ISSN: 2377-6196
The American Journal of
SCIENCE AND MEDICAL RESEARCH, 1(3), 101-107

Research Article Open Access

Metabolic effects of protease inhibitors in human immunodeficiency virus (HIV) infected patients

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Abstract

The present study focuses on the prevalence and characteristics of the metabolic syndrome in HIV-infected patients and possible related factors, including individual antiretroviral drug exposure. A cross-sectional study was carried out on 720 HIV-infected patients managed at the outpatient Infectious Disease Unit of the Mahatma Gandhi Memorial Hospital, Warangal, Andhra Pradesh, over a period of 1 year, from September through August 2007. Age, sex, HIV disease status according to Disease Control and Prevention (CDC) classification of HIV disease, HIV exposure (mutually exclusive in the following order: intravenous drug use, male homosexual activity, heterosexual activity), and type and duration of ART were recorded. The results shows that one or more features of metabolic syndrome were seen in 492 (69.3%) patients, two or more in 254 (35.8%), three or more in 121 (17%) and four or more in 32 (4.5%), and five features were seen in 1 patient (0.1%). Thus, 121 patients (86 men, 35 women) metabolic syndrome criteria, yielding a prevalence of 69.2% (492/710). This was significantly increased in age 31-40 years of HIV infected patients. A total of 116 patients were on combination ART, and 5 were naive HIV-infected patients. This study concludes that, a significant positive correlation was observed between the level of neutropenia and anemia in HIV infected subjects. It is hoped that ongoing research into the molecular mechanisms of insulin resistance and lipodystrophy in the context of HIV infection and antiretroviral therapy will ultimately provide viable treatment options for patients with metabolic syndrome.

Key words: Protease inhibitors, HIV, ART, Metabolic syndrome, Adilabad

INTRODUCTION

HIV/AIDS is one of the greatest crisis being faced by mankind today History tells us that whenever there has been a crisis there have also been those who have exploited the crisis (Henry et al, 1997). HIV/AIDS is no exception to this historic truism. The self-serving HIV/AIDS industry is very industriously exploiting the global HIV/AIDS crisis. Joint United Nations Program on HIV / AIDS and WHO has estimated that on December' 2006 (Aldrich, 2000), there might be around 39.9 million people have been infected with Human Immunodeficiency Virus (HIV). HIV / AIDS was first recognized in 1981, but probably existed at a low endemic level in central Africa before the HIV epidemic spread to several areas of the World during 1980s (Barardinelli, 2004).

Two decades into the epidemic and there is still no vaccine and no "cure" for AIDS. There is considerably more information now available on how the HIV leads to AIDS, its spread, and wealth of "lessons leased" in implementing prevention strategies and increased understanding about what constitutes effective management of HIV / AIDS patients. The social and economic conditions of that facilitate the spread of HIV are also well understood. Combination antiretroviral therapy (ART) has positively modified the natural history of HIV infection, leading to a significant reduction in morbidity and mortality (Clarke, 1999). However, long-term toxicity is becoming recognized, and a variety of metabolic abnormalities including dyslipidemia, fat

How to Cite this Article:

T. Shivalingu (2015). Metabolic effects of protease inhibitors in human immunodeficiency virus (HIV) infected patients. The American Journal of Science and Medical Research, 1(3):101-107. doi:10.17812/ajsmr2015133

Received 24 July, 2015; Accepted 28 August, 2015
Published online 20 September, 2015

redistribution, high blood pressure, and insulin resistance have frequently been associated with this therapy, particularly when it contains protease inhibitors (Matthews et al, 1985). This fact has raised the concern that the HIV-infected population in the long term may be at increased risk for cardiovascular disease, as has recently been described in two large prospective studies.

The metabolic syndrome is affecting the general population in epidemic proportions and is frequently associated with increased risk of cardiovascular morbidity and mortality. Insulin resistance plays a key role in the pathogenesis of the metabolic syndrome and is frequently detected among HIV patients on ART. Furthermore, several traits of the metabolic syndrome in the general population overlap with common features of metabolic side effects associated with combination ART in the HIV-infected population. The present study focuses on the prevalence and characteristics of the metabolic syndrome in HIV-infected patients and possible related factors, including individual antiretroviral drug exposure.

