Prevalence of and Risk Factors for Prediabetes in Patients Infected With HIV

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ABSTRACT

Background. The use of highly active antiretroviral therapy (HAART) has resulted in a dramatic decrease in morbidity and mortality in HIV-infected patients. Components of HAART (e.g., protease inhibitors and nucleoside reverse transcriptase inhibitors), as well as HIV infection itself, can have significant effects on developing new-onset diabetes. The goals of this study were to determine the prevalence of prediabetes and to assess risk factors associated with prediabetes in a cohort of HIV-infected patients.

Methods. This is a retrospective, cross-sectional study of 249 HIV-infected patients in an outpatient multidisciplinary HIV clinic in a university hospital. Patients with prediabetes were identified and compared with patients without prediabetes. The association between the prevalence of prediabetes and risk factors was analyzed.

Results. Among 249 HIV-infected patients, the mean age was 46.3 years, and 54% were male. Prevalence of prediabetes was approximately 30%, and BMI ≥30 kg/m^2 was found to be a significant risk factor for developing prediabetes.

Conclusion. A high prevalence of prediabetes was observed in this cohort of HIV-infected patients. Interventions targeting HIV-infected patients with increased risk of prediabetes, especially individuals with a high BMI, is needed.

Unprecedented progress has been made in understanding HIV during the past 2 decades. The introduction of highly active antiretroviral therapy (HAART) in 1996 as a standard of care has progressively transformed HIV infection from an acute, fatal illness to a manageable chronic disease (1,2). As a result of HAART, the death rate from HIV infection in the United States has decreased by ~85% in the past 2 decades (3). However, the incidence of metabolic disorders such as diabetes, lipodystrophy, and dyslipidemia in HIV-infected patients has increased and is considered to be associated with HAART (4).

HAART is based on the drug classes protease inhibitors (PIs), nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and integrase inhibitors, which have been used extensively as potent antiretroviral therapy. Not all PIs have the same metabolic effects. For example, indinavir induces insulin resistance, whereas lopinavir and ritonavir increase free fatty acid and fasting triglyceride levels (5). NRTIs such as stavudine, zidovudine, and didanosine can cause insulin resistance, lipodystrophy, and mitochondrial dysfunction (6). Previous studies have demonstrated that antiretroviral therapies, especially NRTIs and PIs, can affect glucose metabolism, are associated with metabolic disorders, and may add further

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complexity to the standard of care and management of HIV-infected patients (4–6). For many patients, these adverse effects can significantly impair quality of life and lead to long-term complications.

Although antiretroviral therapy appears to contribute to some of the cardiometabolic abnormalities in HIV infection, HIV infection itself can potentially cause atherosclerosis and cardiovascular disease, especially in patients >50 years of age (7,8). Recent data suggest that chronic HIV infection can play an important role in activating immune response and inflammatory cytokines, which may lead to metabolic syndrome and diabetes (9,10). In a case-control study, Brown et al. (11) demonstrated that inflammatory cytokine tumor necrosis factor (TNF)-α, which is responsible for inflammatory cascade and is highly expressed in HIV-infected patients, is independently associated with developing diabetes. Therefore, both HAART and HIV infection may lead to diabetes, lipodystrophy, and dyslipidemia in this patient population.

According to the American Diabetes Association (ADA), prediabetes is defined as a blood glucose level higher than normal and is the precursor to diabetes (12). Individuals with an A1C of 5.7–6.4% or fasting plasma glucose of 100–125 mg/dL after fasting for ≥8 hours or 2-hour plasma glucose of 140–199 mg/dL after a 75-g oral glucose tolerance test are considered to have prediabetes (12). According to the Centers for Disease Control and Prevention (CDC) 2014 National Diabetes Statistic Report, >37% of U.S. adults have prediabetes, and 9 out of 10 people do not know they have prediabetes (13). Similar to diabetes, prediabetes can also increase the risk for developing macrovascular complications such as cardiovascular disease and stroke. The risk of prediabetes increases with the presence of certain risk factors, such as overweight or obese, physical inactivity, family history of diabetes, certain ethnicities, and gestational diabetes (12). According to the 2014 CDC report (13), unless individuals with prediabetes change their lifestyle (e.g., lose weight and engage in moderate physical activity), 15–30% of people with prediabetes will develop type 2 diabetes within 5 years. ADA guidelines recommend that patients with prediabetes enroll in an intensive diet and physical activity behavioral counseling program targeting a weight loss of 7% and aiming to perform moderate-intensity exercise for 150 minutes per week (12). There is evidence of potential benefit of metformin pharmacotherapy to prevent diabetes in prediabetic patients with a BMI >35 kg/m^2 but not as much as lifestyle intervention in patients >60 years of age (14). ADA recommends metformin therapy only for high-risk patients with prediabetes (i.e., those with a history of gestational diabetes, BMI >35 mg/m^2, rising A1C despite lifestyle intervention, or severe or progressive hyperglycemia) (12).

