International Journal of Medical Research Professionals
P-ISSN: 2454-6356; E-ISSN: 2454-6364
DOI: 10.21276/ijmrp

IJMRP

Original Research Article.

Diabetes Mellitus, Insulin Resistance and Metabolic Syndrome in HIV Positive Patients at a Tertiary Care Hospital

Sarvesh Kumar[1], Himanshu Dutt Sharma[2*]

[1]Assistant Professor, Department of General Medicine,
Krishna Mohan Medical College and Hospital, Mathura, Uttar Pradesh, India.
[2]Assistant Professor, Department of General Medicine,
Saraswathi Institute of Medical Sciences, Hapur Road, Anwarpur, Uttar Pradesh, India.

ABSTRACT

Introduction: HIV (*human immunodeficiency virus*) is a classical virus that attacks cells which help the body's immune system, making the person more susceptible to other infections and diseases. An international cross-sectional study conducted with 788 HIV-infected adults screened at 32 centers to study the prevalence of metabolic syndrome using International Diabetes Federation (IDF) and U.S. National Cholesterol Education Program Adult Treatment Panel III criteria, associated to body composition (whole-body dual-energy X-ray absorptiometry and abdominal computed tomography), lipids, glycaemic parameters, insulin resistance, leptin, adiponectin and C-reactive protein (CRP).

Materials and Methods: This study was set up as a cross-sectional study involving all the HIV-positive patients which was conducted in the Department of General Medicine, Krishna Mohan Medical College and Hospital, Mathura, Uttar Pradesh, India. Inclusion criteria include those patients were aged over 18 years, had HIV infection over a period of 12 months and those were on ART (ART-treated group) or had HIV infection for more than 12 months but were not on ART (ART-naïve group). The demographic details were collected from each patient. The anthropometric measurements were measured by a skilled nutritionist and these measurements include height, weight and waist circumference, measured using height scale, weighing machine and an inch tape, respectively. Blood samples were collected from each patient after fasting for the whole night. Following this, 75 g glucose was orally administered, and at after every 2 hours another blood sample was collected. The total cholesterol was assessed by the cholesterol oxidase and cholesterol esterase method. High-density lipoprotein (HDL) cholesterol was evaluated by the automated enzymatic method. Triglycerides were determined by using the lipoprotein lipase/glucokinase enzymatic procedure.

Results: A total of 80 patients were included in the study. 40 patients were ART-naïve, and 40 were treated with ART. The mean duration of ART was 41.68 months (range 12–108 months). There were 33 males and seven females in the ART-treated group and 31 males and nine females in the ART-naïve group. The mean age of patients in the ART treated group was 41.68 (±10.94), while that in the ART group was 40.65 (±9.48).

Conclusion: The effective management of diabetes in HIV infected patients requires a thorough and clear understanding of pathophysiology and pharmacology. The choice should be based on the aetiopathogenesis and pathophysiology of the disease. Patients with pre-existing diabetes should be counselled about a possible deterioration in metabolic function, and the chances of drug interactions.

Keywords: Insulin Resistance, Metabolic Syndrome, Obesity, HIV.

***Correspondence to:**

Dr. Himanshu Dutt Sharma,
Assistant Professor,
Department of General Medicine,
Saraswathi Institute of Medical Sciences,
Hapur Road, Anwarpur, Uttar Pradesh, India.

Article History:

Received: 17-10-2017, **Revised:** 09-11-2017, **Accepted:** 28-11-2017

Access this article online	
Website: www.ijmrp.com	Quick Response code
DOI: 10.21276/ijmrp.2017.3.6.120	

INTRODUCTION

HIV (*human immunodeficiency virus*) is a classical virus that attacks cells which help the body's immune system, making the person more susceptible to other infections and diseases. Patients affected with human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS) are gradually increasing in high numbers, which could partly be attributed to improved screening, earlier diagnosis, better modes of treatment and greater accessibility as well as acceptance of the therapy amongst

the population. Numbers from the United Nations reveal that the total number of patients reported with HIV is 33 million, with 2.7 million new infections in 2007 have been documented.[1] Due to greater advancements in the research field, Improved methods of detection of HIV, earlier diagnosis, and better management have helped in greatly enhancing the survival rates of these patients. The availability and access to the potent retroviral therapy has highly transformed into lesser acute morbidity and mortality thereby increasing the longer lifespan.[2] HIV/AIDS patients, however, frequently present with diabetes mellitus type – 2 and metabolic complaints. As the treatment of HIV develops and the access to the therapy greatly enhances the incidence of HIV-associated diabetes is bound to be grown.

