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Prevalence of and Clinical Factors Associated with Lipoatrophy in HIV-Infected Koreans Receiving Highly Active Antiretroviral Therapy

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Lipoatrophy is the long-term adverse effects developed in human immunodeficiency virus (HIV)-1-infected subjects receiving highly active antiretroviral therapy (HAART). This cross-sectional study aimed to evaluate the prevalence of and clinical factors associated with lipoatrophy in HIV-infected Koreans receiving HAART for more than 6 months. Lipoatrophy was diagnosed by concordance between physical examination and history taking performed by a single physician. Various covariates were examined, including diabetes mellitus (DM), lipid profiles after HAART, and HAART regimen and duration. Among total 144 patients (6 females and 138 males), 35 patients (24.3%) were diagnosed with lipoatrophy. The prevalence of lipoatrophy was significantly higher in females than that in males [83.3% (5/6) vs. 21.7% (30/138), $p = 0.010$] and higher in patients with DM than patients without DM [66.7% (4/6 DM) vs. 22.5% (31/138 non-DM), $p = 0.030$], or in patients with high total cholesterol levels than patients with low total cholesterol levels [31.9% (23/72 patients with high cholesterol) vs. 16.7% (12/72 patients with low cholesterol), $p = 0.035$]. Moreover, patients with stavudine treatment history (> 12 months) had a higher prevalence of lipoatrophy than patients who never received stavudine [50.0% (15/30) vs. 16.5% (17/103), $p < 0.001$]. In the multivariate logistic analysis, stavudine treatment for > 12 months (OR, 3.67; $p = 0.011$) and being female (OR, 24.93; $p = 0.009$) are independently associated with lipoatrophy. In conclusion, the prevalence of lipoatrophy in HIV-infected Koreans receiving HAART is not uncommon. Limited use of stavudine and regular monitoring are warranted to reduce lipoatrophy. ———— Lipoatrophy; HIV; Highly active antiretroviral therapy; Stavudine; Korea.

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Lipodystrophy is the important long-term adverse effects developed in human immunodeficiency virus (HIV)-1-infected subjects receiving highly active antiretroviral therapy (HAART), as it is associated with other metabolic complications such as insulin resistance, diabetes mellitus (DM), and dyslipidemia, which are important risk factors for the development of cardiovascular disease (Grinspoon 2005; Milinkovic and Martinez 2005; Brown 2008; Wierzbicki et al. 2008). Furthermore, lipodystrophy, especially facial lipoatrophy, may reduce adherence to HAART by stigmata through changes in the patient's cosmetic appearance and therefore result in treatment failure (Ammassari et al. 2002; Milinkovic and Martinez 2005; Fernandes et al. 2007).

Lipoatrophy and lipohypertrophy are thought to occur independently from each other and to have different risk factors (Jacobson et al. 2005; Wohl et al. 2006; Waters and Nelson 2007; Brown 2008; Wierzbicki et al. 2008). Because two phenomena are distinct processes, it should be considered separately rather than collectively as a single syndrome of lipodystrophy (Brown 2008). However, many studies reported the prevalence and risk factors of lipodystrophy in general, not lipoatrophy specifically (Waters and Nelson 2007).

Previous cross-sectional studies, which were performed in continents outside Asia, revealed that the prevalence of lipoatrophy ranged between 13 and 38% (Lichtenstein et al. 2001; Bacchetti et al. 2005; Jacobson et al. 2005; Waters and Nelson 2007). In 2002, Chang et al. reported that lipodystrophy was observed in only 2 (3.5%)

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of 57 HIV-infected Koreans receiving HAART and metabolic complications of HAART were rare (Chang et al. 2002). However, this study was performed in the early years of HAART in Korea and there were no further studies reporting the prevalence of and risk factors for lipoatrophy among patients living in East Asia region including Korea. The risk factors of lipoatrophy, including race, genetic variation, anthropometric parameters, state of HIV disease and regimens of antiretroviral drugs, as well as life style in patients living in developed countries on other continents, may be different from those of patients living in East Asia. Therefore, we performed this study to evaluate the prevalence of, and clinical factors independently associated with the diagnosis of lipoatrophy in HIV-infected Koreans in the era of HAART.

