multiple opportunistic infections and some neoplasm. Targeting of the immune system by the virus causes profound disruption of the cytokine network from the earliest stages of HIV infection. Cytokines like hS-CRP, tumor necrosis factor, IL-6, IL-1β and urokinase plasminogen activator receptor (suPAR) are increased in the initial stages of HIV infection and these not only contributes to viral replication but also initiates the earliest changes leading to development of metabolic syndrome in future.[25] Some genes responsible for suppressing inflammation like tyrosine kinase RON (Recepteur d'Origine Nantais) are downregulated in HIV infection leading to continuing inflammatory response and increased HIV transcription.[26] Even after institution of HAART (Highly Active Antiretroviral Therapy) with HIV levels below detectable range, the blood levels of these cytokines remain elevated. In the SMART trial, participants bearing ≤400 copies/mL of HIV RNA also had elevated hsCRP and IL-6 levels in 38% and 60%, respectively, in comparison to normal individuals form cohorts for cardiovascular outcomes.[27]

The earliest changes in the treatment naïve HIV patients are probably dyslipidemia with plummeting of HDL levels. As the disease progresses, LDL-C decreases followed by an increase in triglycerides, apolipoprotein levels and VLDL in the advance course of the disease. Hypertriglyceridemia may be due to decreased clearance of triglycerides and increased production of VLDL.[28]

Once the patients are initiated on HAART, the impact on the components of MetS is more pronounced. Some of the initial changes found in the early stages of HIV infection get exacerbated with addition of more components. These changes depend on the medications on the HAART regime. Hypertriglyceridemia in general worsens with Ritonavir

based PI (Protease Inhibitor) regime with an increase of up to 83% in one study and could be due to effect of Ritonavir's inhibitory effect on degradation of apolipoprotein B.[29]

Insulin resistance can occur in HIV patients on therapy, but probably the mechanism is different from the general population. Multiple antiretroviral drugs - zidovudine, lamivudine, stavudine, efavirenz and most of the protease inhibitors have been found to have influence on glucose metabolism though by different mechanisms some of which are still not well understood. Studies have shown that PIs selectively inhibit glucose transport in adipocytes without affecting early insulin-signaling events or translocation of intracellular GLUT4 transporters to the cell surface.[30]

The resultant effects of HIV infection with or without therapy lead to a state of immune dysfunction with profound influence on lipid metabolism, body habitus and vascular architecture leading to a prothrombotic state thereby enhancing the risk of cardiovascular diseases manifold.[31]

Metabolic complications and abnormal fat distribution were frequently observed after a few years of antiretroviral therapy and, as the array of antiretroviral drugs became broader, long term metabolic alterations are becoming far more common worldwide. Nevertheless, the risk of not being on HAART is overwhelmingly greater than the metabolic adverse events in terms of morbidity and mortality events.[24]

HIV/HAART-induced metabolic imbalances overlap to some extent the components of Metabolic Syndrome (MetS) and its high rates in the HIV population place infected individuals in an elevated CVD risk category.[32]

The introduction and widespread use of highly active antiretroviral therapy (HAART), has led HIV-infected individuals to experience a dramatic decline in immunodeficiency-related events, including causes of death.[33-35] As a consequence, life-expectancy increased, which exposed them to the effects of aging itself, including the influence of the same environmental risk factors known to act in the general population and contributing to the occurrence of obesity, diabetes mellitus (DM), and cardiovascular diseases (CVD).[36-37] However long term toxicities are emerging after prolonged exposure to antiretroviral therapy and are becoming challenges to successful HIV management. Exposure to combination antiretroviral treatment, for instance increased the incidence of MI by 26% per year in developed nations.[38]

According to the Third National Health and Nutrition Examination Survey, prevalence of MetS in the general US population has been estimated as 25% and this number has been growing continuously over time [39]. MetS encompasses a cluster of risk factors leading to CVD as primary clinical outcome and contribute to higher risks of DM. Such factors include obesity (mainly central adiposity), defective glucose metabolism (DM, impaired glucose tolerance, or impaired fasting glycaemia), raised blood pressure, and elevated TG and low HDL-C levels.[24,32]

Of all the nucleoside reverse transcriptase inhibitors (NRTI's), Stavudine is most commonly cited antiretroviral agent that is being associated with MetS and HIV related fat accumulation.[40] Moreover Protease Inhibitors (PI) in general have been reported to be highly associated with MetS.[41] The pathways underlying such alterations are not always known but an in vitro assay with PIs and NRTIs showed altered adipocyte functions and decreased adiponectin, a positive regulator of insulin sensitivity, due to an increased expression and secretion of pro-inflammatory cytokines.[42] Even without commencing ART, elevated lipid levels have been linked with HIV infection itself.[43]

Aims and objectives

To estimate the Prevalence of Metabolic Syndrome among HIV positive patients with or without HAART.