An international cross-sectional study conducted with 788 HIV-infected adults screened at 32 centers to study the prevalence of metabolic syndrome using International Diabetes Federation (IDF) and U.S. National Cholesterol Education Program Adult Treatment Panel III criteria, associated to body composition (whole-body dual-energy X-ray absorptiometry and abdominal computed tomography), lipids, glycaemic parameters, insulin resistance, leptin, adiponectin and C-reactive protein (CRP).[3] The prevalence of metabolic syndrome was observed to be around 14% (n = 114; 83 men) by IDF criteria and 18% (n = 139; 118 men) by ATPIII criteria. Half of the patients (49%) exhibited two or more features of metabolic syndrome but were not classified as having the syndrome because they had normal or below normal waist circumferences or waist-to-hip ratios.

Metabolic syndrome was reported to be more common in those at the receiving end of protease inhibitors (P = 0.04). Type 2 diabetes prevalence was 5-9% higher in those with metabolic syndrome.[3] The strongest relationship with diabetes was the exposure to stavudine whereas treatment with zidovudine and didanosine was also associated with a high risk of diabetes mellitus.[4] Management of HIV/AIDS is gradually widening to include the chronic and metabolic complications associated with the disease and the adverse effects associated with its treatment protocol.

MATERIALS AND METHODOLOGY

This study was set up as a cross-sectional study involving all the HIV-positive patients which was conducted in the Department of General Medicine, Krishna Mohan Medical College and Hospital, Mathura, Uttar Pradesh, India. Inclusion criteria include those patients were aged over 18 years, had HIV infection over a period of 12 months and those were on ART (ART-treated group) or had HIV infection for more than 12 months but were not on ART (ART-naïve group). Those patients who are affected with diabetes mellitus, hypertension, dyslipidemia, coronary artery disease, malignancy, sleep apnea, or chronic renal failure were present prior to starting ART or if they were nonadherent to ART were directly excluded from the study. Patients who had fulfilled the inclusion criteria were informed about the study and a written informed consent form was signed priorly. The demographic details were collected from each patient and recorded in the proforma. The anthropometric measurements were measured by a skilled nutritionist and these measurements include height, weight and waist circumference, measured using height scale, weighing machine and an inch tape, respectively. Bodily measurements like height were measured to the closeby centimeter, and weight was recorded to the nearest 0.5 kg. Waist circumference was measured at the point between the iliac crest and the lower margin of the ribs and rounded to the nearest centimeter. Blood samples were collected from each patient after fasting for the whole night. Following this, 75 g glucose was orally administered, and at after every 2 hours another blood sample was collected. The total cholesterol was assessed by the cholesterol oxidase and cholesterol esterase method. High-density lipoprotein (HDL) cholesterol was evaluated by the automated enzymatic method. Triglycerides were determined by using the lipoprotein lipase/glucokinase enzymatic procedure. The lipid profile was estimated with the help of *Dade Behring* equipment. Fasting insulin levels were measured using chemiluminescence method on immulite equipment. The lab is under quality control and is National Accreditation Board for Testing and Calibration Laboratories (NABL)-accredited. Quantitative measurements of CD-4 cells were done in the department of microbiology. Metabolic syndrome was defined using National Cholesterol Education Program–Adult Treatment Plan III (NCEP–ATP III) 2001 criteria.[5]

Prior permission was obtained from the Institutional Ethical Review Board before the commencement of the study. All patients were provided with details and an informed consent form was signed by all patients who were included in the study. The data were analysed using SPSS software (version 16; SPSS Inc., Chicago, IL). Student's t-test was done to compare numerical variables in the two groups. Chi square test or Fisher's exact test were used for ordinal variables.