Subjects and Methods

Study design and Subjects

We performed the cross-sectional study from August 2007 to March 2008 at Severance Hospital, a 2,000-bed tertiary care university hospital and referral center in Seoul, Korea. HIV-infected Koreans who were > 18 years of age were eligible if they had been receiving HAART successively for more than 6 months with continuous good adherence to antiretroviral drugs and gave written informed consent for study participation. We excluded patients who were transferred from other clinics after HAART initiation or did not regularly visit every 3-6 months before enrollment. Also, patients who were currently taking peroxisome proliferator-activated receptor-gamma agonists, statins, metformin or growth hormone were excluded because these medications may affect changes of body fat (Mallewa et al. 2008). We also screened and ruled out other current medical conditions that can produce muscle or fat wasting and mimic lipoatrophy, such as HIV/AIDS-associated wasting syndrome (Polsky et al. 2004) according to the definition of the Centers for Disease Control and Prevention (CDC) published in 1987 (Centers for Disease Control and Prevention 1987), any opportunistic infection or malignancy undergoing current treatment, or underlying conditions of chronic liver or renal disease according to the International Classification of Disease, 10th Revision (World Health Organization 2006).

The eligible patients with exclusion criteria were not enrolled into this study through previous screening for medical history. Because all eligible patients without exclusion criteria agreed to study participation, there were no patients who did not give informed consent or were dropped from this study.

The time of HAART initiation and the choice of HAART regimen were individually decided by clinicians before enrollment according to international guidelines and the clinical states of patients. Tenofovir, emtricitabine, fosamprenavir, and saquinavir were not available in Korea until the end of this study. All patients who participated in this study were regularly followed up every 3-6 months with measurement of CD4+ T-cell and HIV-RNA viral load until the time of enrollment. Although quantitative measurements were not performed, adherence to antiretroviral drugs was regularly monitored by clinicians and patient self-reports at every visit. Patients with poor adherence were ineligible for this study.

The diagnosis of lipoatrophy and measurements of anthropometric parameters were performed in the cross-sectional study and the retrospective data for various covariates were collected by review of the medical records. The clinical factors associated with the diagnosis of lipoatrophy were evaluated by case-control study defining case group as the patients with lipoatrophy and control groups as those without lipoatrophy. This study was approved by the Institutional Review Board of the Clinical Research Institute of the local institution.

Case definition of lipoatrophy

Diagnosis of lipoatrophy was based upon the concordance between lipodystrophy-specific physical examination and history taking performed by a single physician (Carr et al. 2003; Milinkovic and Martinez 2005; Estrada et al. 2006; Wohl et al. 2006; van Griensven et al. 2007; Wierzbicki et al. 2008). The physician made the detailed examination for the morphological changes by noting subcutaneous fat loss in the face, buttocks and upper or lower extremities, such as wasting and vascular prominence in the extremities, hollowing of the cheeks or flattening of the buttocks (Carr et al. 2003; van Griensven et al. 2007). Also, the same physician completed the detailed lipodystrophy-specific questionnaire based on the Lipodystrophy Case Definition Study (Carr et al. 2003; van Griensven et al. 2007). This questionnaire was composed of questions to help identify the presence of body shape changes which definitely developed after HAART, such as changes of facial or buttocks shape, slimmed extremities (Carr et al. 2003; Brown 2008).

Measurement of anthropometric parameters and carotid intima-media thickness

We performed bioelectrical impedance analyses (Inbody 4.0; Biospace Co., Ltd., Seoul, Korea) for the measurements of body and abdominal adiposity such as waist-to-hip ratio (WHR), body mass index (BMI), total body fat mass, and visceral adipose tissue area (VAT). Waist circumference was measured by physical examination.

Abdominal ultrasonography was performed to evaluate the subcutaneous or visceral abdominal fat thickness. Through vertical scanning along the abdominal median from the xiphoid process to the umbilicus, we measured the maximal thickness of the preperitoneal fat (Pmax) at the anterior surface of the liver and the minimal thickness of the abdominal subcutaneous fat (Smin), and calculated the abdominal wall fat index (AFI) as the ratio of Pmax to Smin (Suzuki et al. 1993). We also measured the maximal thickness of the abdominal subcutaneous fat (Smax), defined as the distance from the echogenic line between the skin and subcutaneous tissue to the external face of the rectus abdominis muscle and intra-abdominal fat distance (IAD), defined as the distance from the internal face of the rectus abdominis muscle to the anterior wall of the abdominal aorta by the same vertical scanning (Ribeiro-Filho et al. 2001). The abdominal visceral to subcutaneous fat area ratio (VSR) was defined as the ratio of IAD to Smax (Ribeiro-Filho et al. 2001).

