Prevalence and Incidence of Diabetes in HIV-Infected Minority Patients on Protease Inhibitors

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In HIV-infected patients, the use of protease inhibitors (PIs) is associated with a constellation of abdominal obesity; buffalo hump; decreased facial and subcutaneous fat; hyperlipidemia and type-2 diabetes mellitus, a so-called HAART-associated dysmetabolic syndrome. The incidence and prevalence of one of its components, the type-2 diabetes mellitus, among minority population is unknown.

In August and September 1999, we reviewed 101 charts of HIV-infected patients who visited an inner-city HIV outpatient clinic. The age, gender, ethnicity, BMI, fasting plasma glucose, random serum glucose, triglycerides, CD4 counts, and the type and duration of antiretroviral drugs were recorded. Three years later (2002), the same patient charts were reviewed for evidence of new-onset diabetes.

Ten percent of the subjects were identified as diabetic at baseline. The prevalence of diabetes was 12% among those who were taking PIs, compared to 0% among those who were not taking PIs. The incidence of newly diagnosed diabetes during this three-year period was 7.2%. Diabetes occurred only in the group taking PIs. Diabetic subjects were older than their nondiabetic counterparts. All were African Americans.

Our study suggests that PIs increase the likelihood of diabetes developing with increasing age in African Americans infected with HIV.

Key words: protease inhibitors ■ HIV infection ■ diabetes mellitus ■ minority ■ incidence ■ prevalence

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INTRODUCTION

Increasing numbers of AIDS patients are receiving protease inhibitors (PIs) for the treatment of their HIV infection. This treatment had dramatically decreased the number of opportunistic infections and mortality in AIDS. After introduction of PIs and highly active antiretroviral therapy (HAART) in the treatment of AIDS/HIV infection, many patients have developed a clinical constellation comprising three aspects[1]:

1) lipodystrophy, with abdominal obesity, decrease of subcutaneous fat in extremities and face, and development of a buffalo hump and sometimes massive enlargement of breasts;
2) hyperlipidemia, with hypertriglyceridemia, decrease of HDL cholesterol, increase of low and very-low-density lipoprotein cholesterol, as well as apolipoproteins B and E[2], which are highly atherogenic;
3) insulin resistance and sometimes type-2 diabetes.[1] Recently, aseptic necrosis of the hip and osteopenia were added to this picture.[3] Different names were given for this entity, such as pseudocushing, HIV-associated or PI-associated lipodystrophy syndrome, fat redistribution syndrome and fat maldistribution syndrome. However, the term *HAART-associated dysmetabolic syndrome* will be used to define this entity in this study.

Among clinicians, HIV and AIDS were considered to have a protective effect on the development of diabetes. In our personal observation, among a cohort of 240 homosexual HIV-infected subjects from 1984–1990, when PIs were not yet available, only one patient developed diabetes mellitus type-2.[4] In 1999, we observed an increasing number of HIV-infected patients with diabetes, which led us to assess the prevalence and incidence of diabetes mellitus among our patients at King/Drew Medical Center.

METHODS

This longitudinal cohort study was conducted among an inner-city HIV outpatient clinic in south

central Los Angeles. The population covered by this clinic consists of 1,500 patients/year at different stages of their HIV/AIDS disease. At baseline, all the patients seen at the OASIS clinic every Tuesday in August and September of 1999 were studied. The charts of these patients were reviewed the same or the next day of their visit. All data were obtained from the charts. Data included age, ethnicity, weight, height, date of the serodiagnosis of HIV infection, CD4 counts, random serum glucose, fasting plasma glucose and fasting serum triglyceride levels. Four patients did not have glycemic values, and their data were excluded from the analysis. The details of antiretroviral treatment, including the duration and dose of each antiretroviral medication and any medications for diabetes, were recorded from the charts as well. The anti-HIV treatment of each patient was subdivided to nucleoside reverse transcriptase inhibitors (AZT, ddI, ddC, d4T and 3TC), Protease inhibitors (saquinavir, ritonavir, indinavir and nelfinavir) and non-nucleoside reverse transcriptase inhibitors (elfavirinez). Only those antiretroviral treatment were available at the time of the study in our institution. A total of 101 patient charts were reviewed.

