Pilot Study

Lipodystrophy and Dyslipidemia in Human Immunodeficiency Virus-Infected Thai Patients receiving Antiretroviral Therapy

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Background: *Lipodystrophy and dyslipidemia are increasing problems in HIV-infected patients receiving antiretroviral therapy (ART).*

Objective: *Determine the prevalence and predicting factors for lipodystrophy and dyslipidemia in these patients.*

Material and Method: *A cross-sectional study was performed on HIV-infected patients receiving ART in January 2006. Clinical assessment for lipodystrophy and blood tests for lipid profile were obtained.*

Results: *There were 56 patients with a mean age of 42.3 years and 71.4% were male. Lipodystrophy was detected in 66.1%. Baseline characteristics between patients with and without lipodystrophy were similar except for age, history of receiving d4T and undetectable HIV-RNA (p < 0.05). There was a high prevalence of dyslipidemia (53.6%). By logistic regression, undetectable HIV-RNA (odds ratio (OR) 6.4, p = 0.016) and receiving d4T (OR 7.4, p = 0.022) are predicting factors for lipodystrophy.*

Conclusion: *Lipodystrophy and dyslipidemia in HIV-infected Thai patients receiving ART are common. Clinical monitoring for these abnormalities during ART is highly recommended.*

Keywords: *Lipodystrophy, Dyslipidemia, HIV, Prevalence, Antiretroviral therapy*

Antiretroviral therapy (ART) has dramatically modified the natural history of HIV infection, leading to a significant reduction in morbidity and mortality and a better quality of life. Unfortunately, long-term toxicity from ART is becoming more and more recognized. A variety of metabolic abnormalities including dyslipidemia, abnormal fat redistribution (lipodystrophy), high blood pressure, diabetes mellitus, and insulin resistance have been associated with this therapy[1-8]. Recent studies have suggested that HIV-infected patients treated with ART could present a risk for cardiovascular disease[9,10]. Some of the metabolic complications from HAART may play roles for this problem.

Previous cross-sectional epidemiological studies have reported a wide variable prevalence of lipodystrophy ranging from 5% to 83%[1-8]. A previous study in Thailand determined a prevalence of lipodystrophy in HIV-infected Thai patients at 17%[11]. However, the study mentioned study was conducted in the year 2001-2002 when ART was less accessible than in the current situation and the study included patients who either did or did not receive ART. Thus, the prevalence from the study may not represent the prevalence of lipodystrophy in patients receiving ART. In addition, the study did not demonstrate the predicting factors of lipodystrophy in HIV-infected Thai patients.

The present study aimed to determine the prevalence, clinical characteristics, and predicting factors of lipodystrophy and dyslipidemia in HIV-infected Thai patients receiving ART.

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Table 1. Clinical characteristics of 56 HIV-infected patients

Characteristics	Number of patients (%) (n = 56)
Age, years, mean $\pm$ SD	42.3 $\pm$ 8.6
Gender: Male	40 (71.4%)
Female	16 (28.6%)
Body weight, Kgs, mean $\pm$ SD	60.8 $\pm$ 11.9
Height, Kgs, mean $\pm$ SD	1.65 $\pm$ 0.07
Body mass index, Kgs/M^2, mean $\pm$ SD	22.2 $\pm$ 3.7
Waist/hip ratio, mean $\pm$ SD	0.9 $\pm$ 0.1
HIV acquired from: Sexual transmission	45 (80.4%)
IVDU	2 (3.5%)
Unknown	9 (16.1%)
Duration of HIV infection, months, mean $\pm$ SD	72.9 $\pm$ 42.1
History of opportunistic infections	18 (32.1%)
Duration of ART, months, mean $\pm$ SD	46.3 $\pm$ 36.5
History of d4T	43 (76.8%)
History of NNRTIs	46 (82.1%)
History of PIs	10 (17.9%)
Current ART regimens	
NNRTI-based ART	41 (73.2%)
PI-based ART	10 (17.9%)
Others	5 (8.9%)
Systolic blood pressure, mmHg, mean $\pm$ SD	130.3 $\pm$ 17.4
Diastolic blood pressure, mmHg, mean $\pm$ SD	79.8 $\pm$ 11.7
CD4 cell counts, cells/mm^3, mean $\pm$ SD	354.0 $\pm$ 219.0
HIV RNA, copies/mL, median (range)	<50 (<50-488000)
Patients with HIV RNA < 50 copies/mL	34/51 (66.7%)

Material and Method

Study design

A cross-sectional study was carried out in HIV-infected patients being cared for at the Infectious Disease Clinic of Ramathibodi Hospital in January 2006. Inclusion criteria were as follows: 1) age of 15 years old or older, 2) on ART and 3) had signed informed consent. Exclusion criteria included 1) known dyslipidemia prior to ART, 2) discontinuation of ART, 3) denied informed consent. All participants were evaluated by the investigators after giving their informed consent.

