Relationship of Postprandial Nonesterified Fatty Acids, Adipokines, and Insulin Across Gender in Human Immunodeficiency Virus–Positive Patients Undergoing Highly Active Antiretroviral Therapy

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Abstract

Background: Metabolic derangements are common in human immunodeficiency virus (HIV)-positive subjects undergoing antiretroviral therapy, but little is known about postprandial conditions.

Methods: We investigated the relationship between leptin, adiponectin, nonesterified fatty acids (NEFA), and insulin in response to a day-long meal pattern and evaluated gender differences in HIV-positive men ($n = 12$) and women ($n = 13$) undergoing highly active antiretroviral therapy (HAART).

Results: For both men and women, a significant decrease in postprandial NEFA levels was observed following breakfast (0.53 vs. 0.22 mmol/L, $P < 0.001$, baseline and at 3 hours, respectively), whereas day-long postprandial leptin and adiponectin levels showed small nonsignificant oscillations. In contrast to NEFA and adiponectin, postprandial leptin levels were significantly higher among women compared to men ($P < 0.05$). Postprandial NEFA levels correlated positively with fasting insulin levels ($r^2 = 0.25$, $P = 0.016$), and the postbreakfast decrease in NEFA levels correlated significantly with the postbreakfast increase in insulin levels ($r^2 = 0.17$, $P = 0.038$). No significant association between postprandial adipokines and insulin was observed.

Conclusions: In HAART-treated, HIV-infected men and women, levels of NEFA, but not adipokines, showed significant postprandial variation. Furthermore, food intake resulted in significant NEFA suppression in proportion to the food-stimulated insulin increase.

Introduction

THE USE OF HIGHLY active antiretroviral therapy (HAART) in human immunodeficiency virus (HIV) infection has been associated with a constellation of metabolic risk factors, including insulin resistance, dyslipidemia, visceral lipohypertrophy, and peripheral lipoatrophy.^{1–10} This phenotypic pattern is compatible with a high-risk metabolic milieu. Notably, the dyslipidemia observed in HIV/HAART has features common with that of the metabolic syndrome, and includes hypertriglyceridemia and low high-density

lipoprotein cholesterol (HDL-C) levels.^{11–13} Studies to date indicate that HIV infection, HAART regimen, or the two in combination might underlie these changes.^{5,14} Implicating a direct role of HAART, impaired insulin action on glucose homeostasis has been reported after administration of indinavir to healthy HIV-negative human volunteers.¹⁵

Studies under the HIV-negative condition have established that the postprandial state has features associated with cardiovascular risk.¹⁶ Although many postprandial studies to date have been carried out using a high caloric

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challenge, resulting in metabolic stress conditions, fewer studies have explored the effects of a physiological food intake.¹⁶ To address this void in HIV/HAART and to assess the effect of antiretroviral therapy on postprandial conditions with a normal food intake in normolipidemic subjects, we recruited HIV-positive patients without signs of fasting dyslipidemia. In addition, because there have been few studies in HIV-positive minority populations across gender, we largely recruited African American men and women.

An endocrine role of adipose tissue is now well recognized, and increasing attention has been paid to the relation of adipokines, such as leptin and adiponectin, to cardiovascular disease.^{17–19} A complex relationship between leptin and insulin has been established, whereas adiponectin is negatively associated with insulin resistance, obesity, and cardiovascular risk.^{17–19} A number of studies have demonstrated changes in adipokine levels and expression associated with changes in proinflammatory cytokines during HIV-positive conditions.^{20–22} However, most of these have studies addressed fasting condition. In view of the presence of insulin-resistance features, including high nonesterified fatty acids (NEFA) levels, during HIV/HAART, we tested the hypothesis that levels of adipokines, NEFA, and insulin would respond to physiological food intake across gender in normolipidemic HIV-positive subjects undergoing HAART. In the present study, we report findings on gender differences on postprandial levels of NEFA and adipokines and their relation to insulin levels and food intake.