We also performed carotid ultrasonography to evaluate the intima-media thickness (IMT) and identify the presence of atherosclerotic plaques in the common carotid arteries (CCA) according to the previously described method (Pignoli et al. 1986; Zureik et al. 1999). Bilateral CCAs were scanned obliquely from the anterior and posterior directions and the IMT values were measured on the far wall of the bilateral CCAs as far as 10 mm proximal to the bifurcation of the carotid artery (Pignoli et al. 1986). The distance between the inner echogenic line representing the luminal-intimal interface and the outer echogenic line representing the media-adventitia interface was calculated by automatic IMT measurement software (Intimascope®; Media

Cross Co., Ltd., Tokyo, Japan) (Pignoli et al. 1986; Yanase et al. 2006). The mean of the bilateral maximal CCA IMT was used as the carotid IMT values in our analyses, because it has been shown to have the strongest association with cardiovascular risk factors (O'Leary and Polak 2002; Mangili et al. 2007). The atherosclerotic plaques were defined as localized echo structures protruding from the vessel lumen. The plaque thickness between the media-adventitia interface and the lesion surface facing the lumen was measured at the site of maximal protrusion perpendicular to the vessel wall. Only lesions for which the thickness was ≥ 1 mm at either the right or left CCA were considered as carotid plaques (Zureik et al. 1999). One specialist performed the carotid and abdominal ultrasonography simultaneously, using a high-resolution real-time B-mode ultrasonography with a 10 MHz linear probe (LOGIQ 7®; GE Medical Systems, Milwaukee, WI, USA).

Laboratory measurements and data collection

Plasma glucose was determined using an enzymatic colorimetric assay (Hitachi, Tokyo, Japan) and insulin was measured by a radioimmunoassay kit (DAINABOT, Tokyo, Japan) after a 12-hour overnight fast. Homeostasis Model Assessments of Insulin Resistance (HOMA-IR) as a marker for insulin resistance was calculated according to the following formula: [fasting glucose (mmol/L) × fasting insulin (μU/mL)/22.5] (Matthews et al. 1985). Quantitative Insulin Sensitivity Check Index (QUICKI) as a marker for insulin sensitivity was calculated using the following formula: 1/[log(fasting insulin) (μU/mL) + log(fasting glucose) (mg/dL)] (Katz et al. 2000).

Age, gender, history of hypertension and DM, hepatitis B/C virus (HBV/HCV) seropositive status, nadir CD4+ T-cell counts, HIV-RNA viral load, CDC classification, fasting glucose and lipid profiles such as total cholesterol, triglycerides (TG), high-density lipoprotein (HDL) cholesterol, and low-density lipoprotein (LDL) cholesterol, known duration of HIV infection, and duration or regimens of HAART were collected by retrospective review of the medical records and laboratory results and these findings were included as covariates. All of the data for the fasting glucose/lipid profiles measured after HAART initiation and the HIV-RNA measured before HAART initiation were collected, and the mean values of each of them were calculated and included in the analyses. CDC classification at enrollment was evaluated according to the 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults published by CDC in 1992 (Centers for Disease Control and Prevention 1992). LDL cholesterol was calculated using the Friedewald formula, except in patients with TG levels higher than 400 mg/dL (Friedewald et al. 1972). HBV/HCV seropositive status was defined as the detection of HBs Ag or IgG antibodies to HCV (Telatela et al. 2007).