Three years later, in August and September of 2002, the same patient charts were reviewed again for evidence of diabetes. This study was approved by the Institutional Review Board Committee at Charles R. Drew University of Medicine and Science.

Diabetic subjects were selected based on their fasting plasma glucose if >126 mg/dl and/or any random blood glucose >200 mg/dl at two different times and/or use of any antidiabetic medications. Impaired fasting (111–125 mg/dl) and impaired postprandial glucose levels (126–199 mg/dl) were not considered as a diagnosis of diabetes mellitus.

Statistical Analysis

All data are expressed as means ± SEM unless mentioned otherwise. Student's t test was used for comparison of means between diabetic and nondiabetic groups, and between PI-treated and nontreated patients. Paired t test was used for pairs of variables from the first year compared to the third year of the study. Chi-squared test was used for comparison of nonparametric variables. The software package SPSS for Windows® was utilized for statistical analyses. Inferences were made at the 0.05 level of significance.

RESULTS

At Baseline

Among 101 patients with HIV infection, 77.6% were African Americans and 17.4% were Latinos. Seventy percent were male. In 83 subjects (82%), PIs were combined with other antiretroviral therapy, whereas in 18 subjects (18%) PIs were not used in the antiretroviral therapy since the diagnosis of their disease. There were no differences among their age, ethnicity, BMI, gender, stage of their disease and their CD4 count. However, the duration of HIV infection from the serodiagnosis was longer in PI users compared to non-PI users (Table 1). Patients who were taking PIs had higher serum triglyceride levels compared to those who were not taking PIs (265 ± 30 vs. 143 ± 16, p=0.02). Fasting plasma glucose was higher in HIV patients taking PIs compared to non-PI-treated subjects (109 ± 6.8 vs. 81.1 ± 3.8, p=0.007). Among those who were taking PIs, 10 subjects (12%) were found to have diabetes compared to 0% among those who were not taking PIs.

Comparison was made between diabetic and nondiabetic HIV-infected patients on PIs (Table 1). Diabetic patients compared to their nondiabetic coun-

Table 1. Comparison of patients at baseline. Non-PI users are those in whom protease inhibitors were not included in their treatment. PI users are those who in their treatment protease inhibitors were included. The PI users were subdivided into diabetic and non diabetics. All results were presented as mean ± SEM.

Characteristics of Patients at Baseline	Non-PI Users N=18	PI Users N=83	P	Diabetic PI Users N=12	Nondiabetic PI Users N=71	p
Age (mean ± SEM)	36 ± 2.5	40 ± 1	0.05	47.7 ± 5	39.4 ± 3	<0.05
Ethnicity (% AA)	78	78	NS	100	78	NS
Gender (% male)	61	71	NS	83	67	NS
BMI	27.8 ± 1.5	26.8 ± 0.5	NS	29 ± 2	26.5 ± 0.5	NS
Duration of HIV after serodiagnosis (years)	2.25 ± 0.7	4.08 ± 0.37	<0.05	4.5 ± 1.3	4.02 ± 0.3	NS
Stage IV of HIV (%)	5.2	15.6	NS	25	14	NS
CD4 counts (mm^3)	589 ± 70	471 ± 36	NS	452 ± 121	474 ± 37	NS
Triglycerides (mg/dL)	143 ± 16	265 ± 30	<0.05	292 ± 83	143 ± 16	<0.05
Fasting plasma glucose (mg/dl)	81 ± 3.8	109 ± 6.8	<0.05	259 ± 51	83 ± 2	<0.05
Diabetes type-2 (%)	0	12	<0.05	100	0	<0.05

NS: not significant

terparts were significantly older (47.7 ± 5 vs. 39.44 ± 3, P=0.004), and all were African Americans (100% vs. 78%, p=0.06). Diabetic subjects on PIs also had significantly higher serum triglyceride levels (292 ± 83 vs. 143 ± 16, p=0.03). However, the BMI of diabetic patients was not significantly different (29 ± 2 vs. 26.5 ± 0.5 kg/m^2) compared to nondiabetic PI users.