Granulocytopenia is a problem commonly encountered in patients with HIV infection. Although low granulocyte counts usually reflect the toxicity of therapies for HIV infection or associated conditions, studies of untreated patients have also shown a high incidence of granulocytopenia, particularly in patients with more profound immunodeficiency (Zon et al, 1987). For example, the Multicenter AIDS Cohort Study found that 0.8% of HIV-seropositive patients with mean CD4+ T lymphocyte counts of greater than 700 cells/mm3 had abnormally low granulocyte counts, whereas granulocytopenia was present in 13.4% of those with mean CD4+ T lymphocyte counts below 249 cells/mm^3. Zon and Groopman noted low granulocyte counts in 13% of asymptomatic HIV-seropositive patients and in 44% of those with frank CDC-defined AIDS.

The present study was thus conducted to find out the prevalence of hematological and also metabolic studies among HIV infected patients.

MATERIALS AND METHODS

Cross-sectional Study:

A cross-sectional study was carried out on 720 HIV-infected patients managed at the outpatient Infectious Disease Unit of the Mahatma Gandhi Memorial Hospital, Warangal, Andhra Pradesh, over a period of 1 year, from September through August 2007. The protocol study approved by the local ethics committee consisted of physical examination and laboratory analysis after a 12-h overnight fast. All participants were 20 years of age or older and were evaluated by trained physicians after giving their informed consent. Exclusion criteria included withdrawal of combination ART and evidence of clinical signs of active AIDS in the 3 months before entry because of their possible impact on anthropometric and laboratory parameters.

Sample Criteria:

Age, sex, HIV disease status according to Disease Control and Prevention (CDC) classification of HIV disease, HIV exposure (mutually exclusive in the following order: intravenous drug use, male homosexual activity, heterosexual activity), and type and duration of ART were recorded. Lipodystrophy was defined and categorized by the physician-assessed presence of peripheral lipoatrophy (face, arms, legs, buttocks, and prominent veins), central lipohypertrophy (abdomen, breasts, dorsocervical region) and mixed lipodystrophy. Weight, height, and waist circumference were measured by standard methods. After the patient had rested for 10 minutes seated in a quiet room, blood pressure was measured in the left arm with the elbow flexed at heart level by the same physician using a 1042 Riester sphygmomanometer. Three readings were obtained, and the average of the second and third systolic and diastolic blood pressure readings was used in the analyses.

Participants:

Participants of the following criteria were defined as having the metabolic syndrome: waist circumference >102 cm in men and >88 cm in women; triglycerides 150 mg/dl (1.69 mmol/l); HDL cholesterol <40 mg/dl (1.04 mmol/l) in men and <50 mg/dl (1.29 mmol/l) in women; blood pressure 130/85 mmHg; and fasting glucose 110 mg/dl (6.1 mmol/l).

Biochemical profile:

Total cholesterol and triglycerides were determined using standard enzymatic methods. HDL cholesterol was measured using by standard diagnostic kits. Glucose was measured by the oxidase method.

Hematological parameters of hemoglobin, white cell count, platelet count, erythrocyte sedimentation rate and differential leucocyte count were determined by standard hematological diagnostic procedures.

Statistical Analysis:

The prevalence of clinical findings of lipoatrophy, Lipodystrophy, insulin resistance and the presence of metabolic abnormalities was obtained for each treatment group. Data was analyzed using multipurpose statistical Software. Computed factors in the univariate analysis were age, sex, BMI, HIV clinical stage, Lipodystrophy, and other hematological parameters and metabolic abnormalities.

