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Original Article

Metabolic Abnormalities in HIV-Positive Patients Receiving Highly Active Antiretroviral Therapy

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ABSTRACT

Background and Objective: **Dyslipidemia has become a common problem in human immunodeficiency virus (HIV) disease, especially in patients on combination antiretroviral therapy. In this study we aimed to determine the prevalence of dyslipidemia and metabolic abnormalities in 2 groups of HIV infected patients receiving highly active antiretroviral therapy (HAART) and antiretroviral-naive patients.**

Patients and Methods: **Forty HIV infected patients treated by HAART as a case group (6 females and 34 males) with a mean age of 40.7 ± 10 years and 15 HIV naïve as a control group (2 females and 13 males) with a mean age of 38.40 ± 8.3 enrolled in this study. The two groups were well matched in respect to age, sex and CD4 cell counts. A standardized questionnaire with epidemiological, clinical, and therapeutic data was completed by physicians. Blood samples were obtained for metabolic measurements. CD4 positive cell count was measured by f1owcytometry.**

Results: **Levels of total cholesterol, triglycerides, LDL, HDL, lactate, and FBS were elevated in 24%, 37%, 3.7%, 44.4%, 29.6% and 11% of patients respectively. There was a significant difference regarding mean total cholesterol and LDL between treated group and controls ($p<0.05$). There was also no significant difference between treated group and controls regarding triglyceride, HDL, lactate and FBS levels.**

Conclusion: **Our study demonstrated that metabolic abnormalities are relatively common in HIV-infected patients receiving HAART. Therefore, it is recommended to screen the HIV infected patients on HAART for metabolic disorders, potential of morbidity, and possible long-term cardiovascular risk factors.**

Key words: **Dyslipidemia, Hyperglycemia, HIV, Highly active antiretroviral therapy**

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Introduction

The availability of highly active antiretroviral therapy (HAART) has contributed to a dramatic decrease in mortality and opportunistic infections associated with HIV/AIDS. However, since patients have begun to live longer, new complications have emerged. Over the last several years, clinicians have seen perplexing changes in fat distribution and metabolism (1). These changes include abnormal fat distribution, dyslipidemia, and abnormal glucose metabolism (2,3). Large cohort studies from Europe, North America, Asia and Australia have shown that metabolic abnormalities are common among HIV-infected patients who received treatment with antiretroviral drugs (4-6).

Dyslipidemia is common in people with HIV infection. The typical pattern in patients on HAART includes elevated total cholesterol and low density lipoprotein (LDL) cholesterol, and decreased high density lipoprotein (HDL) cholesterol, and elevated triglycerides including severe hypertriglyceridemia in some patients. The lipid abnormalities may be associated with insulin resistance and glucose intolerance (7). Exposure to protease inhibitors (PIs) is clearly associated with this entire range of metabolic abnormalities. Between 15% and 30% of HIV-infected patients have dyslipidemia; estimates approach 60% in patients taking a PI (8). Impaired glucose tolerance has been reported in 47% of patients on PI treatment (9). The prevalence of hyperglycemia has been estimated at 3-5% in patients receiving a PI; approximately 1% of these patients have clinical evidence of diabetes (10). PI-naive patients on NRTIs may develop lipodystrophy, insulin resistance, hypercholesterolemia, and possibly modest elevations in triglycerides, but not severe hypertriglyceridemia, which appears to be linked to PIs alone (7).

Dyslipidemia including increased triglycerides, increased total cholesterol and low density lipoprotein (LDL) cholesterol, and decreased high density lipoprotein (HDL) cholesterol has raised concern about increased risk for atherogenesis and atherosclerotic vascular disease (11). Patients may also develop problems with glucose homeostasis, even in the absence of morphological changes, that may lead to diabetes mellitus and diabetes-associated health problems (12).

