PRELIMINARY COMMUNICATION

Metformin in the Treatment of HIV Lipodystrophy Syndrome

A Randomized Controlled Trial

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Context A syndrome of lipodystrophy, characterized by fat redistribution and insulin resistance, has been estimated to affect the majority of human immunodeficiency virus (HIV)–infected individuals who are treated with combination antiretroviral therapy. There are no proven therapies for the metabolic disturbances associated with HIV lipodystrophy syndrome.

Objective To determine the safety and efficacy of metformin therapy in HIV-infected patients with fat redistribution and abnormal glucose homeostasis.

Design and Setting Randomized, double-blind, placebo-controlled pilot study conducted in a university hospital between December 1998 and January 2000.

Patients Twenty-six HIV-infected, nondiabetic patients with fat redistribution and abnormal oral glucose tolerance test (OGTT) results, hyperinsulinemia, or both.

Interventions Patients were randomly assigned to receive metformin, 500 mg twice daily (n=14), or identical placebo (n=12), for 3 months.

Main Outcome Measures Insulin area under the curve (AUC), calculated 120 minutes following a 75-g OGTT at baseline vs at 3-month follow-up and compared between treatment groups.

Results Patients treated with metformin demonstrated significant reductions in mean (SEM) insulin AUC 120 minutes after OGTT (–2930 [912] vs –414 [432] μIU/mL [–20349 {6334} vs –2875 {3000} pmol/L]; $P=.01$), weight (–1.3 [0.6] vs 1.1 [0.4] kg; $P=.005$), and diastolic blood pressure (–5 [4] vs 5 [2] mm Hg; $P=.009$) vs controls, respectively. Metformin therapy was associated with a decrease in visceral abdominal fat (VAT; –1115 [819] vs 1191 [699] mm^2; $P=.08$) and a proportional reduction in subcutaneous abdominal fat (SAT); the VAT-SAT ratio was unchanged in metformin-treated vs placebo-treated patients. No increase in lactate or liver transaminase levels was observed with metformin treatment. Mild diarrhea was the most common adverse effect of metformin. No patient discontinued therapy because of adverse effects.

Conclusions This study suggests that a relatively low dosage of metformin reduces insulin resistance and related cardiovascular risk parameters in HIV-infected patients with lipodystrophy.

JAMA. 2000;284:472-477 www.jama.com

A LIPODYSTROPHY SYNDROME characterized by fat redistribution, including accumulation of truncal fat and loss of extremity and facial fat, has been recognized increasingly among patients infected with human immunodeficiency virus (HIV), particularly in those receiving combination antiretroviral therapy.[1-6] Mounting evidence indicates that HIV lipodystrophy syndrome is also associated with significant insulin resistance.[7-12] In non–HIV-infected patients, insulin resistance and hyperinsulinemia are independent risk factors for coronary artery disease (CAD).[13-15] Similarly, as patients with HIV infection live longer, hyperinsulinemia and insulin resistance may increase CAD risk in the expanding population of HIV-infected patients with lipodystrophy syndrome. We hypothesized that treatment with metformin, an insulin-sensitizing agent, would improve insulin resistance and overall cardiovascular risk profile in this population. We conducted a 3-month, randomized, double-blind, placebo-controlled pilot study to assess the safety and efficacy of metformin in HIV-infected patients with fat redistribution and abnormal glucose homeostasis.

METHODS

Patients

Patients were recruited between December 1998 and January 2000 from Massachusetts General Hospital and Brigham and Women's Hospital in Boston and from community-based practices and through newspaper advertisements. Patients were eligible based on the follow-