The data including age, sex, HIV exposure, duration of HIV infection, previous opportunistic infections, history of previous ART, current ART regimen, duration of ART, current CD4 cell counts and HIV RNA and the results of previous serum lipid profile prior to ART were reviewed and collected.

Measurements and Definitions

Lipodystrophy was defined by a change in body fat distribution reported by the patients and assessed by the same investigator (YC) who was trained

for this assessment. This approach has its limits but there was a good correlation between patients' reports and investigator's assessment. In view of the intrinsic limits of the method, the authors employed the following definitions:

Lipodystrophy: at least one morphological alteration in one of the following sites: face, dorsocervical, breasts, abdomen, buttocks, and extremities.

Lipoatrophy (fat wasting): at least one sign of atrophy of adipose tissue on the face, buttocks, or extremities.

Lipohypertrophy (fat accumulation): at least one sign of hypertrophy of adipose tissue on the abdomen, dorsocervical, or breasts.

The presence of lipodystrophy was independently checked by the patients and the investigator. Patients had completed a lipodystrophy-specific questionnaire and underwent a lipodystrophy-specific physical examination by the investigator (data collection forms available from investigator). Before the present study, the investigator underwent training to ensure standardization of the physical examination. Patients and investigators independently recorded any

Table 2. Characteristics of patients with and without lipodystrophy (LD)

Characteristics	LD (n = 37) No. (%)	No LD (n = 19) No. (%)	p-value
Age, years, mean $\pm$ SD	44.4 $\pm$ 8.0	38.2 $\pm$ 8.5	0.010
Gender: Male	28	12	0.326
Female	9	7	
Body mass index, Kgs/M^2, mean $\pm$ SD	21.9 $\pm$ 3.7	23.0 $\pm$ 3.8	0.427
Waist/hip ratio, mean $\pm$ SD	0.9 $\pm$ 0.1	0.9 $\pm$ 0.1	0.713
Duration of HIV infection, months, mean $\pm$ SD	72.2 $\pm$ 37.9	74.2 $\pm$ 50.2	0.864
Duration of ART, months, mean $\pm$ SD	47.4 $\pm$ 32.8	44.2 $\pm$ 43.6	0.759
History of d4T, number (%)	33 (89.2%)	10 (52.6%)	0.006
History of NNRTIs, number (%)	29 (78.4%)	17 (89.5%)	0.467
History of PIs, number (%)	6 (16.2%)	4 (21.1%)	0.720
CD4 cell counts, cells/mm^3, mean $\pm$ SD	381 $\pm$ 221	298 $\pm$ 207	0.172
HIV RNA, copies/mL, median (range)	<50 (<50-204000)	400 (<50-488000)	<0.001
Patients with HIV RNA < 50 copies/mL	27/34	7/17	0.006
Triglyceride level > 200 mg/dl	21 (56.8%)	9 (47.4%)	0.505
Total cholesterol level $\geq$ 240mg/dl	12 (32.4%)	3 (15.8%)	0.220
LDL > 160mg/dl	10 (27%)	2 (10.5%)	0.180
HDL-C < 40 mg/dl	22 (59.5%)	14 (73.7%)	0.462

Table 3. Predicting factors for lipodystrophy (logistic regression)

Factors	Odds ratio	95%CI	p-value
Age	1.05	0.96-1.14	0.298
History of receiving d4T	7.39	1.34-40.82	0.022
Duration of ART	1.01	0.99-1.04	0.227
HIV RNA < 50 copies/mL	6.43	1.42-29.03	0.016

lipoatrophy or diffused fat accumulation in the following areas: face, dorsocervical (posterior lower neck), arms, breasts, abdomen, buttocks, arms, and legs. The degree of lipoatrophy or diffuse fat accumulation at any site was rated as absent (score of 0), mild (noticeable on close inspection, score of 1), moderate (readily noticeable by patient or physician, score of 2), or severe (readily noticeable to a casual observer, score of 3).