RESULTS & DISCUSSION

Enrollment:

Among the 1,016 HIV-infected patients managed at the outpatient clinic of our hospital during 2006, 209 were excluded for age, overt clinical disease that required hospital admission. Of the 807 eligible patients,

only 720 (88%) completed the study protocol. Of these, 626 (88.2%) were on combination ART and 84 (11.8%) naive. Clinical characterisitics of HIV infection, metabolic syndromes and hematological abnormalities are determined all these patients. Hematological parameters of hemoglobin, white cell count, platelet count and white blood cell count were determined. Data was analyzed using a multipurpose statistical computer software package.

Clinical characteristics of HIV infection and metabolic syndrome traits:

Clinical characteristics of HIV infection and metabolic syndrome traits are listed in Tables 1 and 2, respectively. This shows that one or more features of metabolic syndrome were seen in 492 (69.3%) patients, two or more in 254 (35.8%), three or more in 121 (17%) and four or more in 32 (4.5%), and five features were seen in 1 patient (0.1%). Thus, 121 patients (86 men, 35 women) metabolic syndrome criteria, yielding a prevalence of 69.2% (492/710). This was significantly increased in age 31-40 years of HIV infected patients. A total of 116 patients were on combination ART, and 5 were naive HIV-infected patients.

Table-1. Demographic, Anthropometric and HIV infection characteristics of the 710 patients

Characteristics	Values
Age (Yrs)	41.9±9.2
Male/Female	511/199
BMI (Kg/m2)	23.4±3.9
Waist circumference (cm)	
Men	86.7±9.9
Women	80.9±11.4
Transmission groups (%)	293 (41.3%)
Intravenous drug users	240 (33.8%)
Homosexuals	158 (22.2%)
Heterosexuals	19 (2.7)
Other and unknown	

Data are means ± SD and n (%) unless otherwise indicated

Characteristics of the metabolic abnormalities of the 710 HIV-infected patients:

Lipodystrophy was more common among participants with the metabolic syndrome compared with those without (50.4 vs. 33.8). Hypertriglyceridemia (95%) was the most frequent trait of the metabolic syndrome, followed by low HDL cholesterol (71.1%), high blood pressure (67.8%), abdominal obesity (47.1%), and high blood glucose levels (46.3%).

Age-wise, gender-wise analysis of metabolic abnormalities in HIV infected patients:

Metabolic syndrome-age and gender wise related factors in the univariate analysis are shown in Table 3. Patients with the metabolic syndrome presented higher age, BMI and lower percentage of intravenous drug users compared with those without the metabolic syndrome. Moreover, lipodystrophy and ART were associated with the metabolic syndrome. Lipodystrophy could indirectly be considered a component trait of the metabolic syndrome because its definition involves fat redistribution and, frequently, insulin resistance; thus, it was not included in the logistic regression analysis.

Table-2. Characteristics of the metabolic abnormalities of the 710 HIV-infected patients

Variables	Values *n* (%)
Waist circumference	
>102 cm in men	43 (8.4%)
>88 cm in women	46 (23.1%)
Blood pressure ≥130/85 mmHg	187 (26.3%)
HDL cholesterol	
<40 mg/dl in men	173 (33.9%)
<50 mg/dl in women	80 (40.2%)
Triglycerides ≥150 mg/dl	306 (43.1%)
Glucose ≥110 mg/dl	82 (11.5%)

Clinical characteristics of HIV-infected metabolic syndromic and HIV-infected non metabolic syndromic patients:

The clinical and biochemical characteristics of the 710 patients with HIV-associated fat accumulation are shown in Table 4. The prevalence of metabolic complications in HIV-infected individuals is high. The level of fasting glucose and HDL cholesterol is low in HIV-infected metabolic syndromic patients compared to HIV-infected non-metabolic syndromic patients. 208 patients were developed fasting hypoglycemia associated with Lipodystrophy. The levels of LDL (119+10), triglycerides (256+19) high in metabolic syndromic HIV-infected patients compared to HIV-infected non-metabolic syndromic patients. No significant changes were seen in direct or calculated LDL cholesterol levels ad triglycerides levels. There was a small increase in HDL cholesterol levels (36+2 mg/dL to 43+2 mg/dL) compared with baseline, but values remained within the normal range. Triglyceride levels reduced to 256+40 mg/dL to 152+31 mg/dL in HIV infected non metabolic syndromic patients compared to HIV-infected metabolic syndromic patients.