RESULTS

A total of 80 patients were included in the study. 40 patients were ART-naïve, and 40 were treated with ART. The mean duration of ART was 41.68 months (range 12–108 months). There were 33 males and seven females in the ART-treated group and 31 males and nine females in the ART-naïve group. The mean age of patients in the ART treated group was 41.68 (±10.94), while that in the ART group was 40.65 (±9.48). The mean duration of disease (HIV) was 53.2 (±27.76) months in the ART-treated group and 17.33 (±9.18) months in the ART-naïve group. Readings summarizes in table 1 shows demographic details, components of metabolic syndrome, insulin resistance and CD - 4 counts in the ART treated and ART-naïve groups.

Applying NCEP–ATP III criteria, a total of 16 patients out of 60 were diagnosed to have metabolic syndrome. Of these, 13 (81.3%) were on ART, while three (18.7%) were not treated with ART (P = 0.028). Of the 60 patients, all had at least one component of metabolic syndrome. Four patients who had fulfilled four criteria and all of them were on ART. The details of the number of patients with combinations of criteria are demonstrated in Table - 1.

The majority of patients with metabolic syndrome were males (12/16). When the patients with metabolic syndrome were grouped into two, based on age (age #40 years and age .40 years), nine were aged 40 years or younger. Four patients with metabolic syndrome had body mass index (BMI) less than 18.5, 10 had BMI ranging from 18.5 to 24.9, and two had BMI more than 25. There was none in the obese range with BMI above 30. Among the parameters used for diagnosis of metabolic syndrome, the most observed was low HDL, occurring in all patients. For

evaluating the occurrence of metabolic syndrome with respect to the type of ART, the patients were classified into three groups: 1) non-protease inhibitor (PI), non-stavudine (d4T), 2) non-PI d4T, and 3) PI-based regimens. Of the 30 patients in the ART group, three were exposed to PIs, 18 to d4T, and nine received the non-PI, non-d4T regime. All three patients exposed to PI had metabolic syndrome. In the non-PI d4T group, 6 out of 18 had metabolic syndrome, and in the non-PI, non-d4T group 4 out of 9 had metabolic syndrome. Of these, 15 (62.5%) were on ART, while nine (37.5%) were ART naïve (P = 0.11). Thirteen were aged 40 years or less, whereas the rest were over this age. Eighteen patients with IR were male, and six females.

Table 1: Comparison between ART-treated and ART-naïve groups

Study characteristic	ART (n=40)		ART-naïve (n=40)		P - value
	Mean	SD	Mean	SD	
Age (years)	41.68	10.99	40.65	9.55	0.699
Duration of disease (months)	53.2	27.88	17.33	9.22	<0.001
Male: Female	33:7	-	31/9	-	-
BMI (Kg/m$^{2)}$	20.35	3.93	18.66	4.31	0.082
Waist circumference (cms)	83.3	11.93	76.9	9.72	0.036
Fasting blood sugar (mg/dL)	98	25.26	89.72	19.9	0.361
Two-hour OGTT (mg/dL)	112.21	58.55	131.43	28.57	0.095
Total cholesterol (mg/dL)	158.3	43.62	149.34	40.02	0.457
HDL cholesterol (mg/dL)	32.93	13.34	25.65	9.55	0.019
LDL cholesterol (mg/dL)	86.98	32.98	78.65	21.72	0.292
Triglycerides	201.52	163.73	155.54	70.21	0.172
CD-4 counts (cells/µL)	211.01	172.92	170.72	131.51	0.328

Abbreviations: ART, antiretroviral therapy; BMI, body mass index; BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein;