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Financial Disclosure: Drs Sax and Grinspoon have given lectures sponsored by Bristol-Myers Squibb.
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ing inclusion criteria: documented HIV infection, aged 18 to 60 years, stable antiviral therapy regimen for at least 6 weeks prior to study enrollment, impaired glucose tolerance (blood glucose level 140-200 mg/dL [7.8-11.1 mmol/L] at 120 minutes following standard oral glucose tolerance test [OGTT])[16] and/or hyperinsulinemia (fasting insulin level >15 µIU/mL [104 pmol/L]), abnormal waist-hip ratio (for men, >0.9; for women, >0.8), and evidence of fat redistribution. Fat redistribution was scored as present or absent based on evidence of fat accumulation in the trunk, breast, or neck, and/or loss of fat in the face or extremities on physical examination. All patients had evidence of significant fat redistribution in 1 or more areas. Patients were excluded if they had history of renal failure; a serum creatinine level of 1.5 mg/dL (133 µmol/L) or more; history of congestive heart failure; an elevated aspartate aminotransferase level; an alkaline phosphatase level or prothrombin time of more than 2.0 times the upper limit of normal; a hemoglobin level of less than 8 g/dL (80 g/L); history of diabetes mellitus or diabetic response to an OGTT (fasting glucose level >126 mg/dL [7.0 mmol/L] or 120-minute glucose level >200 mg/dL [11.1 mmol/L][16]); concurrent therapy with insulin; use of antidiabetic agents, glucocorticoids, testosterone, megestrol acetate, growth hormone, estrogen, or anabolic steroids; concurrent substance abuse; opportunistic infection within the past 6 weeks; or pregnancy. In addition, patients discontinued the study if they changed their antiviral regimen for any reason during the 3-month study period (n=1).

Protocol

All patients gave written informed consent and the study was approved by the Human Research Committee of Massachusetts General Hospital and the Committee on Research of Human Subjects of the Massachusetts Institute of Technology. Eligible patients were randomly assigned to receive either metformin (500 mg orally twice per day) or an identical placebo for 3 months. Randomization was stratified by sex and age (<40 years or ≥40 years) and assigned in blocks of 4 based on randomly generated numbers. Randomization was performed by the Massachusetts General Hospital pharmacy. All investigators and patients were blinded to drug assignment.

Each patient completed a standard 75-g OGTT following a 12-hour overnight fast on the day of randomization and at 3-month follow-up.[16] Serum insulin and glucose levels were measured at 0, 30, 60, 90, and 120 minutes following the OGTT. In addition, fasting total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides, lactate, aspartate aminotransferase, HIV viral load, and CD4 cell count measurements were determined at baseline and 3-month follow-up. Patients underwent a physical examination and brief intercurrent medical history to assess potential adverse effects at baseline and at the 1-month and 3-month visits. Patients were instructed to return unused study medication, and compliance was determined from the difference between expected and actual pills used. Height, weight, blood pressure, waist circumference (at the umbilicus), and hip circumference were measured at each visit. In addition, patients completed a 4-day food record prior to the baseline and 3-month visits. Diet records were reviewed with each patient by a trained dietitian and analyzed using a computerized nutrition software program (NDS Version 2.92-NDS-R, Regents of the University of Minnesota, Minneapolis) to determine the mean daily energy intake.

Cross-sectional abdominal computed tomography scans were performed as described by Borkan et al[17] at baseline and 3-month follow-up to assess distribution of subcutaneous and visceral abdominal fat (SAT and VAT, respectively). A lateral scout image was obtained to identify the level of the L_4 pedicle, which served as the landmark for the 1-cm single-slice image. The primary outcome measure for efficacy was insulin area under the curve (AUC), calculated from the post-OGTT insulin measurements. Secondary end points included glucose AUC, lipid levels, body mass index (BMI), waist-hip ratio, VAT-SAT ratio, and blood pressure. Development of lactic acidosis was the primary safety outcome measure.