Therefore, in this study we aimed to determine the prevalence of dyslipidemia and metabolic abnormalities in 2 groups of HIV infected patients receiving highly active antiretroviral therapy (HAART) and antiretroviral-naive patients.

Patients and Methods

In this cross sectional study 55 subjects who were known to have HIV infection (as determined by positive results of enzyme-linked immunosorbent assay (ELISA) and Western blot assay) were asked to participate in the study. All patients provided written informed consent. A standardized questionnaire with epidemiological, clinical, and therapeutic data was completed by physicians. Forty HIV infected patients treated by HAART as a case group (6 females and 34 males) with a mean age of 40.7 ± 10 years and 15 HIV naive as a control group (2 females and 13 males) with a mean age of 38.40 ± 8.3 years enrolled in this study. The two groups were well matched with respect to age, sex, and CD4 cell counts. Meanwhile, PI in combination with nucleoside transcriptase inhibitors (NRTI) are considered to be the standard of care for optimal antiretroviral therapy. Case group received combination therapy with 2 NRTIs (zidovudin and lamivudin) and a PI (nelfinavir).

Blood samples were obtained from patients. Levels of total cholesterol, HDL and LDL cholesterol, triglyceride, fasting serum glucose, and lactate were measured using standard enzymatic techniques. The following definitions were used for dyslipidemia: total cholesterol ≥ 200 mg/dl, low-density lipoprotein cholesterol ≥ 150 mg/dl, triglycerides ≥ 150 mg/dl, and high-density lipoprotein cholesterol < 40 mg/dl. In addition, Hyperglycemia was defined as a glucose concentration ≥ 110 mg/dl. An elevated lactate level was defined as a concentration ≥ 20 mg/dl, the upper limit of the normal laboratory range. In all patients absolute CD4 lymphocytes counting was done by flowcytometry and defined as cells/mm^3.

For statistical analysis, Chi-square and t^2 test were used using SPSS program (version 11.5). Data are presented as means ± standard deviations or when indicated, as percentage. A p-value less than 0.05 was considered significant.

Results

A total of 55 HIV positive patients were enrolled in our study. In this respect, 85.4% of them were males and 14.6% were females with a mean age 40.1 ± 9.5 years. Meanwhile, 72.7% of them were intravenous drug abusers (IDUs), 18.2% heterosexual, 2% had

Table 1. Metabolic characteristics of HIV infected patients receiving HAART (case) and antiretroviral-naive patients (control).

	Case	Control	P -value
FBS (mg/dL)	99.3±29.2	89.6± 10.6	NS
TG (mg/dL)	152.6± 115.5	133.6± 46.6	NS
Lactate (mg/dL)	16.7± 7.3	16.07± 7	NS
Total cholesterol (mg/dL)	177.1± 49.6	150.8±24.3	P<0.05
LDL (mg/dL)	97.2± 34.1	66.3± 27.5	P<0.05
HDL (mg/dL)	44.3± 18.2	40.4± 7.3	NS

NS: Not significant,Values are mean±S.D.

infected blood and blood products transfusion and 7.1% had no identified way of HIV acquisition. The CD4-positive lymphocytes were between 34 and 329 cell/mm^3 (with a mean of 172.5 ± 80.3).

Level of total cholesterol, triglycerides, LDL and HDL cholesterol, lactate and FBS were elevated in 24%, 37%, 3.7%, 44.4%, 29.6% and 11% of patients respectively. Mean cholesterol level in case group was 177.1 ± 49.26 mg/dl and in control group was 150.8 ± 24.87 mg/dl. Mean LDL level in case and control groups was 97.2 ± 34.1 and 66.3 ± 27.5 mg/dl respectively. We also found significant difference regarding total cholesterol and LDL between treated group and controls ($p<0.05$). There was also no significant difference between treated group and controls regarding triglyceride, HDL cholesterol, lactate, and FBS level (Table 1).