Studies have been conducted on the prevalence of diabetes in HIV-infected patients, but no recent studies have looked at the prevalence rate of prediabetes in this patient population in the United States (15). Additionally, there is no study or consensus agreement on how to manage HIV-infected patients with prediabetes. Because prediabetes can increase the risk of macrovascular complications and progression to diabetes, it is imperative to identify prediabetes and its risk factors in HIV-positive patients to prevent diabetes and mitigate the complications of these endocrine disorders.

Materials and Methods

A retrospective, cross-sectional study was performed that identified the prevalence and risk factors of prediabetes in a cohort of HIV-infected patients from an outpatient HIV clinic. Patients were enrolled in the study if they were ≥18 years of age and took antiretroviral therapy. Patients who were pregnant or had preexisting diabetes were excluded. The study was approved by the clinic's institutional review board. Patients' medical records were reviewed to collect demographic data and identify risk factors for developing prediabetes (e.g., age, sex, race, BMI, smoking history, medication history including antidepressants/anxiolytics and PIs, and hepatitis C virus status). Data on antiretroviral regimen, duration of HAART, CD4 and viral load count, participation in risk behaviors (i.e., men who have sex with men and intravenous drug users), blood pressure, and lipid levels were also collected. Patients were stratified into two groups: patients with HIV without prediabetes and patients with HIV with prediabetes.

Statistical Analysis

The association between the prevalence of prediabetes and risk factors was analyzed with multiple logistic regression. For continuous data, the Mann-Whitney *U* and *t* tests were used. For categorical data, the Fisher exact and χ^2 tests were used. A *P* value of <0.05 was considered statistically significant.

Results

A total of 249 patients were studied with a mean (± SD) age of 46.3 ± 12.1 years, and 134 patients (54%) were male. Baseline characteristics are summarized in Table 1. All patients were receiving HAART, and 142 (57%) were on a PI regimen. The mean (± SD) duration of HAART was 13.7 ± 8.0 years. The mean (± SD) CD4 count was 544.8 ± 290.9. A total of 58 patients (23%) were on antidepressant/anxiolytic therapy, 81 (33%) had risk behaviors (such as men who have sex with men and intravenous drug users), 31 (12%) were seropositive for anti–hepatitis C virus antibody, and 104 (42%) had a positive smoking history. The majority of patients (81%) were African American. The mean (± SD) BMI, systolic blood pressure, diastolic blood pressure, HDL cholesterol, and LDL cholesterol were 27.6 ± 7.1