DISCUSSION

The results of this study showed that there is a high prevalence rate of metabolic syndrome and IR in patients treated with ART. The overall prevalence rate of metabolic syndrome in HIV-positive patients was estimated at 26.6%; 43.3% in the ART-treated group and 10% in the ART-naïve group. These results suggested a statistically significant data and increase in the ART group (P = 0.028). Studies conducted from Spain and other parts of the world have reported the prevalence rates of 17%–18% on HIV populations using NCEP–ATP III criteria.[9,10] There are certain Indian studies on uninfected individuals have noted prevalence rates ranging from 18.4% to 30.9% using NCEP–ATP III criteria.[11,12] Thus, in our study the overall prevalence rate seems to be similar to the Indian population but higher than other HIV populated areas. The prevalence rate seen in our ART-treated group is much higher at 43.3%. Generally, all the patients included in this study had at least one criterion for metabolic syndrome and the most frequently observed was low HDL. In the Spanish study, of the total 710 study patients (both ART-treated and -naïve), one or more criteria were fulfilled by 69.3%, two or more by 35.8%, three or more by 17%, four or more by 4.5% and all five criteria were seen only in one patient.[9] Though not directly comparable, these results suggest that unlike in our patients, 31.7% did not have any feature of metabolic syndrome, implying that these metabolic derangements may be more prevalent in the Indian population. In our study, low HDL cholesterol was the most observed parameter, whereas in the Spanish study, hypertriglyceridemia was the most commonly recognized. Though there are certain differences, the dyslipidemia observed in our patients is in concordance with HIV associated dyslipidemia. Hence, it is the confirmed risk factor for macrovascular disease.[13] The mechanism of IR and metabolic syndrome in nucleoside reverse transcriptase inhibitor-treated patients is hypothesized to be mitochondrial toxicity.[14] It should be noted that the affluent nations have moved on to less toxic drugs while developing countries like India still administer these kind of drugs as a part of national treatment regime programs.[15] The individual contributions of each drugs could not be evaluated in this study due to inadequate numbers of patients, though 10 out of 27 patients on nucleoside reverse transcriptase inhibitor-based regimes had metabolic syndrome and 12 out of 27 developed IR. All the three patients who were on protease inhibitors in this ART-treated group had metabolic syndrome and IR. Both the fasting and post-glucose load blood glucose values were suggestive of a high proportion of patients with dysglycemia with six patients in the ART group satisfying diagnostic criteria for diabetes. In the view of high usage of nucleoside reverse transcriptase inhibitors in our ART regimes the results obtained appear to be alarming. It is to be observed that nucleoside reverse transcriptase inhibitors used as the first-line drugs in India that have been strongly implicated in the development of insulin resistance and subsequent development of diabetes.[16] The number of patients affected with metabolic syndrome in the ART-naïve group was three out of a total of 30. One notable difference between ART-treated and ART-naïve patients was the duration of disease. It is also of note that, 9 out of 24 patients who had IR were not on ART, while 15 were. In addition, dysglycemia was observed in nine patients in the ART

group. While mitochondrial toxicity is responsible for the development of IR in nucleoside reverse transcriptase inhibitor-treated patients, HIV proteins Tat, Vpr, Vif, Rev and Nef, as well as inflammatory cytokines interleukin-2 and tumour necrosis factor-α are implicated in ART-naïve patients.[1] The BMI of our study participants, both with metabolic syndrome and insulin resistance, was observed to be in the range of 18.5–24.9, in keeping with the lean fat Indian phenotype with central obesity.[4] The ages of patients with IR and metabolic syndrome show a high tendency towards younger groups which is in contrast to the studies conducted in Western countries with a mean age of HIV-infected patients with these conditions is reportedly higher.[9,10] The increased cardiovascular risk for South Asians with central obesity has been widely studied.[3,4] Also, the risk for the development of diabetes and cardiovascular risk in patients with metabolic syndrome is very-well established.[17] An increased cerebrovascular and cardiovascular risk due to metabolic syndrome in HIV has been highly noted by the Data Collection on Adverse Events of Anti-HIV Drugs (DAD) study.[2] However, in a population which is risk-prone, the additional burden conferred by ART/ HIV-induced metabolic syndrome needs to be evaluated. This will have implications on future drug policies for HIV-infected patients. Even though the limitation of the small number of patients in our study, there is an increase in metabolic syndrome, diabetes mellitus and insulin resistance in patients on ART. Larger population-based studies are needed to assess the actual prevalence rate of metabolic syndrome and IR and the macrovascular risk referred by these conditions.