Prevalence of hematological abnormalities In HIV infected patients:

Hematological parameters were determined in 710 HIV infected patients. Out of 710 HIV infected patients

hematological abnormalities found in 542 (76.3%) patients. Of these 542 HIV patients the prevalence of anemia (Hb <7 g/dL) was 59.4% (322/542), Thrombocytopenia, neutropenia and leucopenia are present in 55.4% (301/542), 33.2% (180/542) and 57.5 % (312/542) respectively. The incidence of anemia (59.4%) and leucopenia (57.5%) were significantly higher in HIV infected patients. In female anemia and leucopenia were high (67.1% and 54.8%) compare to male (32.9 % and 45.2%) HIV infected patients. A statistically significant difference was observed between the hemoglobin, platelet count and the WBC count of HIV infected individuals. A significant positive correlation was observed between the level of neutropenia and anemia in HIV infected subjects.

Table-3. Association between age, sex, HIV disease characteristics, Lipodystrophy, ART and the metabolic syndrome.

Characteristics	Patients with metabolic syndrome	Patients without metabolic syndrome
N (%)	121 (17)	589 (83)
Age (Years)	45.6±10.2	41.2±8.8
Sex (%)		
Male	86 (71.1)	425 (72.2)
Female	35 (28.9)	164 (27.8)
BMI (kg/m^2)	25.8±3.7	22.9±3.7
Lipodystrophy		
No	60 (49.6)	390 (66.2)
Lipoatrophy	23 (19.0)	129 (21.9)
Lipohypertrophy	38 (31.4)	70 (11.9)
Insulin resistance	24 (20.3)	34 (31.5)
Antiretroviral therapy exposure		
Naïve (%)	5 (4.1)	79 (13.4)
Never protease inhibitors (%)	24 (19.8)	134 (22.8)
Past protease inhibitor (%)	51 (42.1)	215 (36.4)
Current protease inhibitor (%)	41 (33.9)	161 (27.4)

Data are means ± SD and n (%), unless otherwise indicated

Age wise incidence of hematalogical abnormalities among HIV infected patients:

The overall prevalence of hematological abnormalities was 76.3% (542/710) in HIV infected patients. The prevalence of hematological abnormalities in HIV infected patients with age 21-30 years, 31-40 years and 41-50 years is shown in Fig. 8. At a given age for the three different age groups prevalence of hematological abnormalities was slight difference in HIV infected patients. The hematological abnormalities in 21-30 years age group had lowest (54.8%) prevalence and the highest (77.4%) prevalence of hematological abnormalities was in the age group of 31-40 years.

DISCUSSION

This study demonstrates that HIV seropositivity is important, independent risk factors for metabolic abnormalities and hematological abnormalities. 69% of HIV-infected patients in this sample were estimated to have the metabolic syndrome. This estimate is somewhat lower than that reported for the American population using the same clinical definition or for the Spanish population. This could be due at least in part to the low number of women (28%) and patients over age 60 years (5%) in the present study, population subgroups with known higher metabolic syndrome prevalence. However, when comparing the age-specific prevalence of the metabolic syndrome, the prevalence among participants aged 30 through 50 was nearly identical in the present study of HIV-infected patients to that of the uninfected persons.

