Prevalence of Lipodystrophy in Thai-HIV Infected Patients ✦

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To determine the prevalence and clinical characteristics of lipodystrophy in HIV-infected Thai patients, a cross-sectional study was performed on 278 HIV-infected patients at Bamrasnaradura Infectious Disease Institute. Laboratory data related to lipid and glucose metabolism were obtained from both patients who self reported fat maldistribution or diagnosed by a physician. The history of antiretroviral treatment and HIV infection were recorded. Prevalence of lipodystrophy found in the present study was 17%. Lipodystrophy was reported mostly on the face, buttock, legs, arms, and abdomen respectively. Two-thirds of these patients had mixed syndromes of fat accumulation and fat wasting and the others had only fat wasting. Ninety-three percent of lipodystrophic patients had at least 1 abnormality in either lipid or glucose metabolism. Eighty-eight percent had dyslipidemia, 21% had impaired glucose tolerance, 30% had insulin resistance and 27% had diabetes mellitus. Lipodystrophic patients have a high rate of lipid and glucose metabolism abnormalities which are the major risk factors for cardiovascular events.

Keyword : *Lipodystrophy syndromes, HIV infection, Antiretroviral drug, Adverse drug reaction, Prevalence*

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Lipodystrophy syndrome was first observed in patients receiving antiretroviral therapy in 1998[1-2]. Since then, it has been widespread and recognized as an important adverse event in HIV-infected patients. The syndrome is associated with the development of a group of metabolic and morphologic disorders. These include fat wasting in the face, arms, legs and buttocks; fat accumulation in the abdomen, dorsocervical region and breasts in women; as well as hyperlipidemia, hyperglycemia and insulin resistance[3-4]. Previous cross-sectional epidemiological studies have reported a wide variable prevalence ranging from 5% to 83%[5]. The methods of evaluating lipodystrophy in these studies were usually based on patient reports and physical examinations by physicians.

The etiology of lipodystrophy syndrome remains unresolved. Factors related to HIV disease, immune reconstitution and direct effect of antiretroviral agents may play a role in the development of this syndrome. Lipodystrophy was initially considered to be associated solely with PIs treatment[3,6-8], however, NRTIs were later postulated to be involved in the pathogenesis of lipodystrophy as well[9-14].

Several studies in other countries have reported the prevalence and described the characteristics of lipodystrophy. Most of these studies have focused on patients who were treated with antiretroviral drugs. There was no study about this syndrome in HIV-infected Thai patients. The purposes of this study were to estimate the prevalence, determine the clinical characteristics of lipodystrophy in HIV-infected Thai patients who either did or did not receive antiretroviral treatment and determine antiretroviral therapy patterns in these patients.

Patients and Method

The authors conducted a cross-sectional descriptive study at Bamrasnaradura Infectious

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Disease Institute. This study included HIV infected outpatients aged > 18 years who attended antiretroviral clinics from 15 November 2001 to 15 April 2002 and either did or did not receive treatment with antiretroviral drugs. Patients who had active AIDS-related disorders within three months of the first assessment and those receiving anabolic steroids, corticosteroids, or immune-modulating therapy were not eligible to participate in this study. Patients presenting with lipodystrophy syndrome who did not provide consent because they did not want to disclose their infection or whose OPD cards were not available were also excluded.

Lipodystrophic patients were defined by a change in body fat distribution reported by the patients during the interview done by the same researcher or by the physicians diagnosed in their OPD cards. If the patient had lipodystrophy, each body region would be assessed by both the patients and their physicians. Lipodystrophy was classified as fat accumulation (in three regions: abdomen, dorsocervical region and breasts in women) or fat wasting (in four regions: face, arms, buttocks and legs). The severity of lipodystrophy in each region was rated to a score of 0-3. Absence of these symptoms was given a score of 0; mild cases, noticeable on close inspection: a score of 1; moderate cases, readily noticeable by patient/physician: a score of 2; and severe cases, readily noticeable by a casual observer: a score of 3. Total score of each patient was then calculated by adding the scores of each region (except breasts) together. Total scores of 1-6, 7-12, 13-18 were defined as mild, moderate, and severe lipodystrophy, accordingly. As Carr A et al[3], the authors chose a patient-rated score in preference to a physician-rated score as a patient's assessment of the severity of a visible effect is more likely to influence treatment decision.

After questionnaire completion, all lipodystrophic patients were examined to obtain anthropometric data including weight, height, body mass index, and waist to hip ratio. Body fat composition was estimated by bioelectric impedance analysis. HIV-1 infection history and medical treatment history were also collected.

