Prevalence of Dyslipidemia and Metabolic Abnormalities in HIV-Infected Patients

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Abstract- Dyslipidemia has become a common problem in human immunodeficiency virus (HIV) disease, especially in patients on combination antiretroviral therapy. We investigated the prevalence of and factors associated with dyslipidemia in HIV-infected patients in Iran. In this cross-sectional study, 190 HIV positive patients who referring to behavioral disease consulting centers (Shemiranat, Varamin) and Iranian Research Center for HIV/AIDS in Tehran, were studied from December 2005 to December 2006.A standardized questionnaire with epidemiological, clinical, and therapeutic data was completed by physicians. Blood samples were obtained for metabolic measurements. CD4 cell count was measured by flow cytometry. Levels of total cholesterol, triglycerides, and lactate were elevated in 16.9%, 29.9%, and 22.5% of patients, respectively. The prevalence of elevated triglyceride and cholesterol levels was significantly higher among patients receiving antiretroviral therapy than it was among those who were not receiving treatment. Fasting hyperglycemia was noted in 10.1% of patients overall, but this was not significantly associated with antiretroviral treatment group. Low HDL levels were noted in 52.4% of patients overall, and this finding did not vary by treatment group. There is a high prevalence of dyslipidemia in patients taking antiretroviral therapy in Iran. We conclude that the prevalence of and factors associated with metabolic abnormalities in HIV-infected Iranian patients are similar to those reported for Western and Asian studies.

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Key words: Dyslipidemia, lactate, hyperglycemia, HIV, protease inhibitors, antiretroviral therapy, highly active

Introduction

Human immunodeficiency virus (HIV) infection affects approximately 40.3 million individuals in the world. The development of highly active antiretroviral therapy (HAART) has led to significant reductions in morbidity and mortality rates in HIV-infected patients (1). Unfortunately, the use of these agents-particularly protease inhibitors (PIs)-has given rise to the metabolic and morphologic abnormalities collectively termed lipodystrophy syndrome. These abnormalities include abnormal fat distribution, dyslipidemia, and abnormal glucose metabolism (2,3).

Dyslipidemia is common in persons 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 (4). Exposure to PIs is clearly associated with this entire range of metabolic

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abnormalities. Between 15% and 30% of HIV-infected patients have dyslipidemia; estimates approach 60% in patients taking a PI (5). Impaired glucose tolerance has been reported in 47% of patients on PI treatment (6). 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 (7). PI-naïve 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 (4). Dyslipidemia has raised concern about increased risk for atherogenesis and atherosclerotic vascular disease (8). These disorders are associated with increased risk of cardiovascular disease and have become an important cause of morbidity and mortality in HIV-infected patients (9-11).

The purpose of this cross-sectional survey was to estimate the prevalence of metabolic abnormalities in Iranian patients with HIV infection.

Patients and Methods

In this cross-sectional study, 190 HIV positive patients who referred to behavioral disease consulting centers (Shemiranat, Varamin) and Iranian Research Center for HIV/AIDS in Tehran were studied from December 2005 to December 2006. Consecutive male and female patients who were known to have HIV infection (a 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 questionnaire was used to collect their sociodemographic data, medical history, lipid reducer drugs consumption, anti-retroviral medication, stage of the infection (HIV/AIDS) and high risk behaviors for HIV acquisition. Both Patients receiving highly active antiretroviral therapy (HAART) and antiretroviral-naive patients were participated in our study .Protease inhibitors (PI) in combination with nucleoside transcriptase inhibitors (NRTI) are considered to be the standard of care for optimal antiretroviral therapy. At the time of the study, 60.8% of the patients were not receiving antiretroviral treatment, 39.2% were receiving combination therapy with 2 NRTIs (zidovudin and lamivudin) and a PI (nelfinavir).

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

Chi-square and t^2 test were used with the SPSS 11.5 package program for statistical analysis. Data are presented as means ± standard deviations or, when indicated, as percentage. A *P* value of <0.05 was considered significant.

Results

Patients were predominantly male (80.5%), and, with regard to race, 98.8% were Iranian, and 1.2% were "other." The reported risk factors for HIV transmission were injection drug use, for 69.6%; heterosexual contact, for 18.6% of subjects; blood or blood products 3.7% and unknown, for 7.9%. The mean age of the patients was 36.94±9 years (range, 20-59 years)**.** The mean CD4 cell count at the time of study was 394.45±229.2 cells/mm^3 (range, 30-1413 cells/mm^3). Some patients (47.05%) had been diagnosed as having AIDS.

Of the patients who were receiving antiretroviral therapy that included a PI, the total cholesterol level was elevated in 26.6% and the triglyceride level was elevated in 38.1%. These abnormalities were significantly more common in this treatment group than among patients who were not receiving antiretroviral therapy (*P*<0.05). Low HDL levels were noted in 52.4% of patients overall, and this finding did not vary by treatment group. High LDL levels were observed in 2.5% overall but this was not significantly associated with antiretroviral treatment group (4.05% treatment group versus 1.2% untreated patients). Fasting hyperglycemia was noted in 10.1% of patients overall, but there was not significant difference by antiretroviral treatment group (11.6% treatment group versus 8.9% untreated patients). An elevated lactate level was noted in 22.5% of patients overall, and this finding did not vary by treatment group.

