

Derangements in Lipid and Glucose Kinetics in Patients with HIV Infection and Metabolic Complications

DN Reeds*, BW Patterson, WT Cade, WG Powderly, KE Yarasheski, and S Klein

N-132; CROI 2004

Center for Human Nutrition
Washington University School of Medicine, St. Louis, MO

Abstract

Background Metabolic complications (MC) occur in up to 40% of patients receiving highly active antiretroviral therapy (HAART) for HIV infection. The underlying metabolic alterations associated with HIV-MC are poorly understood. We hypothesized that HIV-MC subjects would have blunted insulin-mediated suppression of lipolysis and glucose production, and impaired insulin-stimulated glucose disposal.

Methods. We evaluated lipid and glucose kinetics in 13 subjects with HIV-MC (body-fat redistribution assessed by DEXA, plasma triglyceride [TG] >250mg/dl and/or impaired glucose tolerance) and 15 HIV-infected subjects without MC (HIV-N), matched for body mass index (26 ± 1 kg·m⁻² vs 26 ± 1 kg·m⁻²), during basal conditions and during a low (plasma insulin concentration ~35 μU/ml) and high dose (plasma insulin concentration ~80 μU/ml) euglycemic hyperinsulinemic clamp with infusion of stable isotope labeled tracers. One-way ANOVA was used for group comparisons.

Results. In HIV-MC, all subjects were receiving HAART; 6 receiving protease inhibitors (PI). In HIV-N, 8 were naïve to therapy, 2 were receiving PI-based HAART, and 5 were receiving non-PI based HAART. HIV-MC had greater basal plasma TG (446 ± 45 mg/dl vs 118 ± 16 mg/dl, p<0.01), glucose (97 ± 1 mg/dl vs 92 ± 1 mg/dl, p<0.01) and insulin (14 ± 2 μU/ml vs 7 ± 1 μU/ml, p<0.01) concentrations than HIV-N. At all insulin levels, whole-body lipolytic rates (palmitate Ra; μmol·kgFFM⁻¹·min⁻¹) were greater in HIV-MC than HIV-N; basal (1.12 ± 0.09 vs 0.86 ± 0.07, p=0.05), low (0.57 ± 0.06 vs 0.27 ± 0.02, p<0.01), and high insulin conditions (0.36 ± 0.05 vs 0.20 ± 0.01, p<0.01). Insulin-mediated suppression of lipolysis during low insulin was blunted in HIV-MC vs HIV-N (49 ± 4% vs 67 ± 3%, p<0.01). Glucose production rates (glucose Ra; μmol·kgFFM⁻¹·min⁻¹) were similar between groups (12.4 ± 0.4 vs 12.4 ± 0.5) during basal conditions, but during low dose insulin conditions, suppression of glucose production was blunted in HIV-MC vs HIV-N (4.2 ± 4% vs 7.8 ± 3%, p<0.01). Whole-body glucose disposal rates were markedly lower in HIV-MC vs HIV-N (37 ± 3 vs 60 ± 5 μmol·kgFFM⁻¹·min⁻¹, p<0.01) during high insulin conditions.

Conclusions. Patients with HIV-MC have marked impairment in the ability of insulin to suppress lipolysis and glucose production, and to promote glucose disposal. Increased mobilization of lipid stores likely contributes to dyslipidemia and body fat redistribution seen in HIV infection.

Introduction

• Patients with HIV infection treated with HAART infection, frequently develop metabolic complications, including body-fat redistribution, hypertriglyceridemia and impaired glucose tolerance (1).

• Despite the high frequency of these metabolic complications, the underlying alterations in glucose and lipid metabolism are poorly understood.

→ We hypothesized that patients with HIV metabolic syndrome would have impaired insulin sensitivity in liver, adipose tissue, and skeletal muscle, and greater postabsorptive lipolytic rates, than BMI-matched patients with HIV infection but no metabolic complications.

