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ORIGINAL ARTICLE

Correlation between HIV disease and lipid metabolism in antiretroviral-naïve HIV-infected patients in Japan

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Abstract Antiretroviral therapy alters lipid metabolism in HIV-infected patients. However, interpreting the impact of HIV infection on lipid metabolism is difficult because of various associated factors, including antiretroviral drugs and demographic characteristics. A few studies have associated HIV infection with lipid metabolism in antiretroviral-naïve HIV-infected patients. Because there were no data in this regard from Japan, the present study examined the impact of HIV infection, as well as demographic and clinical features, on lipid metabolism in antiretroviral-naïve HIV-infected patients in Japan. We performed a cross-sectional study to examine the impact of HIV disease, demographic and clinical characteristics on lipid metabolism among 168 HIV-infected Japanese men who were antiretroviral naïve and who did not have hemophilia, including patients who took medication for dyslipidemia. The mean age of the patients was 45.7 years; 0.6% of the patients took medication to dyslipidemia. The mean CD4 lymphocyte count was 289/μL, the mean baseline log10 HIV viral load was 4.2 HIV-1 RNA copies/mL, and 22% of the patients had a history of AIDS-defining events. A higher HDL-C concentration was associated with a higher CD4 lymphocyte count ($p = 0.043$). Also, a higher LDL-C concentration was associated with a higher CD4 lymphocyte count ($p = 0.003$). Infection with HIV was associated with dyslipidemia in antiretroviral-naïve patients. More advanced HIV disease was associated with less favorable lipid homeostatic profiles. These results are similar to findings from other countries.

Keywords Lipids · HIV infection · Antiretroviral naïve

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Introduction

The current treatment has significantly prolonged the survival of patients infected with HIV. Accordingly, the frequencies of not only opportunistic infection but also long-term metabolic complications have increased. Several investigators have reported that metabolic syndrome is more common in HIV-infected patients than in HIV-negative individuals, and altered lipid metabolism has also been reported since the start of the HIV epidemic [1–7]. These outcomes have been ascribed to antiretroviral therapy. Studies [8–11] have demonstrated that high total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and triglyceride (TG) concentrations are associated with protease inhibitor (PI) treatment. High TC and TG concentrations have also been identified in patients on non-PI highly active antiretroviral therapy (HAART) regimens.

Some studies have recently demonstrated that HIV infection and demographic characteristics influence lipid metabolism in patients who are antiretroviral naïve [12–15]. Low high-density lipoprotein cholesterol (HDL-C) concentrations and hypertriglyceridemia have been detected in antiretroviral-naïve HIV-infected patients who do not have a history of antiretroviral therapy. However, participants in these studies were derived from predominantly one or two ethnic groups. The impact of HIV infection on lipid metabolism has never been studied in a Japanese population.

The present study determines the impact of demographic and HIV disease characteristics on lipid metabolism in antiretroviral-naïve HIV-infected patients in a Japanese population.

Patients and methods

Patient population

A total of 218 HIV-infected nonhemophilic patients were treated at Juntendo University Hospital in Tokyo, Japan between October 1992 and March 2010. We retrospectively reviewed their records and selected 168 Japanese male patients from among them, including patients who took medication for dyslipidemia. Thirty-two patients were excluded because antiretroviral therapy was started at another institution and information about their status before that point was unavailable. Also, 17 patients who were female or not Japanese were excluded.

Patients were eligible if they had evidence of HIV infection, in the form of either positive Western blot findings or measurable plasma HIV-1 RNA. The Research Ethics Committee of Juntendo University School of Medicine approved the study protocol.

Assessments and measurements

After we obtained their histories, the patients underwent a baseline physical examination to ascertain demographic and clinical characteristics, HIV risk factors, previous HIV disease-related diagnoses, and current medications. Height and weight were measured following a standard procedure, and body mass index (BMI) was calculated as weight in kg/height in m^2. We tested for HIV antibody using a chemiluminescence enzyme immunoassay (CLEIA).

Venous blood was drawn from all of the patients, and then concentrations of HDL-C or LDL-C were calculated using the Friedewald formula. The most recent blood data were obtained from patients who had never received antiretroviral therapy, and just before initiating antiretroviral therapy from those who had.

Statistical methods

Descriptive statistics are reported as mean values with standard SD and median values. Lipid parameters were compared between patients with or without AIDS-defining events using the Mann–Whitney *U* test and the unpaired *t* test. Correlations of HIV RNA level and CD4 cell counts with lipid parameters were assessed by linear analysis.

The level of statistical significance was defined as $p < 0.05$, and all data were analyzed using JMP version 8 (SAS Institute Inc.).

Results

Patient population

Of the 168 patients included in this analysis, 27% (17/63) were smokers, 1.8% (3/168) had diabetes, and 0.6% (1/168) had a history of intravenous drug use. 0.6% (1/168) of the patients took medication for dyslipidemia. 60% (100/168) of the patients took antiretroviral therapy that generally consisted of two nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) plus either one non-nucleoside reverse transcriptase inhibitor (NNRTI) or a PI (with or without ritonavir boosting), following the guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents [16].