After questionnaire completion, all patients were examined to obtain anthropometric data including weight, height, body mass index, and waist to hip ratio. After the patient had rested for 10 minutes, arterial blood pressure was measured by the same investigator. The patients were appointed for the next visit to have their blood tests for lipid profile measuring the level of triglycerides (TG), total cholesterol (TC), high-density lipoprotein (HDL) cholesterol, and low-density lipoprotein (LDL) cholesterol.

The results of lipid profiles were interpreted according to the diagnostic criteria for lipid abnormalities by NCEP ATP III[12] as follows:

Triglycerides level (mg/dL):
<150	Normal
150-199	Borderline-high
>200	High
$\geq$500	Very high

Total Cholesterol level (mg/dL):
<200	Desirable
200-239	Borderline high
$\geq$240	High

LDL (mg/dL):
<100	Optimal
100-129	Near or above optimal
130-150	Borderline high
160-189	High
$\geq$190	Very high

HDL (mg/dL)
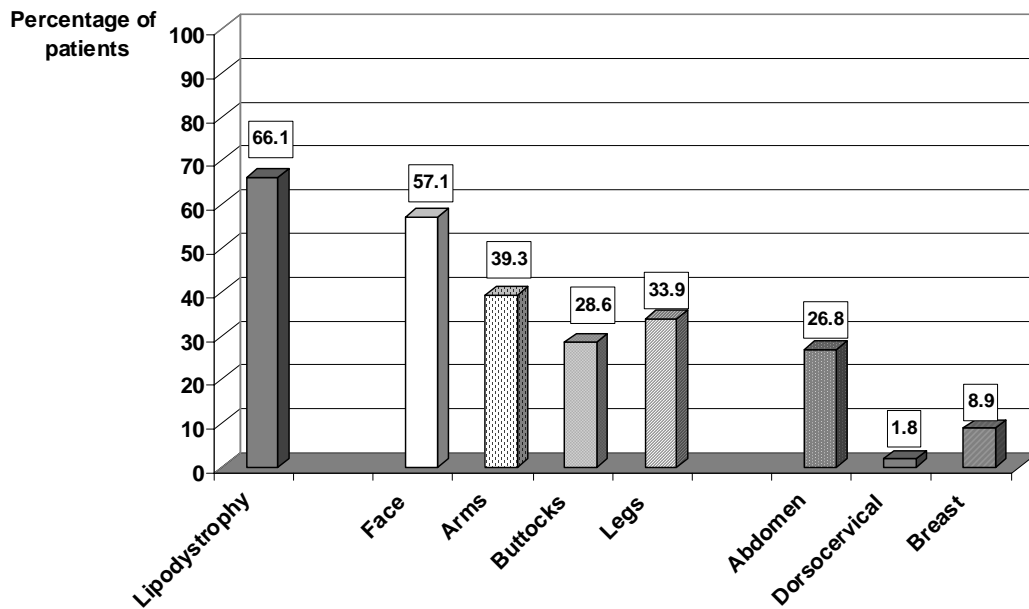|	
<40	Low
$\geq$60	High

Fig. 1 Prevalence of lipodystrophy assessed by investigator in HIV-infected Thai patients receiving ART (n = 56)
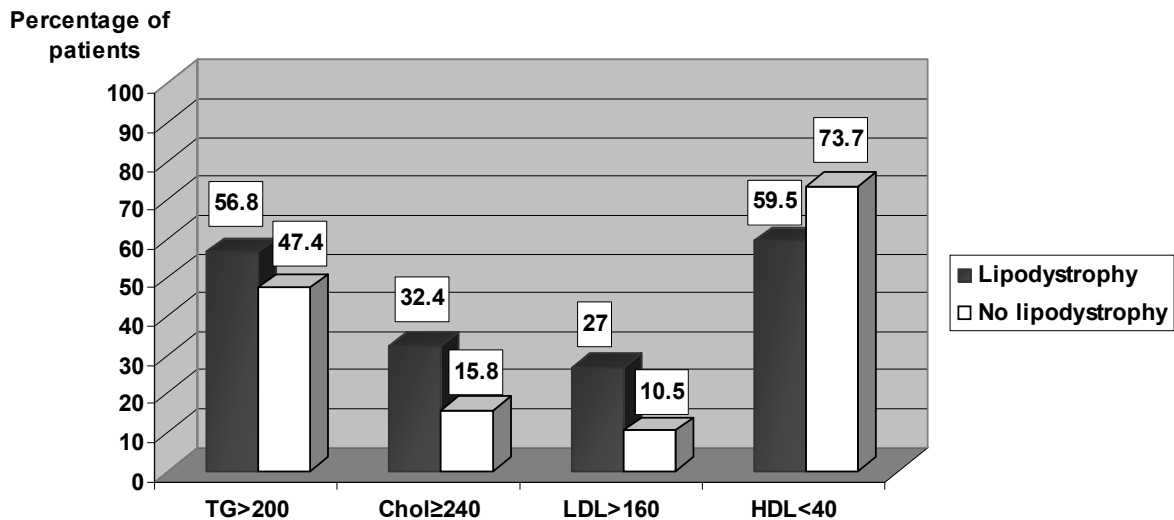