TABLE-4. Baseline clinical characteristics of HIV-infected metabolic syndromic and HIV-infected non-metabolic syndromic patients

	HIV-infected metabolic Syndromic patients (n=492)	HIV-infected non-metabolic syndrome patients (n=208)	Normal controls (n=113)
Fasting glucose			
(mg/dl)	90 ± 2	95 ± 3	91 ± 1
(mmol/liter)	4.79 ± 0.11	5.27 ± 0.17	4.95 ± 0.06
Cholesterol			
(mg/dl)	196 ± 10	169 ± 9	167 ± 7
(mmol/liter)	5.08 ± 0.26	4.38 ± 0.23	4.33 ± 0.18
HDL			
(mg/dl)	36 ± 2	43 ± 2	51 ± 3
(mmol/liter)	0.93 ± 0.05	1.11 ± 0.05	1.32 ± 0.08
LDL			
(mg/dl)	119 ± 10	99 ± 9	100 ± 6
(mmol/liter)	3.08 ± 0.26	2.56 ± 0.23	2.59 ± 0.16
Triglycerides			
(mg/dl)	259 ± 40	152 ± 31	80 ± 10
(mmol/liter)	2.93 ± 0.45	1.72 ± 0.75	0.90 ± 0.11

Although the prevalence of metabolic syndrome has been assessed in several populations, previous data on metabolic syndrome among the HIV-infected population are limited and show an impressively high prevalence. Potential explanations for these dissimilar results include differences in study design, methodological aspects, and differences in the patient populations studied. In this respect, the present study has a relatively high proportion of intravenous drug users with a low prevalence of the metabolic syndrome (13%). On the other hand, when the present HIV-infected group was reanalyzed by the Data Collection on Adverse Events of anti-HIV Drugs Study criteria for age and sex, obesity, hypertension, hypercholesterolemia, low HDL, hypertriglyceridemia, and diabetes, prevalences of these cardiovascular risk factors were quite similar. Nevertheless, we must emphasize that the metabolic syndrome is a heterogeneous disorder, with substantial variability in the prevalence of component traits within and across populations.

The main difference in metabolic syndrome components of the present study compared with other studies conducted with HIV-infected or uninfected subjects was the low prevalence of abdominal obesity

(12.5%). We ensured that blood samples were obtained after a 12-h overnight fast to avoid hypertriglyceridemia and hyperglycemia over diagnosis.

As occurs in uninfected subjects, metabolic syndrome in HIV-infected patients is associated with age and BMI. Among the HIV-infected population, the new findings concern the additional independent association of metabolic syndrome in those with past and current exposure to protease inhibitors. The link between protease inhibitor exposure, lipodystrophy, and metabolic syndrome is not surprising because fat redistribution, hyperlipidemia, insulin resistance, and hyperglycemia have been extensively reported in

Figure-1. Gender wise prevalence of hematological abnormalities in HIV infected patients