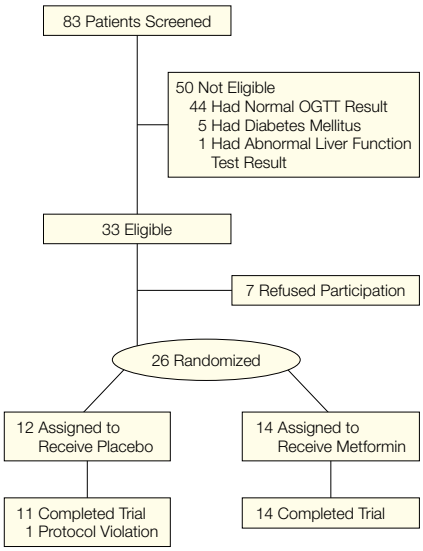
Laboratory Methods

Insulin levels were measured in serum samples using radioimmunoassay (Diagnostic Product Corp, Los Angeles, Calif). Intra-assay and interassay coefficients of variation ranged from 4.7% to 7.7% and 5.5% to 9.2%, respectively. Cross-reactivity with proinsulin at midcurve was at least 40%. CD4 cell counts were determined by flow cytometry (Becton Dickinson Immunocytochemistry Systems, San Jose, Calif), and HIV viral load was determined by ultrasensitive assay (Amplicor HIV-1 Monitor Assay, Roche Molecular Systems, Branchburg, NJ) with limits of detection of 50 to 75 000 copies/mL. Plasma lactate levels were analyzed by spectrophotometry (Smith-Kline Laboratories, King of Prussia, Pa). Glucose was measured with a hexokinase reagent kit (Dade Dimension, Wilmington, Del). Total cholesterol was measured by enzymatic hydrolysis (Dade Dimension); serum triglycerides were measured using a lipase enzymatic method (Dade Dimension); HDL-C was measured after precipitation of LDL-C and very-low-density lipoprotein cholesterol (Dade Dimension); and LDL-C was calculated indirectly.

Statistical Analysis

Baseline clinical characteristics were compared between groups by the *t* test. Treatment effect at 3 months was estimated using analysis of covariance. The measurement obtained at 3 months was the outcome variable, treatment assignment was the main effect, and baseline measurement of the variable was used as a covariate. An estimated sample size of 30 was determined to be necessary to detect a 30% reduction in insulin concentration with 80% power and a 2-tailed α level of .05. Statistical analyses were performed using SAS JMP (SAS Institute Inc, Cary, NC) and statistical

Figure 1. Patient Flow Diagram



OGTT indicates oral glucose tolerance test.

significance was defined as $P<.05$. All data are presented as mean (SEM).

RESULTS

Eighty-three patients were screened for the study, 33 met the inclusion criteria, and 26 (6 women and 20 men) were randomized and received treatment with metformin (n=14) or placebo (n=12) (FIGURE 1). One patient switched antiviral regimens during the study and discontinued the protocol. The remaining 25 patients completed the 3-month protocol. No patient dropped out or was lost to follow-up. Compliance with study medication based on pill count was not different between metformin and placebo groups (97% vs 93%, respectively; $P=.12$).

Baseline clinical characteristics of the patients in each treatment group are presented in TABLE 1 and TABLE 2. The groups were similar in all characteristics with the exception of lactate level; patients randomized to receive metformin had higher lactate levels at baseline ($P=.002$). All patients were taking at least 1 nucleoside reverse transcriptase inhibitor (NRTI), and 22 of 25 patients were receiving a regimen containing a protease inhibitor (PI). All but 2 patients were receiving combination antiretroviral therapy, defined as either 2 NRTIs and at least 1 PI or nonnucleoside reverse transcriptase inhibitor (NNRTI) or a combination containing at least 1 NRTI, 1 PI, and 1 NNRTI. One patient was receiving therapy with 2 NRTIs and 1 was receiving an NRTI and 2 PIs. TABLE 3 provides individual patient data on the most commonly used concomitant medications.

Metformin therapy was associated with significant reductions in insulin levels and