TABLE 1. Baseline Demographic Characteristics

	All (*n* = 249)	Prediabetic (*n* = 74)	Normoglycemic (*n* = 175)	*P*
Age, mean (SD), years	46.3 (12.1)	50.9 (12.0)	44.4 (11.7)	0.0001
Male, *n* (%)	134 (54)	43 (58)	91 (52)	0.41
Race, *n* (%)				0.25
African American	202 (81)	61 (88)	141 (91)	
White	13 (5)	3 (4)	10 (6)	
Hispanic	9 (4)	5 (7)	4 (3)	
PI, *n* (%)	142 (57)	46 (62)	96 (55)	0.33
Duration of HAART, mean (SD), years	13.7 (8.0)	14.9 (7.9)	13.2 (8.0)	0.134
Antidepressant/anxiolytic therapy, *n* (%)	58 (23)	13 (18)	45 (26)	0.19
BMI, mean (SD), kg/m^2	27.6 (7.1)	29.3 (8.1)	26.9 (6.6)	0.03
Risk behavior, *n* (%)	81 (33)	20 (27)	61 (35)	0.3
Diastolic blood pressure, mean (SD), mmHg	78.1 (11.6)	79.0 (13.3)	77.7 (10.9)	0.468
Systolic blood pressure, mean (SD), mmHg	126.7 (16.6)	127.8 (17.1)	126.2 (16.4)	0.492
Smoking history, *n* (%)	104 (42)	30 (41)	74 (44)	0.68
Positive hepatitis C virus status, *n* (%)	31 (12)	10 (14)	21 (12)	0.83
Fasting glucose, mean (SD), mg/dL	92.5 (13.1)	106.0 (13.8)	86.9 (7.8)	<0.0001
A1C, mean (SD), %	5.4 (0.5)	5.8 (0.4)	5.1 (0.3)	<0.0001
HDL cholesterol, mean (SD), mg/dL	45.1 (15.1)	45.3 (15.7)	45.1 (15.0)	0.929
LDL cholesterol, mean (SD), mg/dL	100.5 (34.2)	109.2 (37.5)	96.7 (32.2)	0.017
CD4 count, mean (SD)	544.8 (290.9)	487.5 (275.3)	569.0 (295.5)	0.038
Viral load <20, *n* (%)	159 (64)	46 (62)	113 (65)	0.66

kg/m^2, 126.7 ± 16.6 mmHg, 78.1 ± 11.6 mmHg, 45.1 ± 15.1 mg/dL, and 100.5 ± 34.2 mg/dL, respectively. Mean (± SD) fasting glucose level and A1C were 92.5 ± 13.1 mg/dL and 5.4 ± 0.4%, respectively. A total of 74 patients were found to have prediabetes, resulting in a prevalence of 29.7%.

Data analysis showed that there were significant differences in age, LDL cholesterol, BMI, and CDC count between the groups with and without prediabetes (P <0.05). No significant differences were found between the two arms for the other characteristics recorded (Table 1). Multiple logistic regression analysis (Table 2) showed a positive correlation between BMI ≥30 kg/m^2 and prediabetes (odds ratio [OR] 3.065, 95% CI 1.565–6.003, P = 0.0011).

Discussion

Calza et al. (16) showed that the prevalence of insulin resistance, glucose intolerance, and diabetes varies widely between 4.5% and 12% in HIV-infected patients; however, there is no recent report on the prevalence of prediabetes in HIV-infected patients in the United States. Our study showed that ~30% of HIV-infected patients had prediabetes, which is lower than the estimated national average of 37% (regardless of HIV infection). According to the CDC, 50% of patients with prediabetes

TABLE 2. Multivariate Analysis of Factors Associated With Prediabetes

Risk Factor	OR (95% CI)	*P*
Male sex	1.648 (0.854–3.181)	0.1367
BMI ≥30 kg/m^2	3.065 (1.565–6.003)	0.0011
Smoking history	0.928 (0.478–1.804)	0.8262
Positive hepatitis C virus status	1.047 (0.410–2.671)	0.9237
African American	0.707 (0.251–1.994)	0.5118
Exposure to PIs	1.516 (0.809–2.840)	0.1938
Exposure to antidepressant/anxiolytics	0.611 (0.272–1.370)	0.2318

are ≥65 years of age (13); the lower prevalence of prediabetes in our study could have been because of the inclusion of younger patients, with mean age of 50.9 years.

We found that BMI ≥30 kg/m^2 is a risk factor for developing prediabetes. Obesity is associated with increased production of inflammation-related adipokine, which is considered to play a significant role in developing diabetes and metabolic syndrome (17). Compared to normoglycemic patients, prediabetes patients in our study were found to be older and had higher LDL levels and CD4 counts. Therefore, our study reiterates the correlation between higher BMI, higher LDL level, and older age and the development of prediabetes or diabetes (17,18).