MATERIAL AND METHODS

This cross sectional study was conducted in Department of Medicine in collaboration with ART Centre, Rajindra Hospital, Patiala. Hundred HIV positive patients between the age group of 18 to 70 years who were fulfilling inclusion criteria were selected from various wards of Rajindra Hospital Patiala and those reporting to ART centre from November 2018 to August 2021.

All patients were examined thoroughly. Anthropometric and Laboratory data was collected and results were statistically analysed. All the patients and their relatives were informed about the study in their vernacular language. Written consent was taken. Clinical examination and all the relevant investigations were performed. Results were tabulated and subjected to statistical analysis using SPSS .

Inclusion criteria

1. Previously or newly diagnosed HIV positive patients (ART and Pre-ART).
2. Age more than 18 years.

Exclusion criteria

1. Withdrawal of combination ART
2. Evidence of clinical signs of active AIDS in the 3 months before entry Because of their possible impact on anthropometric and laboratory parameters.
3. Pregnant women and anyone who switched ART combination regimen for any reason.

Diagnostic Criteria for Metabolic Syndrome

U.S. National Cholesterol Education Program Adult Treatment Panel III (ATPIII) criteria (Revised).[58]

According to National Cholesterol Education Program (NCEP) Adult Treatment Panel III guidelines (Revised), Metabolic syndrome was defined as having 3 of the following criteria:[44]

1. Abdominal obesity (waist circumference >102 cm for men and >88 cm for women),
2. Fasting triglyceride (TG) levels ≥150 mg/dL,
3. High-density lipoprotein (HDL) cholesterol level <40 mg/dL for men and <50 mg/dL for women, or use of a lipid-lowering agent**,
4. Fasting glucose levels of ≥100 mg/dL*,
5. Hypertension (blood pressure ≥130/≥85 mm Hg or current receipt of medication for hypertension).

*Fasting blood glucose criteria was modified from ≥110 mg/

Regimen	Frequency	Percent
TLE	29	36.25
TLN	2	2.5
ZLN	47	58.75
ZLE	2	2.5
Total	80	100

Table-1: ART regimen distribution

Range	Frequency	Percent
Below cut-off	90	90
Above cut-off	10	10
Total	100	100

Table-2: Waist circumference distribution

MetS	Frequency	Percent
NO	79	79
YES	21	21
Total	100	100

Table-3: Prevalence of metabolic syndrome

No of Criteria	Frequency	Percent	Cumulative Percent
0	28	28	28
1	29	29	57
2	22	22	79
3	9	9	88
4	10	10	98
5	2	2	100
Total	100	100	

Table-4: Metabolic syndrome criteria distribution

dl in NCEP-ATP III guidelines (2001)[59] to ≥100 mg/dl.
*Use of a lipid-lowering agent was defined as use of a statin, fibrate, or niacin agent.

RESULTS

As it is clear from the Table-1, mostly patients were on ZLN type of ART regimen 58.75% (n=47), 36.25% were on TLE (n=29), 2.5% each on TLN and ZLE (n=2).

As shown in the table-2 above, 90% of HIV patients were below the cut off for the diagnosis of Metabolic Syndrome i.e. <102cm in males and <88 cm in females, while 10% were above the said cut-off.

In our study of 100 HIV patients as shown in the table above, 21% of patients had Metabolic Syndrome (n=21) while 79% of patients didn't meet the required criteria to be labelled as having MetS (Table-3)

As shown in the table-4 above, 28% of the patients (n=28) did not meet any specified criteria, 29% of the patients (n=29) met 1 criteria, 22% of patients (n=22) met 2 criteria, 9% (n=9) met 3 criteria, 10% (n=10) met 4 criteria and 2% (n=2) met all the criteria for diagnosis of MetS.

As shown in the table-5 above, prevalence of metabolic Syndrome was 20% in patients not taking ART (n=4 out of 20 patients) against 21.3% in patients taking ART (n=17 out of 80 patients). On statistical analysis this difference was not significant (p value was 0.90).

As shown in the table -6 above, prevalence of metabolic Syndrome was similar in patients receiving ZLN (21.3%) or TLE (24.1%) based ART therapy. While no patients who were taking TLN/ZLE based therapy were diagnosed with MetS. Again this difference of results were statistically

Art	Frequency	MetS		Total
		No	Yes	
N	Count	16	4	20
	% within ART naive	80.0%	20.0%	100.0%
Y	Count	63	17	80
	% within ART user	78.8%	21.3%	100.0%
Total	Count	79	21	100
	Total %	79.0%	21.0%	100.0%

Table-5: Association of metabolic syndrome with art use

Regimen	Frequency	MetS		Total
		No	Yes	
No	Count	16	4	20
	% within art naive	80.0%	20.0%	100.0%
TLE	Count	22	7	29
	% within regimen	75.9%	24.1%	100.0%
TLN	Count	2	0	2
	% within regimen	100.0%	.0%	100.0%
ZLE	Count	2	0	2
	% within regimen	100.0%	.0%	100.0%
ZLN	Count	37	10	47
	% within regimen	78.7%	21.3%	100.0%
Total	Count	79	21	100
	Total %	79.0%	21.0%	100.0%

Table-6: Association of metabolic syndrome with art regimen

insignificant (p value was 0.87).