The mean age was 45 ± 13 years (mean standard deviation; SD), and 22% (37/167) had AIDS-defining events. The mean baseline CD4 lymphocyte count was 289 ± 249/μL, and the mean baseline log10 HIV RNA was 4.2 ± 0.7 HIV-1 RNA copies/mL (Table 1).

Lipid parameters and demographic characteristics compared according to HIV stage

Patients were assigned for comparisons to paired groups with or without AIDS-defining events (Table 2). There is

Table 1 Patient characteristics

Factor	*n*	Mean ± SD
Age (years)	167	45.7 ± 13.2
BMI (kg/m^2)	130	22.0 ± 3.3
TC (mg/dL)	145	155 ± 35.2
LDL-C (mg/dL)	43	92.2 ± 27.7
HDL-C (mg/dL)	54	38.6 ± 12.4
HIV RNA level (log copies/mL)	148	4.2 ± 0.70
CD4 (cells/μL)	164	289 ± 249
Factor	***n***	**Number (weighted %)**
HIV treatment history	168	100 (59.5)
AIDS-defining event (yes)	167	37 (22.2)
MSM	133	97 (72.9)
Drugs	168	1 (0.6)
Smoker	63	17 (27)
DM	168	3 (2.9)

BMI body mass index, *TC* total cholesterol, *LDL-C* low-density lipoprotein cholesterol, *HDL-C* high-density lipoprotein cholesterol, *MSM* men who have sex with men, *DM* diabetes mellitus

Value are means ± SD and number (weighted %)

Table 2 Comparison of the characteristics of patients with or without AIDS-defining events

Baseline factor	*n*	With AIDS-defining events ($n = 37$)	Without AIDS-defining events ($n = 130$)	*p* value	*Difference	**p* value
TC (mg/dL)	145	152.3 ± 35.1	156.5 ± 35.3	0.549[b]	2.32	0.2347
LDL-C (mg/dL)	43	99.5 ± 8.33	89.7 ± 4.89	0.315[b]	−2.09	0.4733
HDL-C (mg/dL)	54	32.0 ± 10.5	39.9 ± 12.4	0.79[a]	2.17	0.1326

BMI body mass index, *TC* total cholesterol, *LDL-C* low-density lipoprotein cholesterol, *HDL-C* high-density lipoprotein cholesterol, *TG* triglyceride, *DM* diabetes mellitus

Value are means ± SD and number (weighted %). Determined by [a]the Mann–Whitney *U* test and [b]the unpaired *t* test

* Adjusted by BMI, age

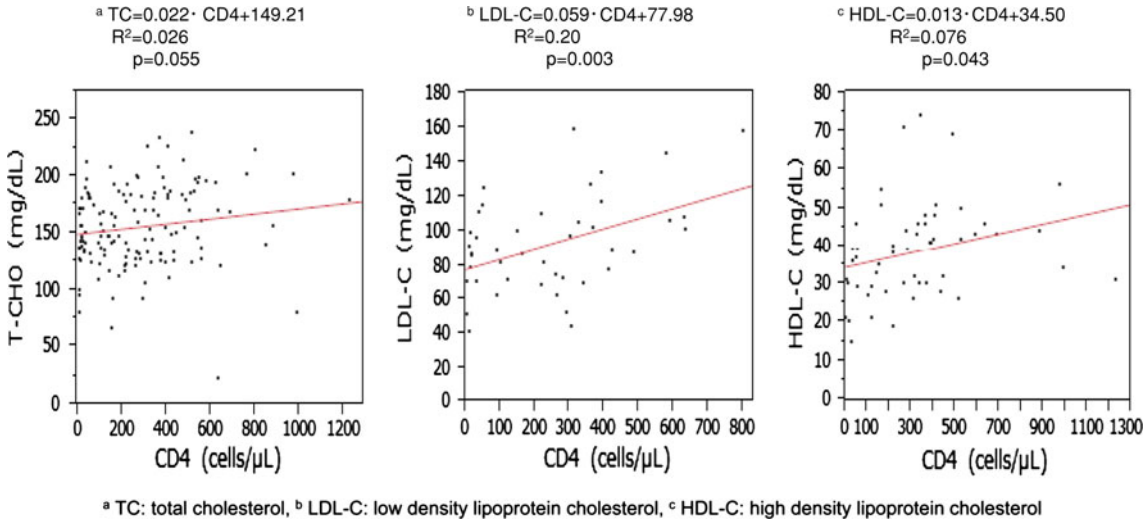

Fig. 1 Correlation of lipid measures with the $CD4^+$ cell count

no significant difference in lipid profile between patients with AIDS and those without AIDS.

Higher concentrations of HDL-C and LDL-C were associated with a higher CD4 lymphocyte count. However, HIV RNA levels were not associated with the lipid profile, and CD4 lymphocyte counts were not associated with TC concentrations (Figs. 1, 2).