Although few studies have examined the prevalence and risk factors of prediabetes in HIV-infected patients in the United States, several retrospective studies have been conducted recently elsewhere. A study conducted by Srivanich et al. (15) in prediabetic HIV-infected patients in Thailand found that the prevalence rate of prediabetes was 27.5%, which is comparable to our result. Additionally, male sex and increases in body weight per 5 kg were associated with prediabetes (95% CI 0.941–8.976, $P = 0.064$, and 95% CI 1.014–1.518, $P = 0.036$, respectively). A similar prediabetes prevalence rate of 22.4% was observed in 134 HIV-infected patients in Ethiopia (19). Similar to our study, positive correlations between age and BMI and plasma glucose level were also found in this study ($P = 0.031$ and $P = 0.03$, respectively) (19). Although these studies had relatively small sample sizes, they were some of the first to identify the high prevalence rate of prediabetes in HIV-infected patients and set the stage for large-scale future prospective studies.

In a retrospective study, Brown et al. (20) found that diabetes is four times more prevalent in HIV-infected men exposed to HAART than in HIV-seronegative men. Additionally, 12 weeks of treatment with PIs demonstrated a 25% reduction in β-cell function and alteration in insulin release (7,21). The risk of developing prediabetes or diabetes is even higher when patients are exposed to both NRTIs and PIs. Furthermore, using pentamidine to treat *Pneumocystis jiroveci*–associated pneumonia in HIV-infected patients was also responsible for β-cell destruction (22), although in our study, 62% of patients with prediabetes received PIs, and we did not find any association between PIs and developing prediabetes (OR 1.516, 95% CI 0.809–2.840). This finding could be due to the retrospective nature and small sample size of our study.

More recently, in a retrospective study of 500 HIV-infected patients in Cameroon, Rhee et al. (23) found that 34% of patients had prediabetes. Larger abdominal circumference was associated with higher prevalence of prediabetes and diabetes (OR 1.07, 95% CI 1.03–1.11). Unlike previous studies, this study found that HAART was associated with a lower prevalence of prediabetes and diabetes (OR 0.46, 95% CI 0.22–0.99) (4–6). This result could be because 90% of the patients with prediabetes/diabetes in this study received an NNRTI-based regimen, and none of the patients received PIs. When compared with a PI regimen, NNRTI-based regimens have been shown to be associated with a decreased incidence of metabolic complications (24).

The 2016 ADA guidelines estimate that prediabetes may be seen in 15% of HIV-infected patients (12). Our study demonstrated that the prevalence of prediabetes is more widespread and almost doubled. ADA recommends checking fasting glucose level before and 3 months after starting antiretroviral therapy and monitoring A1C every 3–6 months (12). However, this recommendation is based on expert opinion (12). Because of the chronic inflammatory nature of HIV infection and potential effect of HAART on developing diabetes, we suspect that the majority of HIV-infected patients with prediabetes will develop diabetes more rapidly than patients not infected with HIV. Because of the high prevalence rate of prediabetes, proper measures should be implemented to screen HIV-infected patients for prediabetes and to intervene early to delay or prevent the progression to diabetes.

Some limitations to our study are its small sample size and retrospective design, which may have caused it to not adequately detect differences and association. More than 80% of our patients were African American and were 1.7 times more likely to develop diabetes than non-Hispanic whites. In addition, all of our patients were enrolled in a single site (12). Therefore, our results may have reduced generalizability and may not portray the prevalence rate of prediabetes in HIV-infected patients nationally. Most of our patients were younger (mean age ~46 years), which may have reduced our prediabetes prevalence rate.

In conclusion, we observed a high prevalence of prediabetes in this HIV-infected patient cohort. Future prospective studies are needed to elucidate this correlation and assess the importance of pharmacological and nonpharmacological interventions to prevent patients with prediabetes from developing diabetes.

Duality of Interest

No potential conflicts of interest relevant to this article were reported.

Author Contributions

S.A. researched data, contributed to discussion, and wrote, reviewed, and edited the manuscript. T.C. researched data and wrote, reviewed, and edited the manuscript. J.Y. researched data and wrote the manuscript. R.S. contributed to discussion and reviewed and edited the manuscript. S.A. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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