Experimental Procedure

Patients

HIV-positive African American and Hispanic patients were recruited from outpatient HIV clinics at Harlem Hospital Center in New York. The detailed recruitment procedure, inclusion and exclusion criteria, and clinical characteristics of this population have been described previously.²³ Briefly, 25 normolipidemic HIV-positive patients, 12 men and 13 women, self-reported as African American ($n = 23$) and Hispanic ($n = 2$) and undergoing stable antiretroviral regimen for at least 6 months were recruited. Of the patients, 13 patients were undergoing protease inhibitor (PI)-based HAART (6 on nelfinavir and 7 on indinavir) and 12 patients were undergoing nonnucleoside reverse transcriptase inhibitors (NNRTI)-based HAART (6 each on nevirapine and efavirenz) with no PIs. Adherence to therapy was gauged by history and follow up with the primary care provider. The CD4 count range was 250–1240 ($\bar{x}$ 654); viral load was undetectable in 15 patients and was <2900 in 10 patients. The study was approved by the Institutional Review Boards at Columbia University, Harlem Hospital Center, St. Luke's–Roosevelt Medical Center, VA Northern California Health Care System, and University of California Davis, and informed consent was obtained by all participants.

Study design

The patients were admitted to the Columbia University General Clinical Research Center (GCRC) on the evening before the study. After admittance, the patients fasted until the morning breakfast at 9 A.M. the following day. Blood draws were obtained hourly from 8 A.M. until 8 P.M., when

the patient was discharged. At meal times (9 A.M., 12 noon, and 5 P.M.), the blood draw was obtained prior to serving the meal. Following the 8 P.M. blood sample, the catheter was removed and the patients discharged. Because the first meal was given after the first blood sample (1 hour), we defined the baseline levels as the average of the 0-hour and 1-hour time points. All meals were prepared by the GCRC Bionutrition Unit, and the diet composition, menu choices, and the distribution of calories over the meals have been reported elsewhere.²³ Briefly, the caloric distribution was designed to provide 25–28% of total energy for breakfast, 35% for lunch, and 37–40% for dinner. The distribution of caloric content was based on the National Cholesterol Education Program (NCEP) Step I recommendations, with 55% of calories from carbohydrates, 15% from protein, and 30% from fat.²⁴ The diets provided an average of 24 grams of fructose and 18 grams of fiber per day.

Laboratory analyses

Immediately following each blood draw, plasma and serum were separated by centrifugation at 3000 rpm for 20 minutes at 4°C, aliquoted, and immediately frozen at –80°C, and then stored until analysis. Plasma lipid, lipoprotein, and glucose levels were determined as previously described.²³ Plasma insulin levels were analyzed using commercially available reagents without cross-reactivity with pro-insulin (Linco Research, St. Charles, MO). The interassay coefficient of variation for this measurement was 6–8%.²⁵ Plasma adiponectin and leptin levels were measured using radioimmunoassays (Linco Research Inc., St. Louis MO) with intraassay and interassay coefficients of variation of 5.5% and 9.3%, 5.0% and 8.7%, respectively.²⁶ Plasma NEFA levels were determined by a colorimetric commercial assay (Biochemical Diagnostics, Brentwood, NY) as described previously.²⁵

Statistics

Analysis of data was done with SPSS statistical analysis software (SPSS Inc, Chicago, IL). Levels of insulin, homeostasis assessment of insulin resistance (HOMA-IR), leptin, adiponectin, and triglycerides (TG) and were transformed logarithmically to achieve normal distributions prior to statistical analysis. Normally distributed variables were described as mean $\pm$ standard deviation (SD), and nonnormal data as median and interquartile range. Comparisons of means between groups were made by the Student *t*-test or analysis of variance (ANOVA), as appropriate. Univariate relationships between differences in insulin and NEFA levels before and after the breakfast meal were described by Pearson correlation coefficients. Statistical significance was set at $P < 0.05$.