Statistical analysis

Normally distributed continuous variables by the Kolmogorov-Smirnov test were expressed as the mean ± S.D., whereas variables with a skewed distribution were represented as the median (interquartile range [IQR]). Categorical variables were reported by number (%). We have analyzed the effect of HAART on lipoatrophy with stratification of cumulative exposure duration into 0-12 months and more than 12 months in patients who received specific antiretroviral drugs at some point. The unpaired independent two sample *T*-test was used to compare the mean values of variables normally distributed between two independent groups. For variables with skewed distributions, we used the Mann-Whitney *U*-test. The chi-squared test was performed to analyse the differences in nominal variables between the groups. To identify the clinical factors independently associated with the diagnosis of lipoatrophy, a multivariate logistic regression analysis was performed with the covariates with a p-value < 0.10 in the univariate analysis. All of the covariates were simultaneously entered into the final logistic regression model. The results of the univariate and multivariate analyses were expressed as an odds ratio (OR) with a 95% confidence interval (CI). Statistical significance was determined as p-values < 0.05, and all of the reported p-values were two sided. All of the statistical analyses were performed using the SPSS software package version 13.0 (SPSS Inc., Chicago, IL, USA).

Results

Prevalence and clinical or metabolic characteristics of lipoatrophy

Among the total 144 HIV-infected patients, 35 (24.3%) were diagnosed with lipoatrophy. Waist circumference, WHR, BMI, total body fat mass, VAT, AFI, VSR, glucose, total cholesterol, TG, HDL/LDL cholesterol, QUICKI, and HOMA-IR levels did not show any significant differences between the groups with and without lipoatrophy. Also, there was no difference in the carotid IMT values, presence of carotid atherosclerotic plaques, or the duration of HIV infection between the two groups (Table 1).

Clinical Factors associated with the diagnosis of lipoatrophy

The prevalence of lipoatrophy in females or groups with DM was significantly higher than in males or those without DM (83.3% vs. 21.7%; OR, 18.00; 95% CI, 2.03-160.00; $p = 0.010$ or 66.7% vs. 22.5%; OR, 6.93; 95% CI, 1.21-39.71; $p = 0.030$, respectively). Patients with higher total cholesterol levels were also more likely to have lipoatrophy than those with total cholesterol levels lower than the median value (31.9% vs. 16.7%; OR, 2.35; 95% CI, 1.06-5.19; $p = 0.035$). However, age, nadir CD4+ T-cell count, HIV-RNA before HAART, CDC classification, history of hypertension, HBV/HCV seropositive status, duration of HIV infection, glucose, TG, HDL/LDL cholesterol levels did not result in any significant differences in the lipoatrophy prevalence. In the HAART analysis, the prevalence of lipoatrophy in patients who had received stavudine (d4T) for > 12 months was significantly higher than in patients who had never received d4T (50.0% vs. 16.5%; OR, 5.06; 95% CI, 2.09-12.26; $p < 0.001$). However, the prevalence of lipoatrophy was not different between the patients with a history of zidovudine (AZT) treatment for > 12 months and those who had never received AZT (20.3% vs. 24.4%, OR, 0.79; 95% CI, 0.32-1.90; $p = 0.594$). Also, the total duration of HAART, history or cumulative duration of didanosine (ddI), non-nucleoside reverse transcriptase inhibitors (NNRTIs), or protease inhibitors (PIs) use did not affect the prevalence of lipoatrophy (Table 2).

In the multivariate logistic regression analysis, the female (OR, 24.93; 95% CI, 2.25-276.49; $p = 0.009$) and

Table 1. Characteristics of total study participants and a comparison of the clinical and metabolic characteristics between the groups according to the presence of lipoatrophy.