Discussion

This study demonstrated the impact of HIV diseases on lipid metabolism in antiretroviral-naïve patients selected from the Japanese male population. The relationships between the markers of HIV infection and lipid parameters in this study were consistent with those of previous reports based on other ethnic populations [12–15]. Patients with lower CD4 lymphocyte counts were more likely to have lower LDL-C and HDL-C levels. A recent study found that HIV seroconversion is associated with decreased TC, HDL-C and LDL-C concentrations [17]. Constans et al. [18] suggested that the alterations in cholesterol metabolism that occur in HIV-infected patients could be explained by lipid peroxidation. The cytokine tumor necrosis factor (TNF)-α plays a role in plasma lipoprotein peroxidation in HIV-infected patients by stimulating the production of reactive oxygen species [19]. These modifications might have major effects on the immune system.

A low HDL-C concentration increases the risk for coronary artery disease [20–22]. Others have found that a lower HDL-C concentration is associated with a higher risk of cardiovascular disease (CVD) in HIV-infected patients in US and European populations [23, 24]. However, no such study had previously been performed for a Japanese population. The HDL-C concentration of HIV-infected patients in this study (38.6 ± 12.4 mg/dL) was <51 mg/dL, which is considered to indicate an increased risk for CVD [25]. There is evidence for relationships between BMI and age to HDL-C concentration [26, 27]. However, small sample size limited our ability to assess causal relationships in this study.

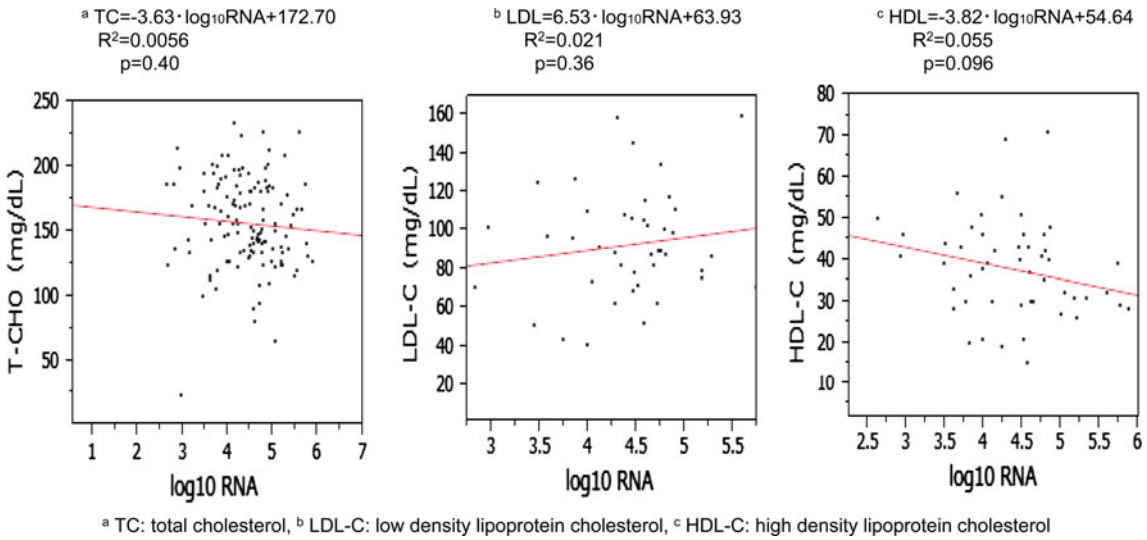

Fig. 2 Correlation of lipid measures with the HIV RNA level

Numerous studies have implicated antiretroviral therapy, and in particular PIs, as an important risk factor for metabolic syndrome including dyslipidemia when controlling for other demographic and traditional risk factors. On the contrary, Mondy et al. [5] showed that metabolic syndrome is closely associated with traditional risk factors rather than with antiretroviral therapy-related effects. Therefore, these and the present findings suggest that the assessment of lipid parameters is an essential component of routine clinical care for HIV-infected patients.

This study has some limitations. The cross-sectional study design and small sample size limited the ability to assess causal relationships between HIV diseases and lipid parameters. Antiretroviral therapy has significantly prolonged the survival of HIV-infected patients, and only lately has more attention has been directed toward long-term metabolic syndrome. Therefore, the lipid data set we obtained was rather small. We also could not always ensure overnight fasting when we took a blood sample because of the retrospective study design. Finally, whether or not lipid data was taken during the treatment of the HIV-infected patient depended on the doctor's subjective judgement, suggesting potential biases.

In conclusion, the present findings indicate that HIV disease itself is associated with lipid metabolism in antiretroviral-naïve patients in the Japanese male population. More advanced HIV disease was also associated with an unfavorable lipid profile. Antiretroviral therapy, together with the stage of HIV disease as well as demographic and clinical characteristics, should be considered when interpreting dyslipidemia in HIV-infected patients.

Conflict of interest The authors declare that they have no conflict of interest.

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