Results

Clinical characteristics and baseline characteristics of the subjects are given in Table 1. As seen in this table, there were no gender differences in age, lipoproteins, glucose, insulin, NEFA, and adiponectin levels and in CD4 cell counts. Women were more obese, and had higher HOMA-IR values and leptin levels compared to men.

Day-long postprandial levels of NEFA, leptin, and adiponectin by gender are presented in Fig. 1. There was no

TABLE 1. CLINICAL CHARACTERISTICS OF STUDY PATIENTS

	All (n =25)	Men (n =12)	Women (n =13)	<i>P</i> value men vs. women
Age (years)	42.7 ± 9.5	39.2 ± 9.9	45.6 ± 8.4	NS
BMI (kg/m ²)	27.7 ± 5.1	25.1 ± 2.3	29.9 ± 5.7	0.013
Total cholesterol (mg/dL)	179 ± 35	166 ± 33	191 ± 34	NS
LDL-C (mg/dL)	124 ± 38	123 ± 38	124 ± 40	NS
HDL-C (mg/dL)	42 ± 16	37 ± 12	46 ± 18	NS
Triglycerides (mg/dL)	132 (83–171)	99 (63–159)	140 (90–194)	NS
Glucose (mg/dL)	103 ± 17	97 ± 7	108 ± 21	NS
Insulin (μU/mL)	16.9 (9.7–30.7)	11.0 (7.3–20.6)	23.1 (14.0–34.5)	NS
HOMA-IR	4.7 (2.5–8.3)	3.0 (1.8–5.5)	7.0 (3.6–9.3)	0.029
NEFA (mmol/L)	0.53 ± 0.25	0.50 ± 0.29	0.56 ± 0.22	NS
Leptin (ng/mL)	2.2 (1.2–3.1)	3.3 (1.1–6.1)	21.6 (11.0–31.2)	<0.001
Adiponectin (μg/mL)	3.6 (2.5–8.7)	3.8 (2.6–8.0)	3.4 (2.1–9.3)	NS
CD4 cells	667 ± 296	551 ± 158	765 ± 353	NS

Data are means ± SD or for nonnormally distributed variables as median (interquartile range). Group means were compared using the Student *t*-test. Values for triglyceride, insulin, HOMA-IR, leptin, and adiponectin were transformed logarithmically before analyses.

Abbreviations: NS, not significant; BMI, body mass index; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; NEFA, nonesterified free fatty acids.

gender difference in levels of NEFA throughout the postprandial period (Fig. 1A). Mean fasting NEFA levels at baseline (at the end of the overnight fasting period) were 0.53 mmol/L and significantly decreased at 2 hours after the breakfast meal to 0.22 mmol/L ($P < 0.001$). No significant differences in NEFA levels were noted in response to the lunch or dinner meals. Mean day-long postprandial leptin levels were significantly higher among women compared to men; however, the postprandial curves were very similar in both genders (Fig. 1B). For adiponectin, small, nonsignificant oscillations in levels in response to meals were noted and, overall for both men and women, levels remained stable during the postprandial state (Fig. 1C).

Pearson correlation coefficients between fasting levels of NEFA, adiponectin, and leptin with other variables across gender are shown in Table 2. In men, but not women, levels of NEFA were positively correlated with fasting glucose, insulin, and HOMA-IR levels ($r = 0.617$, $P < 0.05$; $r = 0.698$, $P < 0.05$; and $r = 0.742$, $P < 0.01$, respectively). Adiponectin levels were positively correlated with HDL-C in both men ($r = 0.589$, $P < 0.05$) and women ($r = 0.740$, $P < 0.01$), and negatively with triglyceride in men ($r = -0.662$, $P < 0.05$), and with apolipoprotein B (apoB) in women ($r = -0.655$, $P < 0.05$). No association of fasting leptin with other variables was seen for both genders.