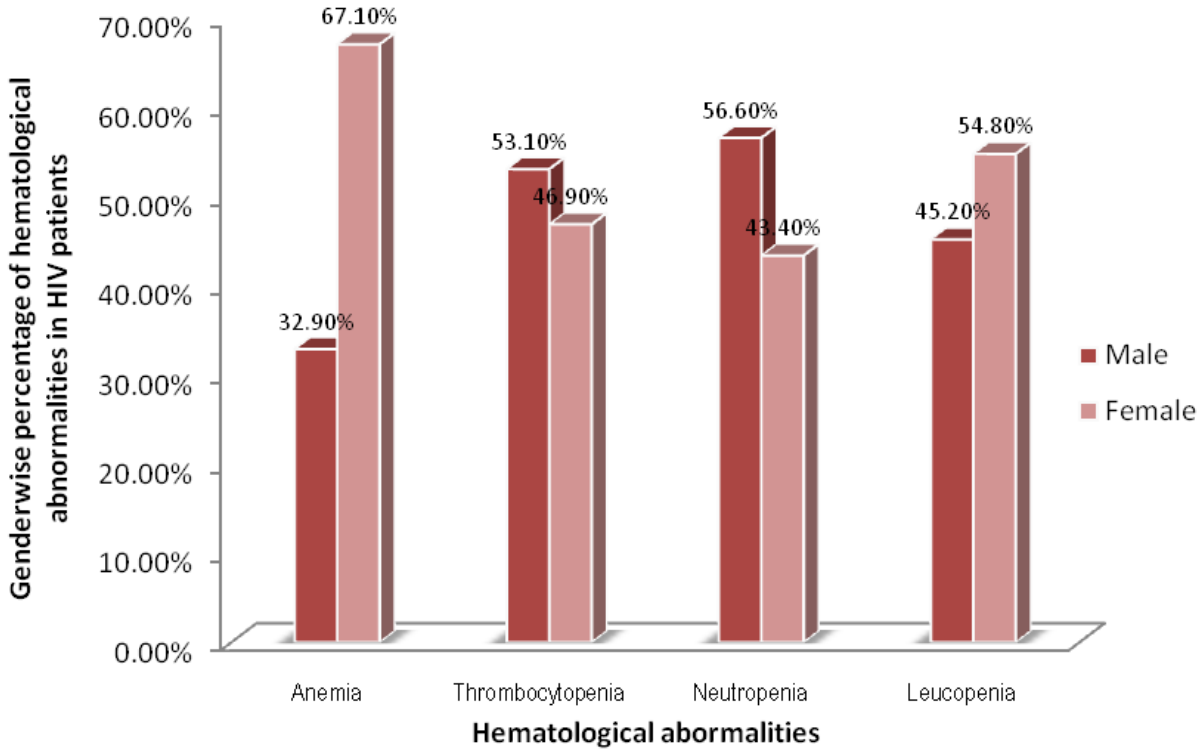
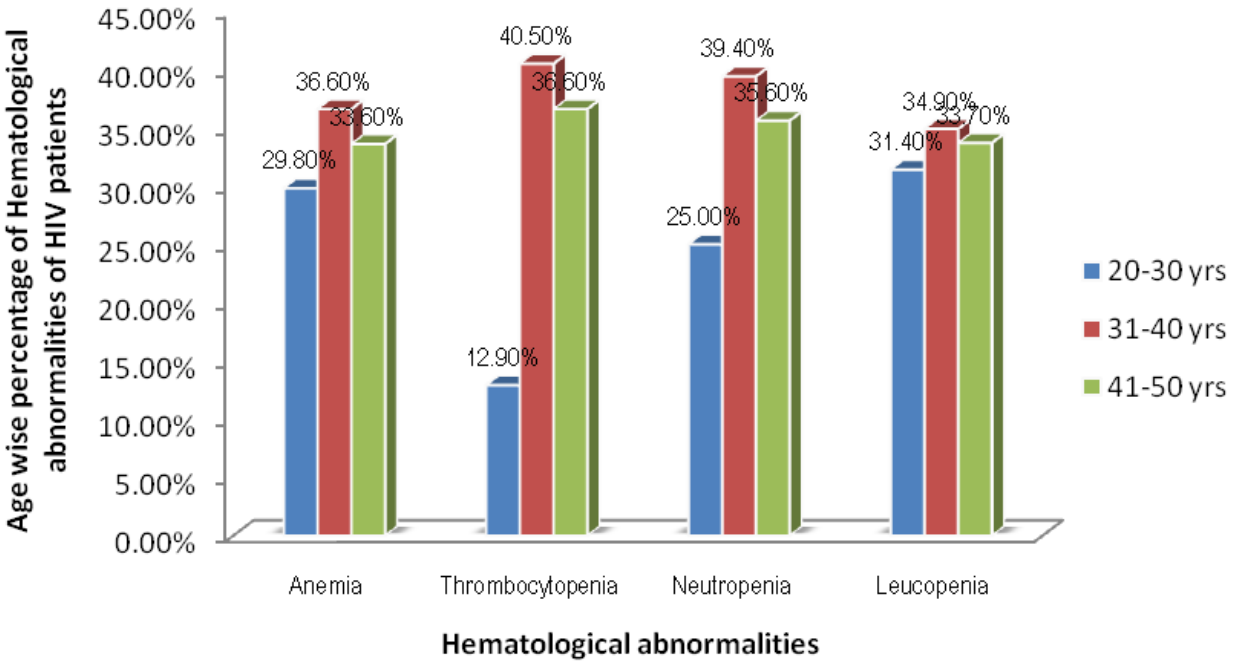


Figure-8. Age wise analysis of hematological abnormalities in 542 HIV infected patients



subjects treated with protease inhibitors.