Fig. 2 Prevalence of dyslipidemia in HIV-infected Thai patients receiving ART with and without lipodystrophy (n = 56)

Statistical methods

Mean ($\pm$ standard deviation, SD), median (range) and frequencies (%) were used to describe the patients' characteristics. Chi-square test was used to compare categorical variables. Student's t test was performed to assess differences between two means. When the variables were not normally distributed, the Mann-Whitney U test was used instead. Logistic regression was used to determine the predicting factors for lipodystrophy and dyslipidemia. All analyses were performed using SPSS program version 12.0. A p-value less than 0.05 was considered statistically significant. The present study was approved by the Institution Review Board.

Results

There were 56 patients in the present study. Patients' baseline characteristics are described in Table 1. Of these, the mean ($\pm$ SD) age was 42.3 ± 8.6 years and 71.4% were males. Most patients (80.4%) had acquired HIV from sexual transmission. Mean cell count was 354 cells/mm^3 and 66.7% of the patients had undetectable HIV RNA.

The prevalence of lipodystrophy assessed by the investigator was 66.1%. Fat atrophy and abnormal fat accumulation were 62.5% and 30.4%, respectively (Fig. 1). Fat atrophy was frequently detected on the face (57.1%), arms (39.3%), legs (33.9%), and buttocks (28.6%), respectively. Baseline characteristics between patients with and without lipodystrophy are compared in Table 2. The baseline characteristics between the two groups were similar except for a history of receiving d4T ($p = 0.006$), undetectable HIV RNA (< 50 copies/mL) ($p = 0.006$) and age ($p = 0.01$) which was higher in patients with lipodystrophy. By logistic regression, undetectable HIV RNA (odds ratio (OR) 6.43 5 (95% CI $= 1.42$-29.03), $p = 0.016$) and history of receiving d4T (OR 7.39 (95% CI $= 1.34$-40.82), $p = 0.022$) were significantly predicting factors for lipodystrophy (Table 3).

There was a high prevalence of high triglycerides (53.6%), high total cholesterol (26.8%), high LDL-C (23.2%) and low HDL-C (66.1%). There was no significant difference of this prevalence between patients with and without lipodystrophy (Table 2, Fig. 2). By Pearson correlation, there was a significant correlation between serum triglycerides and total cholesterol ($r = 0.323$, $p = 0.015$), i.e. patients who had high triglycerides also had high total cholesterol.

Discussion

The most notable findings from the present study are the high prevalence of lipodystrophy and dyslipidemia in Thai HIV-infected patients receiving ART. The prevalence of lipodystrophy in the present study is much higher than that reported from a previous Thai study (66% versus 17%). As mentioned above, this previous Thai study included patients who either received or did not receive ART[11]. The other explanation for this difference is the fact that the authors conducted the present study in the year 2006 when d4T was widely used in the formulation of a fixed dose combination of d4T, 3TC, and nevirapine[13]. Three-fourths (77%) of the presented patients had a history of receiving d4T. Previous studies have established that the use of d4T is strongly associated with lipodystrophy[2,3]. The results from the present study also demonstrated that receiving d4T was an independent predicting factor for lipodystrophy with an OR of 7.4 (Table 3). This finding warrants caution of wide use d4T in Thailand. In the resource-limited settings, changing from d4T to AZT, ddI, or tenofovir in the nevirapine-based ART may be safer.

The authors also found that undetectable HIV RNA was independently associated with lipodystrophy, while the duration of ART was not. This could be explained by the fact that the effective ART and/or good adherence on ART might lead to the complete viral suppression and this adverse event. Nevertheless, this factor should be considered as an association rather than a risk factor for lipodystrophy. In the present study, patients with lipodystrophy were significantly older than those without lipodystrophy (Table 1). However, the authors could not demonstrate the association between age and lipodystrophy from logistic regression (Table 3).