We next analyzed the relationship of fasting insulin with NEFA, leptin, and adiponectin. There was a strong relationship between insulin and NEFA levels in men ($r^2 = 0.49$, $P = 0.017$), but no significant correlation was observed for women ($r^2 = 0.12$, $P = 0.266$) (Fig. 2A), resulting in an overall significant correlation for the all subjects ($r^2 = 0.25$, $P = 0.016$). The relationship of fasting insulin and fasting leptin levels differed between men and women. Although we observed a positive association of leptin and insulin in men ($r^2 = 0.15$), which was not statistically significant ($P = 0.240$), no association was observed for women ($r^2 = 0.03$). There

was no significant relationship between fasting insulin and the adiponectin level for either gender ($r^2 = 0.13$ and $r^2 = 0.09$, men and women, respectively; data not shown).

In addition, we evaluated the relationship between NEFA and insulin in response to the meals. Because the largest difference observed for both parameters was seen comparing levels before and after the first meal (breakfast), we defined the average of the 0- and 1-hour time points at the end of the overnight fasting period and prior to administration of food as baseline, and the average of the 2- and 3-hour time points, following the breakfast meal, as postmeal conditions. The individual differences in NEFA and insulin levels were expressed in absolute terms (Fig. 2C). As seen in this figure, there was a strong relationship between the differences in NEFA and insulin in men ($r^2 = 0.39$, $P = 0.029$), whereas no significant correlation was observed for women ($r^2 = 0.07$, $P = 0.382$). When all subjects were analyzed together, an overall significant correlation was seen ($r^2 = 0.17$, $P = 0.038$). The results suggest that among the HIV-positive men, the higher the insulin level observed after the breakfast meal, the larger the decrease in NEFA level. When restricting the postmeal time point to the 2-hour sampling time, the results remained essentially similar.

Discussion

In the present study, we explored the relationship between insulin, NEFA, and adipokines in HIV-positive subjects in response to food intake based on a standardized, physiological caloric load using meals within the common food spectrum. In contrast to many other studies using high-fat meals or other experimental nutrition conditions, our study was aimed at investigating the impact of a diet mirroring everyday conditions, recommended for all Americans.^{24,27} Furthermore, the diet tested corresponded to the initially recommended diet intervention pattern in dyslipidemia.^{11,24}

FIG. 1. Hourly levels of (A) nonesterified fatty acids (NEFAs), (B) leptin, and (C) adiponectin by gender. Leptin and adiponectin levels were logarithmically transformed to achieve normal distributions. Meals (arrows) were provided after 1 hour (breakfast), 4 hours (lunch), and 9 hours (dinner).

We found increased fasting baseline levels of NEFA in our HIV-positive subjects, both men and women. Our findings are in agreement with the notion that HIV/HAART is associated with metabolic disorders and dyslipidemia, similar to those of metabolic syndrome, such as lipodystrophy, dyslipidemia (hypertriglyceridemia, decreased HDL-C, and increased free fatty acids) and insulin resistance.^{10,28} Studies in HIV-positive subjects demonstrated that inhibition of lipolysis by acipimox resulted in a significant reduction in lipolysis and NEFA levels.²⁹ Furthermore, a recent study using a high-fat meal showed that increased postprandial NEFA levels were associated with insulin resistance (HOMA-IR) and lipodystrophy in HIV-positive subjects.³⁰ In our study, we observed a dynamic pattern in NEFA levels with a >50% rapid reduction in response to a physiologic meal following a 12-hour fasting period. As all study

TABLE 2. PEARSON CORRELATION COEFFICIENT BETWEEN FASTING LEVELS OF NEFA, LEPTIN, AND ADIPONECTIN WITH OTHER VARIABLES ACROSS GENDER