Table 1. Baseline Clinical Characteristics and Mean Changes at 3 Months*

	Baseline		Mean Change From Baseline at 3 Months		
	Placebo (n = 11)	Metformin (n = 14)	Placebo (n = 11)	Metformin (n = 14)	*P* Value†
Age, y	45.6 (1.9)	44.1 (2.1)	NA	NA	
Male/female	8/3	11/3	NA	NA	
Duration of HIV, y	7.6 (1.4)	6.0 (0.9)	NA	NA	
CD4 Cell count, $\times 10^6$/L	535 (55)	486 (55)	13 (40)	–25 (39)	.32
Viral load, copies/mL	6970 (6803)	1360 (1082)	–5903 (6523)	693 (521)	.39
Systolic BP, mm Hg	127 (4)	118 (6)	–1 (4)	1 (4)	.37
Diastolic BP, mm Hg	77 (2)	78 (3)	5 (2)	–5 (4)	.009
Cholesterol, mg/dL	236 (16)	232 (14)	0.5 (7.4)	6.9 (8.1)	.60
Triglycerides, mg/dL	273 (65)	366 (54)	121 (92)	4 (35)	.13
LDL-C, mg/dL‡	147 (20)	121 (13)	–4 (11)	15 (11)	.45
HDL-C, mg/dL	44 (5)	46 (3)	6 (10)	–4 (4)	.34
AST, U/L	34 (6)	37 (7)	–5 (7)	–2 (4)	.50
Lactate, mg/dL§	12.7 (1.4)	20.4 (1.6)	–2.4 (1.5)	–0.2 (1.8)	.22
Weight, kg	80.8 (3.2)	82.4 (5.0)	1.1 (0.4)	–1.3 (0.6)	.005
BMI, kg/m^2	26.9 (1.1)	27.5 (1.2)	0.4 (0.1)	–0.3 (0.2)	.008
Energy intake, kJ/d	10 163 (954)	9460 (950)	–946 (824)	–280 (494)	.61
Waist circumference, cm	97 (3)	98 (3)	1.1 (0.5)	–1.1 (0.6)	.02
Waist-hip ratio	0.98 (0.01)	1.00 (0.01)	0.008 (0.007)	0.002 (0.005)	.72
VAT, mm^2‖	15 551 (1984)	17 657 (1425)	1191 (699)	–1115 (819)	.08
SAT, mm^2‖	15 253 (3678)	16 185 (2777)	1169 (413)	–695 (836)	.08
VAT-SAT ratio‖	1.3 (0.2)	1.6 (0.3)	–0.04 (0.1)	–0.03 (0.1)	.71

*Data are unadjusted mean (SEM). Reference range for cholesterol is 120-199 mg/dL; for triglycerides, 20-170 mg/dL; for low-density lipoprotein cholesterol (LDL-C), 50-130 mg/dL; for high-density lipoprotein cholesterol (HDL-C), 30-70 mg/dL; for aspartate aminotransferase (AST), 10-37 IU/L; and for lactate, 9-16 mg/dL. To convert cholesterol, LDL-C, and HDL-C from mg/dL to mmol/L, multiply by 0.02586. To convert triglycerides from mg/dL to mmol/L, multiply by 0.01129. To convert lactate from mg/dL to mmol/L, multiply by 0.1110. NA indicates not applicable; HIV, human immunodeficiency virus; BP, blood pressure; BMI, body mass index; VAT, visceral abdominal fat; and SAT, subcutaneous abdominal fat.
†*P* values were calculated by analysis of covariance for effect of treatment, with baseline value as the covariate.
‡LDL-C data not available for patients with triglyceride levels >400 mg/dL (n = 9 for placebo and n = 9 for metformin).
§*P* = .002 by *t* test for lactate levels at baseline in metformin patients (n = 13) vs placebo patients (n = 10).
‖Data were available for 10 metformin patients and 9 placebo patients.

Table 2. Oral Glucose Tolerance Test Results: Baseline Data and Mean Changes at 3 Months*

Glucose and Insulin Levels	Baseline		Mean Change From Baseline at 3 Months		
	Placebo (n = 11)	Metformin (n = 14)	Placebo (n = 11)	Metformin (n = 14)	*P* Value†
Fasting glucose, mg/dL	95.5 (5.1)	87.9 (2.6)	1.9 (2.5)	–0.9 (2.1)	.24
Glucose (120 min), mg/dL	138 (12)	140 (7)	7 (10)	–2 (8)	.51
Fasting insulin, µIU/mL	23.6 (3.3)	31.0 (8.8)	0.2 (2.8)	–4.3 (4.0)	.61
Insulin (120 min), µIU/mL	127 (32)	151 (43)	22 (15)	–40 (24)	.05
Glucose AUC (120 min), mg/dL	18 004 (1046)	16 795 (692)	776 (496)	–563 (695)	.15
Insulin AUC (120 min), µIU/mL	14 146 (2347)	14 340 (3333)	–414 (432)	–2930 (912)	.01

*Data are unadjusted mean (SEM). To convert glucose from mg/dL to mmol/L, multiply by 0.05551. To convert insulin from µIU/mL to pmol/L, multiply by 6.945. AUC indicates area under the curve.
†*P* values were calculated by analysis of covariance for effect of treatment, with baseline value as the covariate.

insulin AUC at 120 minutes after OGTT compared with placebo (insulin AUC, –2930 [912] vs –414 [432] µIU/mL [–20 349 {6334} vs –2875 {3000} pmol/L]; *P* = .01) (FIGURE 2A). The decline in insulin AUC represents an average decrease of 20% from pretreatment levels in metformin-treated patients. There was no significant effect of treatment on fasting glucose or insulin levels or 120-minute OGTT glucose levels or glucose AUC (Figure 2B). However, mean changes in 120-minute OGTT glucose levels and glucose AUC were both increased in the placebo group and decreased in the metformin group (Table 2). Similarly, fasting insulin levels decreased 14% in the metformin group but did not change in the placebo group.