The serum triglyceride levels of diabetic vs. non diabetic subjects regardless of PIs use did not show statistically significant difference possibly due to high variability in both groups (316 ± 257 vs. 235 ± 203, p=0.1) (Mean ± SD).

Follow-Up

Three years later, in August 2002, the charts of the same patients were reviewed. Three patients of the non-PI users (16%) and 15 patients of the PI users group (18%) were lost from follow-up.

In patients who were not taking PIs, pairwise comparison did not reveal significant change in fasting plasma glucose from baseline. None of the non-PI users had developed diabetes during this three-year follow-up. In patients taking PIs, fasting plasma glucose increased from 109 ± 4.5 to 123 ± 7.5 (P=0.03) (Table 2), and four more patients developed type-2 diabetes (7.2% incidence of diabetes on PIs). Therefore, among those who were taking PIs, 20.5% (14/68) of subjects were found to have diabetes compared to 0% (0/16) among those who were not taking PIs. In six other subjects (9.6%) who were taking PIs, random glucose levels were in hyperglycemic range (between 127–199 mg/dl). These subjects were euglycemic at baseline. No hyperglycemia was observed among non-PI users (data not shown).

Among the nondiabetic subgroup of PI users, fasting plasma glucose and serum triglyceride levels did not increase significantly. The mean serum triglyceride levels were above the upper limits of normal among diabetic PI users and did not change significantly during this three-year period (Table 2).

DISCUSSION

Our study in an inner-city HIV clinic in south central Los Angeles demonstrated that among those who attend the clinic, the prevalence of diabetes among patients on protease inhibitors is 12%. None of the patients who were not taking PIs developed diabetes. During the follow-up, the incidence of diabetes was 7.2% over a three-year period (2.4% per year) only among those who were taking PIs. Hypertriglyceridemia was observed among HIV-infected patients on PIs with and without diabetes. BMI was not statistically different between these two groups.

In his study, Carr et al. observed impaired glucose tolerance in 16% of protease-inhibitor recipients and diabetes mellitus in 7%.[5] In a large multicenter study, the incidence of diabetes based on self-reports was 2.5% in HIV-infected women on protease inhibitors.[6] Compared to our study, both studies have similar incidence and prevalence of diabetes among those who are taking protease inhibitors.

However, our data demonstrated higher prevalence of diabetes compared to other published data on HIV infected subjects (12% vs. 5%),[7] possibly because of higher number of African Americans in our population. African Americans are known to have higher prevalence of diabetes compared to Caucasians.[8] In a recent study, it has been observed that among non-HIV-infected African Americans with low or high consumption of fibers, the incidence of diabetes is 18.1% and 19.1% over nine years, respectively,[9] with an average incidence of diabetes of 1.9% per year compared to incidence of 2.4% per year in our HIV subjects on PIs.

To the best of our knowledge, no study examined the prevalence of diabetes in early epidemic of HIV infection when PIs were not available. In our own personal observation of a cohort of homosexual Cau-

Table 2. Comparison of the means of fasting plasma glucose (FPG) and serum triglycerides (TG) levels at baseline and at year 3 (Y3) in HIV-infected PI users and non-PI users and the diabetic and their nondiabetic counterparts. P values in rows represent pairwise comparison of variables from their baseline by paired t test. p values in columns represent comparison of variables between groups by Student's t test.

	Non-PI Users	PI Users	P: (Comparison between Groups)	Diabetic PI Users	Nondiabetic PI Users	P: (Comparison between Groups)
FBG, Baseline	81.1 ± 3	109 ± 7	<0.05	259 ± 51	83 ± 2	<0.05
FBG, Y3	92 ± 1	123 ± 7.5	<0.05	206 ± 21	98.5 ± 2.6	<0.05
p: (comparison from baseline)	NS	0.03		<0.05	NS	
TG, Baseline	143 ± 16	260 ± 24	<0.05	292 ± 83	143 ± 16	<0.05
TG, Y3	197 ± 39	196 ± 16	NS	261 ± 45	177 ± 15	<0.05
P: (Comparison from baseline)	<0.05	<0.05		NS	NS	

casian males infected with HIV[4] from 1984 to 1990 (when PIs were not yet available), only one over 240 patients had developed diabetes mellitus. Acknowledging the limited value of historical data and the possibility of detection bias, and regardless of the previous observation, our current study documented an increase in prevalence of diabetes among PI users from 12% at baseline to 17% at the end of the study.