	NEFA	Adiponectin	Leptin
Men			
HDL-C (mg/dL)	-0.114	0.589 ^a	-0.294
Triglyceride (mg/dL)	0.250	-0.662 ^a	-0.191
Glucose (mg/dL)	0.617 ^a	0.186	0.286
Insulin (μU/mL)	0.698 ^a	-0.372	0.387
HOMA-IR	0.742 ^b	-0.322	0.410
ApoB (mg/dL)	-0.054	-0.392	0.031
BMI (kg/m ²)	-0.068	-0.461	0.337
Women			
HDL-C (mg/dL)	-0.034	0.740 ^b	-0.279
Triglyceride (mg/dL)	0.062	-0.510	0.380
Glucose (mg/dL)	-0.295	-0.131	0.474
Insulin (μU/mL)	0.349	0.302	-0.161
HOMA-IR	0.243	0.289	-0.048
ApoB (mg/dL)	0.108	-0.655 ^a	0.308
BMI (kg/m ²)	-0.040	-0.311	0.549

^a $P < 0.05$.

^b $P < 0.01$.

Abbreviations: NEFA, nonesterified fatty acids; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis assessment of insulin resistance; ApoB, apolipoprotein B; BMI, body mass index.

subjects fasted overnight prior to the initial meal (breakfast), NEFA levels would be expected to be increased. In contrast, lunch and dinner were not preceded by a similar fast, compatible with a less-pronounced meal induced decrease in NEFA levels. Furthermore, this decrease in NEFA levels was proportional to the increase in postmeal insulin levels for men and women.

Interestingly, NEFA levels correlated with glucose, insulin, and HOMA-IR only in men. It should be noted that women were more obese than men. Thus, we cannot rule out that a higher obesity level among women might play a role with regard to gender differences in the association of NEFA with glucose and insulin. Previous studies in HIV-negative patients with type 2 diabetes mellitus have shown a significant relationship between NEFA response and fasting insulin levels.³¹ However, as we have not directly measured NEFA turnover in this study, and because NEFA re-esterification is responsive to an increase in insulin, we cannot directly assess the relative contribution of a decrease in lipolysis or the disposition of NEFA through oxidation and re-esterification. Further studies are needed to resolve these issues.

In regard to leptin metabolism, there were relatively modest fluctuations in postprandial leptin levels. In agreement with previous studies,³² women had significantly higher leptin levels than men. Higher leptin concentrations in women seem to be attributable to the higher amount of subcutaneous fat mass in females, inhibition of leptin by androgens, and stimulation by estrogens.³³ Leptin has been implicated in decreased production and secretion by pancreatic β -cells, and insulin, conversely, stimulates leptin secretion in an adipocyte-insulin feedback loop.^{34,35} No difference was seen over the observation period for adiponectin levels. Although

FIG. 2. Relationship between (A) fasting insulin and NEFA and (B) fasting insulin and leptin by gender (male, triangle; female, circle). Insulin and leptin levels were transformed logarithmically to achieve normal distributions. (C) Relationship between the differences in insulin and NEFA levels before and after the breakfast meal by gender (male, triangle; female, circle). Differences were expressed in absolute terms.

animal studies have suggested a postprandial change in adiponectin levels, our findings are in agreement with a previous study in humans, where adiponectin levels remained stable following a high-fat meal.³⁶

Potential limitations and strengths of the present study need to be discussed. We recruited non-Caucasian subjects, mostly African Americans, and, although they represent an understudied group, our results may not be generalizable to other ethnic groups. Notably, we specifically recruited subjects without frank hyperlipidemia, because we aimed to assess the postprandial response in HIV-positive patients meeting lipid treatment goals. However, our approach made it possible to investigate the postprandial relationship between insulin, NEFA, and adipokines among individuals without major dysregulation of TG levels. Our study provides an impetus for further studies aimed at exploring modulating effects of ethnicity on metabolic phenotypes within HIV.

In conclusion, our studies employing a physiological mixed-meal pattern representing the common food spectrum in African American and Hispanic HIV-positive patients on a HAART regimen demonstrated a correlation between postprandial NEFA suppression and an increase in insulin levels, indicative of a responsiveness to physiologic insulin stimulation through food. Leptin and adiponectin levels did not fluctuate postprandially during the day.

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Author Disclosure Statement

No competing financial interests exist.

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