Patients treated with metformin vs placebo, respectively, demonstrated significant weight loss (–1.3 [0.6] vs 1.1 [0.4] kg; *P* = .005) (Figure 2C), reduced waist circumference (–1.1 [0.6] vs 1.1 [0.5] cm; *P* = .02), and decreased diastolic blood pressure (–5 [4] vs 5 [2] mm Hg; *P* = .009) (Figure 2D). Visceral abdominal fat decreased in metformin vs placebo patients (–1115 [819] vs 1191 [699] mm^2; *P* = .08). Subcutaneous abdominal fat decreased in proportion to VAT and no change was seen in VAT-SAT ratio in response to metformin treatment.

There was no significant effect of treatment on waist-hip ratio, systolic blood pressure, energy intake, CD4 cell count, HIV viral load, aspartate aminotransferase, total cholesterol, HDL-C, LDL-C, or triglycerides, although triglyceride levels tended to increase more in the placebo group.

Table 3. Concurrent Medication Use in Patients Receiving Placebo or Metformin

Patient No.	NRTI	PI	NNRTI	Antihypertensive Medication	Lipid-Lowering Medication	PCP	HSV/CMV Therapy	Antidiarrheal Therapy
				Placebo				
1	+	–	–	–	–	+	–	–
2	+	+	+	–	–	+	+	–
3	+	–	+	–	–	–	–	–
4	+	+	–	–	–	+	+	–
5	+	–	+	–	–	–	–	–
6	+	+	–	–	–	+	–	–
7	+	+	–	+	–	+	–	–
8	+	+	+	–	–	+	+	–
9	+	+	–	–	+	–	–	–
10	+	+	–	–	–	+	+	+
11	+	+	–	–	–	+	–	–
				Metformin				
1	+	+	–	–	–	+	–	–
2	+	+	–	–	–	–	+	–
3	+	+	–	–	–	–	–	–
4	+	+	–	+	–	–	–	–
5	+	+	+	–	–	–	+	–
6	+	+	–	–	–	+	–	–
7	+	+	–	–	–	–	–	–
8	+	+	+	–	+	+	+	+
9	+	+	–	–	+	+	–	+
10	+	+	+	–	+	+	–	–
11	+	+	–	–	–	+	–	–
12	+	+	–	–	–	–	–	–
13	+	+	–	–	–	+	–	–
14	+	+	–	–	–	+	–	+

*NRTI indicates nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; PCP, *Pneumocystis carinii* prophylaxis; HSV, herpes simplex virus; and CMV, cytomegalovirus.

Metformin was well tolerated. No patient discontinued the study because of adverse effects, and no patient developed lactic acidosis. Nine metformin patients (64%) complained of mild-to-moderate diarrhea or an increase in stool frequency from preexisting diarrhea, whereas 3 (27%) of 11 placebo patients experienced new or worsening diarrhea. Most patients (5 of 9 randomized to metformin and 2 of 3 randomized to placebo) had resolution of new or increased diarrhea within 4 weeks of starting therapy. Two patients receiving metformin and 1 receiving placebo complained of gas and/or bloating. There was no increase in lactate level as-

sociated with metformin therapy and both groups had mild decreases in lactate levels at 3 months.