Discussion

Large cohort studies from Europe, North America, Asia and Australia have shown that metabolic abnormalities are common among HIV-infected patients who receive treatment with antiretroviral drugs (12-19). The pattern

and frequency of lipid and glucose abnormalities in our study were similar to those reported in series from the West and Asia (12,13,17,18). Like previous studies, our study revealed that the prevalence of elevated triglyceride and cholesterol levels was significantly higher among patients receiving antiretroviral therapy than it was among those who were not receiving treatment, especially when the regimen included a PI (12,13,17,18). Friis-Møller et al., reporting the results of a large cross-sectional study, noted hypercholesterolemia in 27 percent of subjects receiving combination therapy that included a protease inhibitor, 23 percent receiving a nonnucleoside reverse-transcriptase inhibitor, and 10 percent receiving only nucleoside reverse-transcriptase inhibitors, as compared with 8 percent of previously untreated subjects. The corresponding percentages for hypertriglyceridemia were 40, 32, and 23 percent, as compared with 15 percent among previously untreated subjects. Low levels of high-density lipoprotein (HDL) cholesterol were reported in 27, 19, and 25 percent of the subjects, respectively, as compared with 26 percent of those who were previously untreated (19).

In other studies performed in HIV infected patients receiving HAART and antiretroviral-naive patients, Dyslipidemia were the predominant metabolic abnormality in the treated group, observed in 58 patients (72%). Levels of total cholesterol were increased in 43 patients (53%), and hypertriglyceridemia was noted in 40 (49%). In the control group, metabolic abnormalities were less common than in the treated group: six patients (33%) had one or more metabolic abnormalities (20).

Several case reports (21-23) and cross-sectional studies (24-26) found an association between PI exposure and hypercholesterolemia and hypertriglyceridemia (13). Using 200 to 240 mg/dl as a threshold for "hypercholesterolemia," prevalence rates range from 33% to 82% in patients on PI (27, 28, and 29). The prevalence range for triglycerides >200 to 250 mg/dl was 43% to 66 % in patients receiving PI-containing HAART regimen (27-29).

Vergis et al. demonstrated that adherence to a PI-containing HAART regimen was associated with a greater likelihood of developing elevated LDL cholesterol and severe (>800 mg/dl) hypertriglyceridemia (30). However, we didn't observe severe hypertriglyceridemia (>800 mg/dl) in our cases and high LDL levels were observed only in 4.05% of PI treated patients.

These changes are likely to be important for health, because many of our patients were cigarette smokers and had lipid values in the range for which intervention would be indicated. The major concern of HIV-infected patients who undergo HAART is the potential risk of developing accelerated atherosclerosis and or coronary artery disease (CHD) (31-33). Several cases of "premature CHD" have been reported in HIV patients with dyslipidemias associated with HAART (34,35). The alteration in glucose metabolism in patients with HIV who are receiving PIs range from impaired glucose tolerance to frank diabetes mellitus. Impaired glucose tolerance is the most commonly reported abnormality and develops in approximately 16 to 46% of patients; diabetes mellitus has been reported to occur in 5 to 7% of patients treated with PIs (13,36). The prevalence of hyperglycemia has been estimated at 3-5% in patients receiving a PI (7). 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 (12,13). However, challenge with an oral glucose tolerance test may have revealed that a substantially higher percentage of the patients had reduced insulin sensitivity (37).

Mild-to-moderate, asymptomatic hyperlactataemia has been frequently reported in human immunodeficiency virus (HIV)-infected patients treated with NRTIs, with an estimated prevalence between 15% and 35% (38-44) and, less commonly, in untreated individuals (38,45-47). Multivariate analysis confirmed that there was an increased likelihood of hyperlactatemia in patients who were receiving regimens that contained stavudine, as compared with regimens that contained zidovudine (12,38,42-44,47). These findings are in agreement with our collected data regarding prevalence of hyperlactataemia but we didn't observe any significant difference by treatment group. Our treated cases received regimens that contained zidovudine and lamivudine and these were associated with a lower risk of hyperlactataemia.

In summary, our study revealed that the prevalence of elevated triglyceride and cholesterol levels was significantly higher among patients receiving antiretroviral therapy than it was among those who were not receiving treatment, especially when the regimen included a PI. Therefore, we conclude that metabolic abnormalities and dyslipidemia are relatively common in HIV-infected patients receiving HAAART. These complications may increase these patients' risk of cardiovascular disease. Therefore, patients with HIV infection on HAART should be screened for lipid disorders, given their inci-

dence, potential for morbidity, and possible long-term cardiovascular risk.

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