DISCUSSION

Recent observations have suggested that chronic infectious diseases like HIV and chronic hepatitis B and C are associated with MetS. High blood levels of pro-inflammatory cytokines like CRP have been found in these conditions indicating enhanced inflammation. However, the infectious disease which has been conclusively linked with MetS for more than two decades has been HIV infection even if the patient has responded to antiretroviral therapy.[22-23] However, the Literature is scanty regarding the prevalence of MetS in HIV infected patients in India and particularly in Punjab. Thus study has been contemplated to asess the prevalence of MetS in HIV infected patients in this direction

In our study prevalence of Raised waist circumference is 10% i.e 10 patients had raised WC out of 100. This finding is in contrast to that observed in studies by Gazarusso C et al[45] in 2002 (37.8%) and that in Elgalib A et al[46] in 2011 (32%). This difference may be because of the demography of the study population and also ethnicity of the sample population may have contributed to this difference.In another study done in Indian subcontinent by Bajaj Sarita et al[47] in 2013, they did not find any patient with raised waist circumference.

In our study prevalence of metabolic syndrome is 21% i.e 21 patients had 3 three or more criteria fulfilled for diagnosis of metabolic syndrome as per National Cholesterol Education Programme, Adult Treatment Panel III guidelines (Revised).[44] This finding is comparable to numerous studies done earlier with same criteria. Mbunkah HA et al (2014)[48], Jantrapakde J et al (2014)[49], Tesfaye DY et al (2014)[50], Muhammad S et al (2013)[51], Maloberti A et al (2013)[52], Bajaj Sarita et al (2013)[53].

Two Indian studies have been done to assess the prevalence of Metabolic syndrome in HIV infected patients and both of them yielded similar results. In study conducted by Gupta V et al[54] in 2011 on 68 HIV patients at AIIMS, Delhi prevalence was 25% and in the study done by Bajaj Sarita et al[53] in 2013, prevalence was 20%.

In our study, on statistical analysis no association was found between occurrence of MetS and ART usage (p value was 0.90). This observation is similar to that reported in the studies conducted earlier by Jacobson DL et al (2003)[55], Hansen BR et al(2009)[56], Maloberti A et al(2013)[52], Bajaj Sarita et al(2013)[53], Elgalib A et al(2011)[46], Silva EF et al(2009)[57]. However Muhammad S et al(2013)[51] in their study found association between occurrence of MetS and ART usage

Also In our study, no statistical association was found in prevalence of metabolic syndrome with type of ART regimen used (p value was 0.87). This observation is similar to that reported in studies conducted earlier by Mondy et al (2007)[58] and Hansen BR et al (2009)[56].

CONCLUSION

In present study most common age group affected with HIV was 36-45 years and 46-55 years (33% each) with mean age of 43.76 ± 10.339 years and range of 20-66 years. Prevalence of MetS was max in > 55 years age group (6 out of 13) while no patient <25 years had metabolic syndrome. Male patients were 52% (n=52) and females constituted 48% (n=48). Prevalence of MetS in males was 13.46% against 29.17% in females. This differance is not significant on statistical analysis (p=0.086). Mostly patients were married 66 (66%), rest were - Single (7%), Widowed (26%), Divorced (1%). In our study most of the patients were on ART i.e 80% while 20 % were not on ART. Association of ART use with metabolic syndrome did not yield significance on statistical analysis (p value=0.90). In our study, 47% patients were on ZLN based ART, 29% on TLE while 2% each on TLN and ZLE and 20% were not on any ART treatment. Mean duration of therapy was 24.92 months. Prevalence of MetS was 24.1% (7 out of 29 patients) with TLE based Regimen while with ZLN, prevalence was 21.3% (10 out of 47 patients). Different groups of ART regimen did not have statistical impact on prevalence of MetS (p value=0.87). In our study, only 10% of patients (n=10) had raised waist circumference out of which 4 patients were subsequently labelled as having MetS. Thus our study established the prevalence of Metabolic Syndrome among HIV infected patients to be 21% in this part of the country. In males, prevalence was 13.4% and in females, it was 29.17%. No statistically significant association was found between ART naïve or ART use or type of ART regimen use with the prevalence of Metabolic Syndrome.

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