Study subjects

Subject Characteristics		
	HIV-MC	HIV-N
Age (yr)	43 ± 3	38 ± 3
Body Fat (%)	19 ± 2	23 ± 2
BMI (kg/m ²)	26 ± 1	26 ± 1
Naïve (N=)	0	8
Non-PI (N=)	6	5
PI-HAART (N=)	7	2
CD4 (cells/mm ³)	644 ± 96	514 ± 50
T:A ratio	1.9 ± 0.1*	1.1 ± 0.1

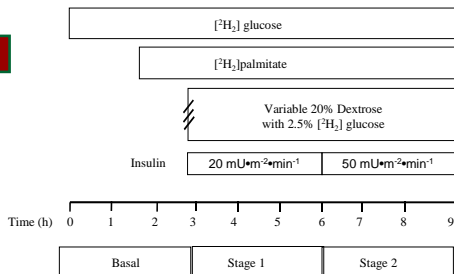
Fasting Plasma Substrate and Hormone Concentrations		
	HIV-MC	HIV-N
Glucose (mg/dl)	97 ± 1	92 ± 1
Insulin (μU/ml)	14 ± 2	7 ± 1
FFA (μmol/ml)	428 ± 39	345 ± 34
Triglyceride (mg/dl)	446 ± 45	118 ± 16
HDL (mg/dl)	35 ± 2	45 ± 3

T:A ratio; Truncal:appendicular ratio assessed by DEX

Values are Mean ± SE, * p<0.05 vs HIV-N

Methods

Figure 1. Schematic diagram of isotope infusion protocol



A two-stage hyperinsulinemic euglycemic clamp, with infusion of stable isotope labeled [2H₂]glucose and [2H₂]palmitate was performed (Figure 1).

Steele's equation for steady state conditions (6) used to calculate palmitate and glucose rates of appearance:

$$Ra = \text{Infusion Rate } (\mu\text{mol}\cdot\text{kgFFM}^{-1}\cdot\text{min}^{-1}) / \text{Tracer:Tracee Ratio}$$

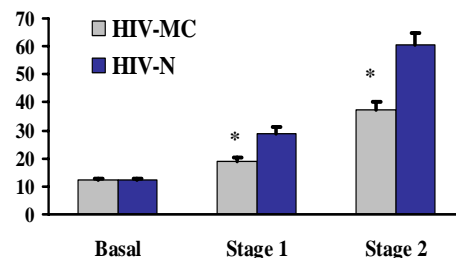
Statistics:

One-way ANOVA was used to calculate differences between groups.

Results

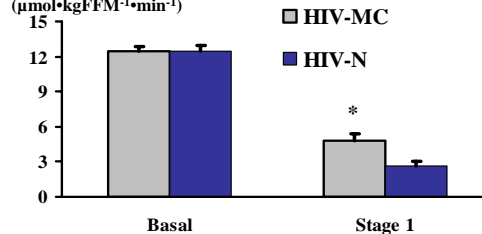
Glucose Disposal

(μmol·kgFFM⁻¹·min⁻¹)



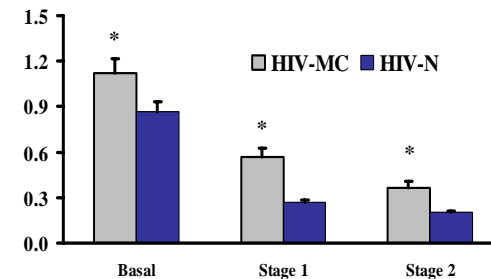
Glucose Ra

(μmol·kgFFM⁻¹·min⁻¹)



Palmitate Ra

(μmol·kgFFM⁻¹·min⁻¹)



Values are Mean ± SE, * p<0.05 vs HIV-N

Conclusions

During postabsorptive conditions plasma glucose and insulin concentrations are greater in patients with HIV-MC than HIV-N patients

Despite greater plasma insulin concentrations during postabsorptive conditions, HIV-MC patients have higher fatty acid turnover than HIV-N patients.

Patients with HIV-MC have reduced insulin sensitivity in skeletal muscle, liver and adipose tissue compared with HIV-N patients.

Increased lipolytic rates during postabsorptive conditions may contribute to the insulin resistance and fat redistribution observed in patients with HIV-associated metabolic complications.

References

1. A. Carr, K. Samaras, A. Thorisdottir, G.R. Kaufmann, D.J. Chisholm and D.A. Cooper. Diagnosis, prediction, and natural course of HIV-1 protease inhibitor-associated lipodystrophy, hyperlipidaemia, and diabetes mellitus: a cohort study. *Lancet* 353 (1999), pp. 2093–2099
2. Unger, R.H. Lipotoxic Diseases. *Annu. Rev. Med.* 53: 319–336, 2002.