PIs significantly decrease mortality and morbidity, and improve malnutrition among HIV-infected patients, but with the advent of PIs and other antiretroviral treatment, a complex metabolic syndrome has emerged.[1] This complex is mostly associated with the use of PIs; however, a contribution of non-nucleoside reverse transcriptase and nucleoside reverse transcriptase inhibitors in the increased risk of development of lipodystrophy has been described.[10]

It appears that PIs facilitate and/or accelerate the process of diabetogenesis. The pathogenesis, however, is not fully understood. Accumulation of intra-abdominal fat and decrease of subcutaneous fat are both known to be associated with dyslipidemia, insulin resistance and diabetes.[11] HAART-associated dysmetabolic syndrome has some similarity with Cushing's syndrome.[12] Even though several studies did not demonstrate an excess of glucocorticoids in the serum of patients with AIDS, an alteration of hypothalamic-pituitary-adrenal axis has been described.[13-14]

The development of diabetes and hypertriglyceridemia could also be related to the development of subcutaneous fat atrophy.[15-17] Adiponectin is a hormone secreted from subcutaneous fat.[15] Reduced levels of adiponectin correlates with severe insulin resistance, which may have a role in the development of insulin resistance and diabetes in patients taking PIs.[15]

The pathophysiology of diabetes in HAART-associated dysmetabolic syndrome has also been attributed to the inhibitory effect of one of PIs (indiniavir) on the glucose transporter 4 (Glut-4) on adipocytes and rat muscle.[18-19] Incubation of muscles with indinavir reduced the insulin-stimulated increase in 3Methyl glucose transport dose dependently up to 58%. Also, the insulin-stimulated increase in cell-surface GLUT4 was reduced by approximately 70%.[19]

Indinavir also downregulates Proteasome Proliferator Activator Receptor γ (PPAR γ) expression in adipocytes in culture. A decrease in the number of newly formed adipocytes and the lower level of the adipogenic protein markers, such as sterol regulatory element-binding protein-1 (SREBP-1), PPAR γ, and the insulin receptor (IR) of the indinavir-treated cells have been shown previously.[20]

In our study, not all subjects were taking indinavir, and these in-vitro studies cannot solely explain the other aspect of the HAART dysmetabolic syndrome.

The third hypothesis suggests a possibility of an increased activity in adipose 11 beta hydroxysteroid dehydrogenase type-1 activity under the effect of protease inhibitors.[21] The increased activity of 11 beta hydroxysteroid dehydrogenase type-1, which is present in visceral fat, would accelerate retrograde conversion of inactive cortisone to the active cortisol, which in turn increases lipolysis and increases free fatty acid in the portal system, causing insulin resistance and hyperlipidemia. This hypothesis may also explain some of the Cushing's aspect of this complex syndrome.[22]

In summary, we observed a high prevalence of diabetes among patients treated with protease inhibitors especially those who were older and African-American. Therefore, we suggest that fasting plasma glucose in HIV-infected patients on PIs be monitored early in the course of therapy, especially among those who are older or who have other risk factors for developing diabetes.

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REFERENCES

1. Carr A, Samaras K, Burton M et al. A syndrome of peripheral lipodystrophy, hyperlipidaemia and insulin resistance in patients receiving HIV protease inhibitors. *AIDS*. 1998;12:F51-F58.

2. Salehian B, Bilas J, Bazargan M, et al. Incidence and Prevalence of Diabetes among HIV-Infected Minority Patients on Protease Inhibitors. *J Investig Med*. 2003;51(suppl 1):194 (abstract).