COMMENT

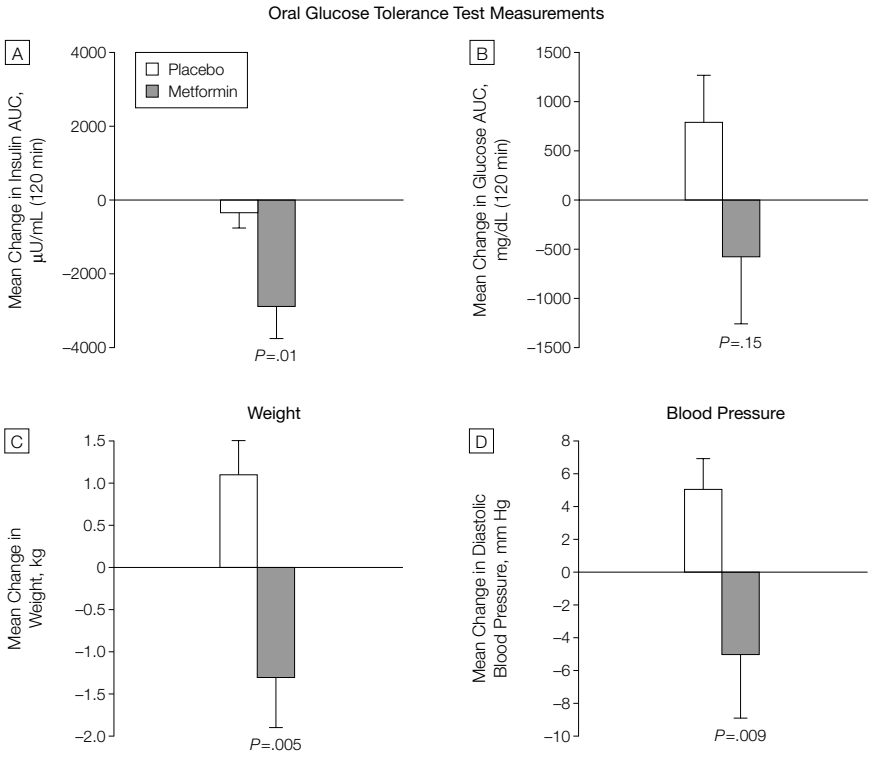
In this study, we demonstrate that low-dosage metformin reduces insulin resistance and improves related clinical parameters in HIV-infected patients with lipodystrophy and abnormal glucose homeostasis. Compared with placebo, treatment with metformin resulted in significant decreases in insulin AUC, BMI, and diastolic blood pressure. Our data suggest that metformin is well tolerated and is not associated with increased lactate levels or liver dysfunction in this population.

To our knowledge, this is the first report of a randomized placebo-controlled trial of an insulin-sensitizing agent for treatment of insulin resistance associated with HIV lipodystrophy syndrome. Walli et al[18] reported on use of troglitazone in a small, nonrandomized study. Potential liver dysfunction with this agent prevented its use in the current study. In contrast, Saint-Marc and Touraine[19] demonstrated a beneficial effect of metformin (850 mg orally 3 times per day) in a open-label, non–placebo-controlled study among HIV-infected patients with insulin resistance and central adiposity. Metformin was associated with decreased fasting insulin levels, insulin response to OGTT, weight, and VAT after 2 months of therapy.[19] Two patients dropped out of that study because of gastrointestinal disorders, including severe diarrhea and abdominal cramps, and the study did not report lactate levels or other safety parameters. In contrast, we used a lower dosage of metformin in a randomized, placebo-controlled, double-blind study. No data on the safety of metformin in this population were available at the initiation of this study, so assessment of safety and tolerability was an important aim of the study.

Our data suggest that metformin is safe and well tolerated in HIV-infected patients with lipodystrophy syndrome at the dosages used in this study. Mild and often transient gastrointestinal symptoms were common, but in no case were severe enough to result in discontinuation of the study. Lactate levels and liver function tests remained stable. Metformin administration is associated with a small risk of lactic acidosis in non–HIV-infected patients.[20] Recently, concern has arisen regarding reports of increased lactate levels in some HIV-infected patients treated with NRTIs because of a potential mitochondrial toxicity syndrome resulting from inhibition of DNA polymerase γ from NRTIs.[21] All patients in this study were receiving concomitant NRTIs; therefore, the absence of a significant effect on lactate levels provides some reassurance that low-dosage metformin can be used safely in this population. However, our results must be interpreted with caution since our sample size was small and strict eligibility criteria precluded participation of patients with known significant liver or kidney disease. Our results cannot be extrapolated to the general population of HIV-infected patients with lipodystrophy syndrome, in whom more severe liver disease may be seen.