Variables	Total (N = 144)	Lipoatrophy		
		Yes (N = 35)	No (N = 109)	p-value
Waist circumference (cm)	83.0 ± 7.3	82.6 ± 7.0	83.1 ± 7.5	0.782[a]
WHR	0.86 ± 0.05	0.86 ± 0.04	0.86 ± 0.05	0.940[a]
BMI (kg/m^2)	23.2 ± 2.9	23.1 ± 2.5	23.2 ± 3.0	0.829[a]
Total body fat mass (kg)	13.7 ± 5.5	13.8 ± 4.6	13.7 ± 5.8	0.896[a]
VAT (cm^2)	90.0 ± 22.3	87.0 ± 23.3	90.3 ± 22.1	0.459[a]
Abdominal wall fat index	1.20 (0.77 - 1.90)	1.21 (0.72 - 2.14)	1.18 (0.77 - 1.85)	0.927[b]
VSR	2.97 (1.98 - 3.98)	3.17 (2.12 - 4.36)	2.90 (1.94 - 3.90)	0.168[b]
Fasting glucose* (mg/dL)	96.8 (91.8 - 102.0)	97.7 (91.0 - 104.4)	96.6 (91.8 - 102.0)	0.534[b]
Total cholesterol* (mg/dL)	172.1 ± 31.6	180.8 ± 31.1	169.3 ± 31.3	0.060[a]
Triglycerides* (mg/dL)	205.0 (149.1 - 306.2)	222.6 (167.3 - 347.5)	195.6 (147.3 - 303.3)	0.195[b]
HDL cholesterol* (mg/dL)	45.9 (40.1 - 53.4)	45.8 (40.2 - 51.1)	46.0 (40.0 - 55.0)	0.887[b]
LDL cholesterol* (mg/dL)	77.8 ± 25.6	82.4 ± 28.2	76.3 ± 24.7	0.279[a]
QUICKI	0.32 ± 0.05	0.32 ± 0.04	0.32 ± 0.05	0.642[a]
HOMA-IR	3.63 (1.86 - 7.29)	3.41 (1.93 - 8.16)	3.71 (1.71 - 6.88)	0.658[b]
Carotid IMT (mm)	0.650 (0.600 - 0.740)	0.675 (0.610 - 0.770)	0.645 (0.593 - 0.738)	0.282[b]
Carotid atherosclerotic plaque, yes	34 (23.6)	11 (31.4)	23 (21.1)	0.211[c]
Known duration of HIV infection (months)	38.0 (22.1 - 70.5)	37.8 (27.3 - 71.5)	38.2 (19.4 - 69.7)	0.430[b]

Data are expressed as mean ± S.D., median (IQR) or number (percent). [a]Independent two sample T-test, [b]Mann-Whitney U test. [c]Chi-square test. *mean values of all data performed after HAART initiation. Abbreviations: WHR, waist-to-hip ratio; BMI, body mass index; VAT, visceral adipose tissue area; VSR, ratio of abdominal visceral to subcutaneous adipose tissue; HDL, high-density lipoprotein; LDL, low-density lipoprotein; QUICKI, Quantitative Insulin Sensitivity Check Index; HOMA-IR, Homeostasis Model Assessments of Insulin Resistance; IMT, intima-media thickness.

d4T use for > 12 months (OR, 3.67; 95% CI, 1.35-9.97; p = 0.011) were factors independently associated with the diagnosis of lipoatrophy (Table 3).

Discussion

This study revealed that the prevalence of lipoatrophy in HIV-infected Koreans receiving HAART is not uncommon and was within the range of that reported in other studies (Lichtenstein et al. 2001; Paton et al. 2002; Bacchetti et al. 2005; Jacobson et al. 2005; Pujari et al. 2005; Waters and Nelson 2007). The previous studies performed in single institute of Asia including South Korea, Singapore, India and Thailand reported the percentage of HIV-infected patients with peripheral fat loss as very wide range from 3.5% to 62.5% (Chang et al. 2002; Paton et al. 2002; Pujari et al. 2005; Chuapai et al. 2007). However, these reports did not analyze the detailed characteristics and risk factors focusing on only lipoatrophy. To our knowledge, this is the first report evaluating the prevalence and clinical risk factors of lipoatrophy in the East Asia region. Because there is no definitive accepted case definition for lipoatrophy, and because the various factors affecting the change of body fat including the regimens of HAART, especially thymidine analogue use, may be different in each study population, the prevalence and risk factors of lipoatrophy vary between reports and those revealed in several studies cannot be compared to each other (Waters and Nelson 2007). Therefore, the multinational, multicenter cohort study is warranted to assess the characteristics of lipoatrophy in patients living in the Asia.

The assessment of body fat changes can be measured by subjective or objective methods, but it is yet neither standardized nor uniformly accepted (Wierzbicki et al. 2008). In our study, we used a subjective case definition for lipoatrophy, which may be of some benefit to optimize the choice of treatment intervention on an individual patient basis (Wierzbicki et al. 2008), without having to take detailed measurements of body fat through dual energy X-ray absorptiometry (DEXA) or fat computer tomography (CT) scans. However, it is not easy that these techniques are routinely adopted for the diagnosis of lipoatrophy because of unavailability or high cost. Also, an objective case definition for HIV-associated lipodystrophy, which is not specific for lipoatrophy, has been developed and evaluated, but may not be amenable to use in a routine clinical setting, because it requires many inputs, including DEXA, CT and lipid test, and the scoring systems are complex (Law et al. 2006). Therefore, the diagnosis of lipoatrophy in usual clinical practice is often made from patient self-referral and through physical examination by clinicians; these are the methods that were applied in our clinical definition in this study.