CONCLUSION

The effective management of diabetes in HIV infected patients requires a thorough and clear understanding of pathophysiology and pharmacology. The choice should be based on the aetiopathogenesis and pathophysiology of the disease. Patients with pre-existing diabetes should be counselled about a possible deterioration in metabolic function, and the chances of drug interactions. Patients who are detected to be diabetic at onset of therapy or later, may benefit from insulin. Insulin is a safe and effective method of treating all these patients, irrespective of type of diabetes.

REFERENCES

1. HIV Data. Accessed 22 December, 2010. [http://www.unaids.org/en/KnowledgeCentre/HIVData/default.asp]
2. Young F, Critchley JA, Johnstone LK, Unwin LC: A review of co-morbidity between infectious and chronic disease in Sub Saharan Africa: TB and Diabetes Mellitus, HIV and Metabolic Syndrome, and the impact of globalization. Globalization and Health 2009, 5:9.
3. Samaras K, Wand H, Law M, Emery S, Cooper D, Carr A: Prevalence of metabolic syndrome in HIV-infected patients receiving highly active antiretroviral therapy using International Diabetes Federation and Adult treatment Panel III criteria. Diabetes Care 2007, 30(1):113-115.
4. De Wit S, Sabin CA, Weber R, Worm SW, Reiss P, Cazanave C, El-Sadr W, Monforte Ad'A, Fontas E, Law MG, Friss-Moller N, Phillips A: Incidence and Risk Factors for New-Onset Diabetes in HIV-Infected Patients. The Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D). Study Diabetes Care 2008, 31(6):1224-9.
5. Naylor BA, Treacher DF, Turner RC. Homeostatsis Model Assessment: insulin resistance and B cell function from fasting plasma glucose concentration and insulin resistance in man. Dibetologia. 1985;28: 412–419.
6. Jericó C, Knobel H, Montero M, et al. Metabolic syndrome among HIV-infected patients: prevalence, characteristics, and related factors. Diabetes Care. 2005;28:132–137.
7. Samaras K, Wand H, Law M, Emery S, Cooper D, Carr A. Prevalence of metabolic syndrome in HIV-infected patients receiving highly active antiretroviral therapy using International Diabetes Foundation and Adult Treatment Panel III criteria: associations with insulin resistance, disturbed body fat compartmentalization, elevated C-reactive protein, and [corrected] hypoadiponectinemia. Diabetes Care. 2007;30(1):113–19.
8. Deepa M, Farooqh S, Datta M, Deepa R, Mohan V. Prevalence of metabolic syndrome using WHO/ATP III and IDF definitions in Asian Indians: the Chennai Urban Rural Epidemiology Study (CURES-34). Diabetes Metab Res Rev. 2007;23:127–34.
9. Gupta R, Deedwania PC, Gupta A, Rastogi S, Panwar RB, Kothari K. Prevalence of metabolic syndrome in an Indian urban population. Int J Cardiol. 2004;97:257–61.
10. Oh J, Hegele RA. HIV-associated dyslipidaemia: pathogenesis and treatment. Lancet. 2007;7:787–96.
11. Fleishman A, Johnsen S, Systrom DM, et al. Effect of nucleoside reverse transcriptase inhibitor, stavudine on glucose disposal and mitochondrial function in muscle of healthy adults. Am J Physiol. 2007;292: E1666–E1673.
12. Antiretroviral therapy for HIV infected adults and adolescents including post-exposure prophylaxis. www.nacoonline.org.
13. De Wit S, Sabin CA, Weber R, et al. Incidence and risk factors for new onset diabetes in HIV-infected patients. The data collection on adverse events of anti HIV drugs (DAD) study. Diabetes Care. 2008;31: 1224–29.

Source of Support: Nil. **Conflict of Interest:** None Declared.

Cite this article as: Sarvesh Kumar, Himanshu Dutt Sharma. Diabetes Mellitus, Insulin Resistance and Metabolic Syndrome in HIV Positive Patients at a Tertiary Care Hospital. Int J Med Res Prof. 2017 Nov; 3(6): 532-35. DOI:10.21276/ijmrp.2017.3.6.120