Defining criteria of lipodystrophy is different among different studies[1-8,11]. Some defined lipodystrophy as metabolic and body shape changes, while others defined the term as only fat maldistribution. Computed tomography, nuclear magnetic imaging and dual-energy X-ray absorption (DEXA), are considered reliable methods to detect lipodystrophy[1-8]. However, these tests are too expensive and not affordable for most Thai patients. For HIV-infected Thai patients, subjective assessment by the patients and objective assessment by the physicians as in the present study may be suitable means for evaluating lipodystrophy.

The present study showed the high prevalence of dyslipidemia, which was concordant to the results from previous studies[1-8,11,13]. Although some studies reported the association of dyslipidemia and lipodystrophy[1], the authors could not demonstrate any difference of lipid profiles between patients with and without lipodystrophy. The authors did find the correlation between triglycerides and cholesterol levels.

The present study has some limitations. First, it is a cross-sectional study. As such, it cannot establish a causal relationship. The present study has a small, sample size due to the nature of a pilot study. The power of the study may not be enough to detect the association of age and lipodystrophy and the difference of lipid profiles between patients with and without lipodystrophy. Nevertheless, the results from the present study may provide clinical data for physicians who take care of HIV-infected patients.

In conclusion, the prevalence lipodystrophy and dyslipidemia in HIV-infected patients receiving

ART are high. Clinical monitoring for these abnormalities during ART is highly recommended. Clinicians should be aware of lipodystrophy and closely monitor it, particularly in patients with a history of receiving d4T or with undetectable HIV RNA. Future large-scaled study is needed to understand the prevalence and natural history of these abnormalities in Thailand.

Acknowledgement

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ความผิดปกติของการสะสมไขมันในร่างกายและภาวะไขมันในเลือดสูงในผู้ป่วยไทยที่ติดเชื้อเอชไอวีและได้รับยาต้านไวรัส

เยาวลักษณ์ เชื้อไผ่, ศศิโสภิณ เกียรติบูรณกุล, กำธร มาลาธรรม, สมนึก สังฆานุภาพ

ภูมิหลัง: *ความผิดปกติของการสะสมไขมันในร่างกายและภาวะไขมันในเลือดสูงกำลังเป็นปัญหาที่พบเพิ่มขึ้น ในผู้ป่วยไทยที่ติดเชื้อเอชไอวีและได้รับยาต้านไวรัส*

วัตถุประสงค์: *การศึกษานี้มีเป้าหมายที่จะประเมินความชุกและปัจจัยชี้นำของความผิดปกติของการสะสมไขมันในร่างกายและภาวะไขมันในเลือดสูงในผู้ป่วยเหล่านี้*

วัสดุและวิธีการ: *การศึกษาแบบตัดขวาง ศึกษาในผู้ป่วยติดเชื้อเอชไอวีที่รับการรักษาด้วยยาต้านไวรัส ในเดือนมกราคม พ.ศ. 2549 ดำเนินการประเมินทางคลินิกถึงความผิดปกติ ของการสะสมไขมันในร่างกายและตรวจเลือดหาภาวะไขมันในเลือดสูง*

ผลการศึกษา: *มีจำนวนผู้ป่วย 56 ราย อายุเฉลี่ย 42.3 ปี และร้อยละ 71.4 เป็นเพศชาย พบความผิดปกติของการสะสมไขมันในร่างกายร้อยละ 66.1 ลักษณะทางคลินิกพื้นฐานระหว่างกลุ่มที่มีและไม่มีความผิดปกติของการสะสมไขมันในร่างกายเหมือนกัน ยกเว้นอายุ ประวัติการได้รับยาดีโฟร์ที และการพบปริมาณไวรัสที่น้อยจนนับไม่ได้มีความชุกของภาวะไขมันในเลือดสูงมากถึงร้อยละ 53.6 การทดสอบโลจิสติก รีเกรสชัน พบว่าการได้รับยาดีโฟร์ที และการพบปริมาณไวรัสที่น้อยจนนับไม่ได้เป็นปัจจัยชี้นำของความผิดปกติของการสะสมไขมันในร่างกายอย่างมีนัยสำคัญทางสถิติ*

สรุป: *ความผิดปกติของการสะสมไขมันในร่างกายและตรวจเลือดหาภาวะไขมันในเลือดสูง เป็นภาวะที่พบบ่อยในผู้ป่วยไทยที่ติดเชื้อเอชไอวีและได้รับยาต้านไวรัส ควรมีการติดตามทางคลินิกเพื่อมองหาความผิดปกติเหล่านี้อย่างยิ่ง*