3. Scribner AN, Troia-Cancio PV, Cox BA, et al. Osteonecrosis in HIV: a case-control study. *J Acquir Immune Defic Syndr*. 2000;1:25:19-25.

4. Salehian B, Jackobson D, Swerdloff R, et al. Testicular pathology and pituitary testicular axis during HIV infection. *Endocrine Practice*. 1997;3:85-92.

5. Carr A, Samaras K, Thorisdottir A, et al. Diagnosis, prediction and natural course of HIV-1 protease-inhibitor-associated lipodystrophy, hyperlipidaemia, and diabetes mellitus: a cohort study. *Lancet*. 1999;353:2093-2099.

6. Justman JE, Benning L, Danoff A, et al. Protease inhibitor use and the incidence of diabetes mellitus in a large cohort of HIV-infected women. *J Acquir Immune Defic Syndr*. 2003;32:298-302.

7. Tsiodras S, Mantzoros C, Hammer S, et al. Effects of protease inhibitors on hyperglycemia, hyperlipidemia and lipodystrophy: a five-year cohort study. *Arch Intern Med*. 2000;160:2050-2056.

8. Harris MI. Diabetes in America: epidemiology and scope of the problem. *Diabetes Care*. 1998;21:C11-C14.

9. Stevens J, Ahn K, Juhaeri, et al. Dietary fiber intake and glycemic index and incidence of diabetes in African-American and white adults: the ARIC study. *Diabetes Care*. 2002;25:1715-1721.

10. Van der Valk M, Gisolf EH, Reiss P, et al. Prometheus study group. Increased risk of lipodystrophy when nucleoside analogue reverse transcriptase inhibitors are included with protease inhibitors in the treatment of HIV-1 infection. *AIDS*. 2001;15:847-855.

11. AACE/ ACE Position statement on the prevention, diagnosis and treatment of obesity. *Endocrine Practice*. 1997;3:162-189.

12. Bujalska IJ, Kumar S, Stewart PM. Does central obesity reflect "Cushing's disease of the omentum. *Lancet*. 1997;349:1210-1213.

13. Dobs DS, Dempsey M, Ladenson P, et al. Endocrine Disorders in Men Infected with Human Deficiency Virus. *Am J Med*. 1988;84:611-616.

14. Laudat A, Blin J, Guechot J, et al. Changes in systemic gonadal and adrenal steroids in asymptomatic human immunodeficiency virus-infected men: relationship with the CD4 cell counts. *Eur J Endocrinol.* 1995:133;418-424.

15. Sutinen J, Korsheninnikova E, Funahashi T, et al. Circulating concentration of adiponectin and its expression in subcutaneous adipose tissue in patients with highly active antiretroviral therapy-associated lipodystrophy. *J Clin Endocrinol Metab.* 2003;88:1907-1910.

16. Yamauchi T, Kamon J, Waki H, et al. The fat-derived hormone adiponectin reverses insulin resistance associated with both lipoatrophy and obesity. *Nat Med.* 2001;7:941-946.

17. Haque WA, Shimomura I, Matsuzawa Y, et al. Serum adiponectin and leptin levels in patients with lipodystrophies. *J Clin Endocrinol Metab.* 2002; 87:2395-2399.

18. Murata H, Hruz PW, Mueckler M. The mechanism of insulin resistance caused by HIV protease inhibitor therapy. *J Biol Chem.* 2000;7:275-279.

19. Murata H, Hruz PW, Mueckler M. Indinavir inhibits the glucose transporter isoform Glut4 at physiologic concentrations. *AIDS.* 2002;16:859-863.

20. Caron M, Auclair M, Vigouroux C, et al. The HIV protease inhibitor indinavir impairs sterol regulatory element-binding protein-1 intranuclear localization, inhibits preadipocyte differentiation and induces insulin resistance. *Diabetes.* 2001;50:1378-1388.

21. Kino T, Mirani M, Alesci S, et al. AIDS-related lipodystrophy/insulin resistance syndrome. *Horm Metab Res.* 2003;35:129-136. ■

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