Baseline CD4 cell counts were relatively high in our study patients, possibly owing to the potent combination antiretroviral therapy received by the majority of patients. These patients represent the population most at risk for lipodystrophy, in contrast with those with more advanced immunodeficiency. CD4 cell count decreased and HIV viral load increased slightly in metformin patients, but not significantly. Our data suggest that metformin does not reduce immunologic function or adversely affect viral load in persons with HIV lipodystrophy syndrome. Investigation of higher dosages of metformin will be necessary to further determine the safety of metformin in HIV-infected persons with lipodystrophy syndrome.

Figure 2. Mean Changes in Insulin AUC, Glucose AUC, Diastolic Blood Pressure, and Weight at Baseline vs 3-Month Follow-up



AUC indicates area under the curve. To convert insulin from μIU/mL to pmol/L, multiply by 6.945. To convert glucose from mg/dL to mmol/L, multiply by 0.05551. Error bars represent SEM.

In this study, 500 mg of metformin twice per day resulted in a 20% reduction in insulin AUC, as well as significant reductions in weight and diastolic blood pressure. The effects of metformin on glucose AUC were less significant, consistent with prior studies that demonstrated greater effects of metformin on insulin levels than on glucose levels in non–HIV-infected, nondiabetic patients.[22] At baseline, our study patients were moderately overweight and significantly hyperinsulinemic, with an increased waist-hip ratio. Among non–HIV-infected patients, increased BMI, hyperinsulinemia, and diastolic hypertension are known independent predictors of CAD.[14,23,24] Pyorala et al[14] demonstrated that insulin response to OGTT was an independent risk for CAD death or nonfatal myocardial infarction. In patients with HIV lipodystrophy syndrome, reduction of hyperinsulinemia, weight, and blood pressure by metformin results in an improved CAD risk profile.

In contrast with the reduction in insulin levels, lipid levels did not change significantly in this study, although there was a tendency toward stabilization of triglyceride levels in the metformin-treated group. Larger dosages of metformin and a longer duration of therapy may be necessary to reduce lipid concentrations in patients with dyslipidemia and HIV lipodystrophy. In addition, we did not assess insulin sensitivity directly using an insulin clamp, but our data, which demonstrate a reduction in insulin AUC and insulin levels 120 minutes after OGTT, suggest an overall improvement in insulin sensitivity.[25] Further studies are necessary to assess directly the effects of metformin on insulin sensitivity in patients with HIV lipodystrophy syndrome.

We demonstrate that VAT decreased by 6% in the metformin group and increased by 8% in the placebo group. In contrast with the study by Saint-Marc and Touraine,[19] which demonstrated a preferential reduction of VAT, our study showed a proportional reduction of SAT and VAT. A number of explanations are possible for this difference with the prior study, including dosage used (lower in our study) and study design (randomized and double-blind vs open-label). Reduction of VAT may be beneficial in patients with HIV lipodystrophy syndrome. Visceral abdominal fat is increased in patients with HIV lipodystrophy syndrome[5] and is associated with increased CAD risk in non–HIV-infected, abdominally obese patients.[26] Further studies are necessary to determine definitively the effects and potential benefits of metformin administration on VAT and VAT-SAT ratio in HIV lipodystrophy syndrome.

Patients with HIV infection and evidence of fat redistribution are at high risk for metabolic abnormalities, including insulin resistance, that may increase cardiovascular disease risk in this population. We demonstrate that relatively low-dosage metformin is safe and generally well tolerated in a pilot study of HIV-infected patients with fat redistribution and abnormal glucose homeostasis. Metformin substantially improves weight, diastolic blood pressure, and hyperinsulinemia. Further long-term investigation is necessary to determine the benefits of insulin-sensitizing agents, including metformin, in the treatment of insulin resistance and fat redistribution in HIV lipodystrophy syndrome.

Funding/Support: This work was supported in part by National Institutes of Health grants M01-RR300088, T32-DK07703, and K23-DK02844.
Acknowledgment: We thank the nursing and dietary staff of the Massachusetts Institute of Technology Clinical Research Center for their dedicated patient care; Gregory Neubauer for his help in performing the radioimmunoassays; Martin Hirsch, MD, for his continued support; and Anne Klibanski, MD, for her thoughtful review of an early version of the manuscript.

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