Hypercholesterolemia and hypertriglyceridemia were observed in 30.8% and 35.8% of cases and in 6.6% and 35% of controls respectively. Low HDL level was noted in 47.8% of treated and 33.3% of naïve patients. High LDL level was observed in 5.1% of cases and 0% of controls. Fasting hyperglycemia was noted in 12.8% of treated and 6.6% of naïve subjects. There was also no significant difference between patients receiving antiretroviral therapy and those who were not receiving treatment regarding the prevalence of theses metabolic abnormalities.

Discussion

Human immunodeficiency virus (HIV) infection affects approximately 40.3 million individuals around the world. The development of highly active antiretroviral therapy (HAART) has led to significant reductions in morbidity and mortality rates in HIV-infected patients (13). Unfortunately, the use of these agents, particularly protease inhibitors (PIs) have given rise to the metabolic and morphologic abnormalities, collectively termed lipodystrophy syndrome (2,3). Dyslipidemia appears to be a prevalent condition among patients receiving HAART (9).

The pattern and frequency of lipid and glucose abnormalities in our study were similar to those reported in series from the West and Asia (4,5,14). Like previous studies, our study revealed that metabolic disorders were more common among patients receiving antiretroviral therapy than those who were not receiving treatment (4,5,14). Henry et al (15) have reported that 47% of PI recipients had lipid abnormalities. Behrens et al (9) have reported that 57% of PI recipients had hyperlipidemia. Similarly, Keruly et al (16) have reported that PI recipients were 4.2 times more likely to experience a 50 mg/dl increase of total cholesterol to a level greater than 200 mg/dl as compared to patients not receiving PI (14% vs. 3%). Tomazic et al showed that dyslipidemia was the predominant metabolic abnormality in the HIV treated group and was observed in 72% of these patients. Level of total cholesterol increased in 53% and hypertriglyceridemia was noted in 49% of these patients. In the control group, none of the patients showed evidence of lipid and metabolic abnormalities (17). Friis-Møller et al reported hypercholesterolemia in %27 of subjects receiving combination therapy that included a PI, 23% of patients receiving a NNRTI, and 10% of cases receiving only NRTI as compared to 8% of previously untreated subjects. The corresponding percentages for hypertriglyceridemia were 40%, 32%, and 23% as compared to 15% among previously untreated subjects. Low levels of HDL cholesterol were reported in 27, 19, and 25% of the subjects respectively, as compared to 26% of those who were previously untreated (6).

Impaired glucose tolerance is the most commonly reported abnormality and develops in approximately 16-46% of patients. Diabetes mellitus has been reported to occur in 5-7% of patients treated with

PIs (5,18). The prevalence of hyperglycemia has been estimated at 3-5% in patients receiving a PI (10). Fasting hyperglycemia was noted in 12% of HIV patients overall in Paton study but this was not significantly associated with a particular antiretroviral treatment group. These findings are in agreement with our collecting data regarding hyperglycemia. Like other studies, our study determined that fasting hyperglycemia was relatively uncommon (4,5). However, challenge with an oral glucose tolerance test may have revealed that a substantially higher percentage of the patients had reduced insulin sensitivity (19).

The major concern of HIV-infected patients who undergo HAART is the potential risk of developing accelerated atherosclerosis and or coronary artery disease (CHD) (20,21). There is now good evidence that the metabolic abnormalities of HIV-infected patients harbor a significant risk for cardiovascular disease with as yet unknown consequences. In addition, several studies report a reduced quality of life in patients with bodily habit changes leading to reduced therapy adherence. Several cases of premature CHD have also been reported in HIV patients with dyslipidemias associated with HAART (21,22).

Conclusion

Our study demonstrated that metabolic abnormalities are relatively common in HIV-infected patients receiving HAART. These changes may increase the risk of cardiovascular diseases in these patients. Therefore, it is recommended to screen the HIV infected patients on HAART for metabolic disorders, potential of morbidity, and possible long-term cardiovascular risk factors.

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