In our study, we confirmed the strong effects of longer d4T use, but not AZT, on the development of lipoatrophy in HIV-infected Koreans, supporting several prior reports per-

Table 2. Univariate analyses for the variables associated with the diagnosis of lipoatrophy.

Variables	Total	Lipoatrophy	Univariate analysis	
	(*N* = 144)	Yes (*N* = 35)	OR (95% CI)	*p*-value
Age				
Median years (IQR)	41 (33 - 46)	41 (34 - 51)		
≤ 40 years*	71 (49.3)	16 (22.5)	—	—
> 40 years	73 (50.7)	19 (26.0)	1.21 (0.56 - 2.60)	0.625
Gender				
Male	138 (95.8)	30 (21.7)	—	—
Female	6 (4.2)	5 (83.3)	18.00 (2.03 - 160.00)	0.010
Diabetes mellitus				
No*	138 (95.8)	31 (22.5)	—	—
Yes	6 (4.2)	4 (66.7)	6.93 (1.21 - 39.71)	0.030
Hypertension				
No*	124 (86.1)	27 (21.8)	—	—
Yes	20 (13.9)	8 (40.0)	2.41 (0.89 - 6.52)	0.083
Hepatitis B virus seropositive status				
No*	109 (75.7)	27 (24.8)	—	—
Yes	9 (6.3)	1 (11.1)	0.38 (0.05 - 3.18)	0.371
Unknown	26 (18.1)	7 (26.9)	1.12 (0.42 - 2.95)	0.820
Hepatitis C virus seropositive status				
No*	100 (69.4)	23 (23.0)	—	—
Yes	1 (0.7)	0 (0.0)	—	—
Unknown	43 (29.9)	12 (27.9)	1.30 (0.58 - 2.92)	0.532
Nadir CD4+ T lymphocytes (cells/mm^3)				
Median (IQR)	155 (61 - 259)	209 (65 - 304)		
≤ median value*	72 (50.0)	14 (19.4)	—	—
> median value	72 (50.0)	21 (29.2)	1.71 (0.79 - 3.70)	0.176
Log[mean HIV-RNA before HAART initiation] (copies/mL)				
Median (IQR)	4.19 (3.52 - 4.81)	4.19 (3.36 - 4.83)		
≤ median value*	59 (41.0)	14 (23.7)	—	—
> median value	60 (41.7)	14 (23.3)	0.98 (0.42 - 2.28)	0.959
Not available	25 (17.4)	7 (28.0)	1.25 (0.43 - 3.61)	0.680
CDC classification at enrollment				
A*	41 (28.5)	11 (26.8)	—	—
B	46 (31.9)	11 (23.9)	0.86 (0.33 - 2.26)	0.755
C	57 (39.6)	13 (22.8)	0.81 (0.32 - 2.04)	0.648
Mean of glucose levels after HAART initiation (mg/dL)				
Median (IQR)	97 (92 - 102)	98 (91 - 104)		
≤ median value*	72 (50.0)	15 (20.8)	—	—
> median value	72 (50.0)	20 (27.8)	1.46 (0.68 - 3.15)	0.333
Mean of total cholesterol after HAART initiation (mg/dL)				
Median (IQR)	169 (150 - 188)	184 (151 - 204)		
≤ median value*	72 (50.0)	12 (16.7)	—	—
> median value	72 (50.0)	23 (31.9)	2.35 (1.06 - 5.19)	0.035
Mean of triglycerides after HAART initiation (mg/dL)				
Median (IQR)	205 (149 - 306)	223 (167 - 348)		
≤ median value*	68 (47.2)	12 (17.6)	—	—
> median value	65 (45.1)	21 (32.3)	2.23 (0.99 - 5.02)	0.053
Not evaluated	11 (7.6)	2 (18.2)	1.04 (0.20 - 5.42)	0.966
Mean of HDL cholesterol after HAART initiation (mg/dL)				
Median (IQR)	46 (40 - 53)	46 (40 - 51)		
≤ median value*	66 (45.8)	17 (25.8)	—	—
> median value	66 (45.8)	16 (24.2)	0.92 (0.42 - 2.03)	0.841
Not evaluated	12 (8.3)	2 (16.7)	0.58 (0.12 - 2.90)	0.504

