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Increased lipoprotein remnant cholesterol levels in HIV-positive patients during antiretroviral therapy

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Abstract

Increased levels of postprandial triglycerides (TG) and remnant like particles (RLP) are associated with cardiovascular disease. We evaluated whether postprandial lipemia differed in HIV-positive patients with or without different antiretroviral regimens. A standardized high fat load was administered to 28 subjects: 11 HIV-positive subjects receiving protease inhibitors (PI), 10 HIV-positive subjects receiving non-nucleoside reverse transcriptase inhibitors (NNRTI) and 7 HIV-positive subjects not receiving highly active antiretroviral therapy, HAART (Naïve). Baseline TG levels and TG area under the curve (AUC) did not differ among the three groups. The postprandial TG concentration curves were similar in the NNRTI and Naïve groups, peaking at 3–5-h. Baseline RLP cholesterol was higher in the NNRTI group compared to other two groups ($P = 0.035$). Both HAART groups (NNRTI and PI) had higher postprandial RLP cholesterol AUC than the Naïve group ($P = 0.024$, ANOVA). In conclusion, during HIV conditions, HAART resulted in a pro-atherogenic pattern with accumulation of remnant lipoproteins.

Keywords: HIV; Protease inhibitors (PI); Non-nucleoside reverse transcriptase inhibitor (NNRTI); Antiretroviral therapy; Postprandial lipemia

1. Introduction

Human immunodeficiency virus (HIV) infection results in a multitude of metabolic, nutritional and clinical manifestations [1]. Disturbances of lipid metabolism, such as decreased LDL and HDL cholesterol and increased triglyceride levels have been observed in HIV-positive individuals prior to introduction of highly active antiretroviral therapy (HAART) based regimens [1]. Further, abnormalities of lipid metabolism including decreased HDL cholesterol, increased triglyceride, and a modest increase in LDL-cholesterol levels have been increasingly recognized also among antiretroviral-treated patients [1–5]. HAART generally involves the combination of three drug categories: nucleoside reverse transcriptase inhibitors (NRTI), non-nucleoside reverse transcriptase inhibitors (NNRTI) and protease inhibitors (PI). Although there are substantial differences between individual drugs, and also within drug classes, dyslipidemia appears to be more prevalent among patients receiving PI's [4,5], but use of other antiretroviral regimens,

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including NRTI's and NNRTIs have also been associated with metabolic changes [6].

Postprandial lipemia is a risk factor for atherosclerosis and postprandial lipoprotein levels are associated with cardiovascular disease [7–10]. However, few studies have focused on postprandial lipemia during HIV/HAART, although several components of the lipid profile associated with HIV/HAART, such as decreased HDL cholesterol and increased triglyceride concentrations, predict the postprandial response [9,11–13]. Compared to healthy HIV-negative control subjects, HIV-positive individuals receiving antiretroviral therapy have delayed clearance of postprandial triglyceride-rich lipoproteins [14]. However, there is a lack of data regarding the postprandial lipid and lipoprotein profile in HIV-positive subjects with or without different types of antiretroviral therapies. As lipid disorders are receiving increasing attention among HIV-positive patients, marked dyslipidemia is becoming more uncommon. However, even in the absence of fasting hyperlipidemia, HIV/HAART might influence lipid features. In the present study, we evaluated whether postprandial lipemia would differ in response to a standardized fat load in a cohort of normolipidemic HIV-infected patients in the absence or presence of different types of antiretroviral therapy.

2. Methods

2.1. Patients

HIV-positive African American and Hispanic patients were recruited from outpatient HIV clinics at Harlem Hospital Center in New York. Eligibility for enrollment in the study was based on the presence of documented HIV infection, ongoing stable antiretroviral regimen for >6 months, and the absence of hyperlipidemia. The detailed inclusion and exclusion criteria have been previously described [15]. 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 from all participants.

Overall, 28 patients were recruited for the study; 16 men and 12 women. Twenty-five patients were African American and 3 were Hispanic; 11 patients were undergoing PI-based HAART, 10 patients were undergoing NNRTI-based HAART, and 7 patients did not receive any HAART. For the 21 patients undergoing HAART, the type of antiretroviral regimen was defined as PI-based for patients taking 2 or more nucleoside reverse transcriptase inhibitors (NRTIs) in combination with at least 1 PI (lopinavir, indinavir or nelfinavir). NNRTI-based HAART regimens were combinations of $\geq$2 NRTIs in combination with 1 NNRTI (efavirenz or nevirapine) [16]. Adherence to therapy was gauged by history and follow-up with the primary care provider, and the CD4 count range was 181–1033 ($\bar{x}$: 515).

2.2. Study design

The subjects were admitted to the Columbia University General Clinical Research Center. In the morning, at 09:00 a standard high fat meal was administered, consisting of 272.0 g ice cream and frozen deserts (Breyers, Green Bay, Wisconsin), 12.0 g safflower oil (Hollywood), 122.0 g coconut milk (Taste of Thai), 2.0 g vanilla extract without alcohol, 60.0 g evaporated skim milk (Carnation), 6.0 g egg yolk powder (Henningson Foods), 27.0 g of a Polycose powder (Promod, Ross Laboratories) and 37.0 g of a ProMod powder (Promod, Ross Laboratories). The nutrient composition of the meal, based on a body surface area of 2 m^2, included 70.4 g fat (51% of total calories) with 40.6 g of saturated fat, 111.3 g carbohydrate (36% of total calories), 47.4 g protein (15% of total calories), 262.0 mg cholesterol, and 1235 calories. The body surface area of the subjects was calculated using the Dubois equation to gauge the appropriate weight of the meal for each subject. The subjects consumed the meal within a 15-min period. Blood was drawn at baseline and at 3, 5, 7, and 10 h following the fat load.

2.3. Laboratory analysis

Immediately after each blood draw, plasma and serum were separated by centrifugation at 30,000 × *g* for 20 min at 4 °C. Plasma and serum samples were aliquotted and immediately transferred to a −80 °C freezer where they were stored until analyzed. Plasma total, LDL, and HDL cholesterol, triglyceride, and glucose concentrations were measured by standard enzymatic techniques as previously described [17]. Plasma non-esterified free fatty acids (NEFA) levels were determined by a colorimetric commercial assay (Biochemical Diagnostics, Brentwood, NY) [18]. Plasma insulin concentrations were measured by using commercially available reagents without cross-reactivity with proinsulin concentrations (Linco Research, St. Charles, MO) [19]. Homeostasis model assessment insulin resistance (HOMA-IR) was calculated using the updated model available from the Oxford Centre for Endocrinology and Diabetes [20]. Lipoprotein remnant-like particle cholesterol (RLP-C) assays were carried out as described previously using commercially available reagents (Otsuka Pharmaceuticals, Beltsville, MD) [21]. The intra-assay coefficient of variance was 5–7% and all assays were carried out in duplicate. Body mass index (BMI) was calculated as weight divided by the square of height.

2.4. Statistics

Analysis of data was done with SPSS statistical analysis software (SPSS Inc., Chicago, IL). Results were expressed as means ± S.D. Triglyceride and insulin levels were logarithmically transformed to achieve normal distributions. Baseline comparisons between the three groups were performed using one-way ANOVA, and *post hoc* analyses were performed by Tukey test for two independent samples. Group means