In the present study, we went a step further because the association between individual antiretroviral drug exposure and the metabolic syndrome was evaluated. Limitations of the present study are mainly related to the observational design and cross-sectional nature of the current analyses as well as the clinical population studied. In this respect, the results reported herein are only associations from which no conclusions regarding causality can be drawn. Furthermore, it is not expected that many measurements will always be conducted in a uniform manner. This includes measurement of waist circumference and blood pressure and laboratory analyses of lipid and glucose levels. Finally, information on other environmental factors such as physical activity or diet was not collected.

In general, HDL and serum glucose levels were somewhat lower among patients in the early phase of HIV disease, In comparison with chronically infected HIV patients or healthy control subjects, and further studs will be necessary to determine the potential mechanisms for these differences (Baratha Jyothi et al, 2014). Current studies suggest that serum glucose may play an important role in metabolic control. Though human studies are limited, there is ample data, for experimental systems, supporting a role for glucose in systematic metabolic control. Administration of glucose to obese mice can improve lipid metabolism and decrease blood cholesterol levels.

The hematologic manifestations of HIV infection and AIDS are common and may cause symptoms that are life-threatening and impair the quality of life of these patients. Some studies show that multiple interacting factors contribute to the haematological manifestations of HIV disease. The effects of HIV-1 infection influence all haemopoietic cell lineages resulting in a spectrum of hematological abnormalities (Estari Mamidala, 2006). Even in the absence of other pathological processes, bone marrow morphology is invariably abnormal, and anaemia, neutropenia and thrombocytopenia are all common during the course of disease. Intercurrent opportunistic infections may cause bone marrow suppression or induce specific cytopenias (Venkanna Lunavath, 2014). Therapies used to treat HIV and its complications are frequently implicated as the cause of haematological dysfunction, and many have significant myelotoxic side-effects. Insights into the molecular basis for many of these abnormalities have permitted a clearer understanding of the pathophysiology of HIV-1 infection.

Thrombocytopenia is caused by immune-mediated destruction of the platelets, in addition to inadequate platelet production. The incidence and severity of cytopenia are generally correlated to the stage of the HIV infection. Other causes of cytopenia in these patients include adverse effects of drug therapy, the secondary effects of opportunistic infections or malignancies, or other preexisting or coexisting medical problems that may be prevalent in the HIV-infected population. Diagnosis of the mechanism and cause of the cytopenia may allow for specific management. Optimal management of the underlying HIV infection is essential, and mild cytopenia in asymptomatic patients may need no specific management (Estari Mamidala et al, 2012).

CONCLUSION

Out of 710 HIV infected patients hematological abnormalities found in 76.3% patients. Of these 542 HIV patients the prevalence of anemia was 59.4%, Thrombocytopenia, neutropenia and leucopenia are present in 55.4%, 33.2% and 57.5 % respectively. The incidence of anemia (59.4%) and leucopenia (57.5%) were significantly higher in HIV infected patients. In female anemia and leucopenia were high (67.1% and 54.8%) compare to male (32.9 % and 45.2%) HIV infected patients. A statistically significant difference was observed between the hemoglobin, platelet count and the WBC count of HIV infected individuals. A significant positive correlation was observed between the level of neutropenia and anemia in HIV infected subjects. It is hoped that ongoing research into the molecular mechanisms of insulin resistance and lipodystrophy in the context of HIV infection and antiretroviral therapy will ultimately provide viable treatment options for patients with metabolic syndrome. Given the heightened risk for the development of cardiovascular disease and hematological disorders in this growing patient population and the decreased mortality now associated with HIV infection.

Ethics statement

Ethics approval was not sought for this article.

Competing interests

The authors have declared that no competing interests exist.

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