Table 2. Continued

Variables	Total	Lipoatrophy	Univariate analysis	
	(*N* = 144)	Yes (*N* = 35)	OR (95% CI)	*p*-value
Mean of LDL cholesterol after HAART initiation (mg/dL)				
Median (IQR)	78 (59 - 93)	80 (67 - 105)		
≤ median value*	57 (39.6)	12 (21.1)	—	—
> median value	56 (38.9)	15 (26.8)	1.37 (0.58 - 3.27)	0.476
Not evaluated	31 (21.5)	8 (25.8)	1.30 (0.47 - 3.64)	0.612
Known duration of HIV infection				
Median months (IQR)	38.0 (22.1 - 70.5)	37.8 (27.3 - 71.5)		
≤ median value*	72 (50.0)	16 (22.2)	—	—
> median value	72 (50.0)	19 (26.4)	1.26 (0.59 - 2.69)	0.560
Total duration of HAART				
Median days (IQR)	835 (439 - 1544)	957 (668 - 1833)		
≤ 2 yr*	63 (43.8)	11 (17.5)	—	—
2-4 yr	43 (29.9)	13 (30.2)	2.05 (0.82 - 5.14)	0.127
> 4 yr	38 (26.4)	11 (28.9)	1.93 (0.74 - 5.01)	0.179
Stavudine treatment				
Median days of cumulative exposure (IQR)	0 (0 - 165)	33 (0 - 826)		
Never received*	103 (71.5)	17 (16.5)	—	—
Received at some point				
0-12 month	11 (7.6)	3 (27.3)	1.90 (0.46 - 7.89)	0.379
> 12 month	30 (20.8)	15 (50.0)	5.06 (2.09 - 12.26)	< 0.001
Zidovudine treatment				
Median days of cumulative exposure (IQR)	431 (0 - 839)	249 (0 - 952)		
Never received*	45 (31.3)	11 (24.4)	—	—
Received at some point				
0-12 month	25 (17.4)	9 (36.0)	1.74 (0.60 - 5.03)	0.308
> 12 month	74 (51.4)	15 (20.3)	0.79 (0.32 - 1.90)	0.594
Didanosine treatment				
Median days of cumulative exposure (IQR)	0 (0 - 317)	0 (0 - 138)		
Never received*	81 (56.3)	22 (27.2)	—	—
Received at some point				
0-12 month	30 (20.8)	6 (20.0)	0.67 (0.24 - 1.86)	0.442
> 12 month	33 (22.9)	7 (21.2)	0.72 (0.27 - 1.90)	0.509
NNRTI-based HAART				
Median days (IQR)	0 (0 - 463)	0 (0 - 684)		
Never received*	73 (50.7)	18 (24.7)	—	—
Received at some point				
0-12 month	28 (19.4)	4 (14.3)	0.51 (0.16 - 1.67)	0.264
> 12 month	43 (29.9)	13 (30.2)	1.32 (0.57 - 3.07)	0.513
PI-based HAART				
Median days (IQR)	582 (2 - 1175)	747 (69 - 1453)		
Never received*	36 (25.0)	5 (13.9)	—	—
Received at some point				
0-12 month	22 (15.3)	6 (27.3)	2.33 (0.61 - 8.80)	0.214
> 12 month	86 (59.7)	24 (27.9)	2.40 (0.84 - 6.90)	0.104

Data are expressed as mean ± S.D., median (IQR) or number (percent). *Reference category Abbreviations: IQR, interquartile range; OR, odds ratio; CI, confidential interval; CDC, the Centers for Disease Control and Prevention; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor

formed in various populations (Saint-Marc et al. 1999; Wohl et al. 2006; van Griensven et al. 2007; Waters and Nelson 2007; Brown 2008). In general, lipoatrophy is clearly linked with HAART, and is especially strongly associated with the use of d4T, and is more likely to improve upon treatment regimen change (Grinspoon and Carr 2005; Pujari et al. 2005; van Griensven et al. 2007; Waters and Nelson 2007; Wierzbicki et al. 2008). Stavudine is known as the

Table 3. Multivariate logistic regression analysis to identify the factors independently associated with the diagnosis of lipoatrophy.

Covariate	Adjusted OR (95% CI)	*p*-value
Female	24.93 (2.25 - 276.49)	0.009
Diabetes mellitus	5.69 (0.83 - 39.01)	0.077
Hypertension	1.65 (0.51 - 5.32)	0.406
Mean of total cholesterol after HAART initiation		
≤ median value*	1.00	–
> median value	1.35 (0.54 - 3.41)	0.521
Mean of triglycerides after HAART initiation		
≤ median value*	1.00	–
> median value	2.11 (0.78 - 5.70)	0.141
Not evaluated	1.57 (0.26 - 9.57)	0.626
Stavudine treatment		
Never received*	1.00	–
Received at some point		
0-12 months	2.40 (0.51 - 11.32)	0.267
> 12 months	3.67 (1.35 - 9.97)	0.011

*Reference category. Abbreviations: OR, odds ratio; CI, confidential interval

antiretroviral drug with the strongest effects on mitochondrial activity, insulin resistance, and adipocyte growth, which are closely associated with the mechanisms of HIV-associated lipoatrophy (Waters and Nelson 2007; Mallewa et al. 2008; Wierzbicki et al. 2008). Stopping d4T treatment or switching to another non-thymidine analogue nucleoside reverse transcriptase inhibitors such as abacavir or tenofovir resulted in a significant gain of peripheral fat mass (Sutinen 2005; Wierzbicki et al. 2008).

The several other known risk factors for lipoatrophy, such as older age, longer durations of HAART, and low CD4/high viral load were not associated with the presentation of lipoatrophy in this study (Waters and Nelson 2007). The AIDS Clinical Trials Group (ACTG) A5142 study recently revealed that lipoatrophy was more frequent with efavirenz than ritonavir-boosted lopinavir when combined with d4T or AZT (Haubrich et al. 2009). However, we did not find any associations between the diagnosis of lipoatrophy and PI or NNRTI use.

In a final model, the female was also an independent factor associated with the diagnosis of lipoatrophy. Galli et al. (2002) reported that the risk of developing body habitus changes was significantly higher in female patients, as found in our data, even if the number of female patients was very small in this study. Further study in a larger cohort will be needed to prove the association of female with the development of lipoatrophy in East Asia region.

In our results, there were no differences in the anthropometric or ultrasonographic parameters, insulin resistance assessed by HOMA-IR/QUICKI, fasting glucose/lipid profiles, and carotid IMT values or plaque between the patients with and without lipoatrophy. Although it is usually known that lipodystrophy is associated with other metabolic abnormalities, only a portion of patients with lipodystrophy have other metabolic complications, while some HIV-infected subjects receiving HAART have metabolic syndrome and/or insulin resistance without having lipodystrophy (Chen et al. 2002; Bergersen et al. 2006; Wierzbicki et al. 2008). Therefore, it may be postulated that metabolic abnormalities occurred before the obvious development of lipoatrophy in some patients (Chen et al. 2002).

There are some limitations in our study. First of all, the more detailed investigations for the objective quantification of the subcutaneous fat mass such as DEXA, fat CT or MRI were not performed. These tools may be especially useful for the early detection and prevention of subclinical lipoatrophy in patients with the risk factors associated with lipoatrophy (Sutinen 2005). Also, the baseline BMI and severity of lipoatrophy were not evaluated. Because this was not a longitudinal, but a cross-sectional study, the causal relationships for the development of lipoatrophy could not truly be determined.

In spite of these limitations, this study was able to emphasize the clinical factors associated with the detection of lipoatrophy in HIV-infected Koreans receiving HAART. Because the recovery process of lipoatrophy after the modification of HAART may be much slower than originally anticipated, prevention of the development of lipoatrophy will be more important (Sutinen 2005). The data also suggest that lipoatrophy will be easier to revert if d4T is replaced before severe lipoatrophy has developed (Sutinen 2005). Therefore, careful observation should be maintained for the early detection of lipoatrophy or subclinical body fat changes in patients with the factors associated with lipoatrophy, especially longer use of d4T.

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