The patients were appointed for a next visit to have their glucose and lipid profile evaluated by measuring the level of fasting plasma glucose, triglyceride (TG), total cholesterol, high-density lipoprotein (HDL) cholesterol and fasting insulin. A standard 75-gm oral glucose tolerance test (OGTT) was also performed[15,16]. Low-density lipoprotein (LDL) cholesterol was calculated by total cholesterol-HDL cholesterol-(TG/5), except in patients with TG level > 400 mg/dl. Homeostasis model assessment (HOMA) index was calculated to assess insulin resistance by using the formula: fasting insulin (μIU/ml) x fasting plasma glucose (mmol/L)/ 22.5[17].

Patients were considered to have glucose abnormalities if their fasting plasma glucose was 110-125 mg/dl (impaired fasting glucose), 2-hour plasma glucose from OGTT 140-199 mg/dl (impaired glucose tolerance), diabetes (FPG > 126 and/or 2-hr-PG > 200 mg/dl), fasting insulin > 15 μIU/ml (hyperinsulinemia), or HOMA index > 4 (insulin resistance). They were considered to have lipid abnormalities if their fasting total cholesterol was > 214 mg/dl, fasting TG > 174 mg/dl, or HDL-cholesterol < 40 mg/dl[3].

Lipodystrophic patients were classified according to their physical features (fat accumulation, fat wasting and mixed syndromes), severity of lipodystrophy (mild, moderate and severe lipodystrophy) and antiretroviral treatment history (therapy na ve patients, patients treated without PIs, patients with duration of PIs treatment > 6 months and patients with duration of PIs treatment < 6 months).

Statistical analyses were performed using computerized statistical programs (SPSS version 10.07). Independent t-test and one-way ANOVA were used to compare mean between two and three groups of continuous variables. The chi-square test was used to evaluate the proportion between groups. A p-value of less than 0.05 was considered to be statistically significant. Kappa (K) was used to measure the agreement of lipodystrophy between the patients and the physicians.

Results

The study patients consisted of 166 men (60%) and 112 women (40%). Two hundred and fifteen patients (77%) had received antiretroviral treatment. Of 278 patients, lipodystrophy was diagnosed in 46 patients (17%). All of these patients had received antiretroviral agents. Seventeen patients (37%) had never received PIs, 23 patients (50%) had been treated with PIs > 6 months, and 6 patients (13%) had been treated with PIs < 6 months. None of the therapy-na ve patients had lipodystrophy. Therefore, the prevalence of lipodystrophy in antiretroviral-experienced patients was 21%. Lipodystrophy was found more frequently in men (19%) than in women (12.5%). The mean age of lipodystrophy patients

was 43.59 ± 10.59 years. The body mass index of these patients were in the normal ranges[26] (22.85 ± 2.62 kg/m^2 in male and 22.87 ± 3.75 kg/m^2 in female). The mean duration of HIV infection and of antiretroviral therapy was 59.93 ± 23.73 and 43.39 ± 17.38 months respectively. Most lipodystrophic patients had high CD4 cell counts and low viral loads at the time of the development of lipodystrophy. The mean CD4 cell count was 350 cells/mm^3 and three-fourths of the patients had an undetectable viral load (< 50 copies/ml).

As presented in Fig. 1, 22%, 56%, and 22% of lipodystrophic patients had started their antiretroviral treatment with monotherapy, double therapy, and HAART respectively. Up until the study time, 9 of 46 patients had never changed the antiretroviral regimens after their initial regimens were started. The average number of antiretroviral regimens administered to the other patients was 4 (range from 2 to 8 regimens). The major reasons for changing antiretroviral regimens were treatment failure, adverse effects and the cost of the antiretroviral drugs. During the time of the study, 87% of lipodystrophic patients received HAART, whereas 9% were given double therapy, 2% were taking monotherapy and 2% had stopped their antiretroviral treatment. One women developed lipodystrophy after she had stopped NRTI double therapy (ddI + d4T) for about 4 months. The HAART regimens mostly used among lipodystrophic patients were 2NRTIs plus NNRTI, PI or the third NRTI, as shown in Fig. 2.

Both the patient and physician assessments similarly showed that the majority of lipodystrophy was present in the face, followed by buttocks, legs, arms, abdomen and dorsocervical region, accordingly. Breast enlargement was reported in 20% of the lipodystrophic women. There were 28%, 54%, and 15% of the lipodystrophic patients who ranked their body changes as mild, moderate, and severe respectively, while physicians rated the severity of fat maldistribution of 60%, 20%, and 2% of the patients as mild, moderate, and severe respectively. One patient reported no fat distribution change but lipodystrophy was found upon physical examination. There were also 7 patients who reported themselves as having lipodystrophy but were found to have no significant body fat distribution changes from physical assessment. There was a poor agreement (K = 0.16) between the patients' and their physicians' assessment of lipodystrophy. Two-thirds of the

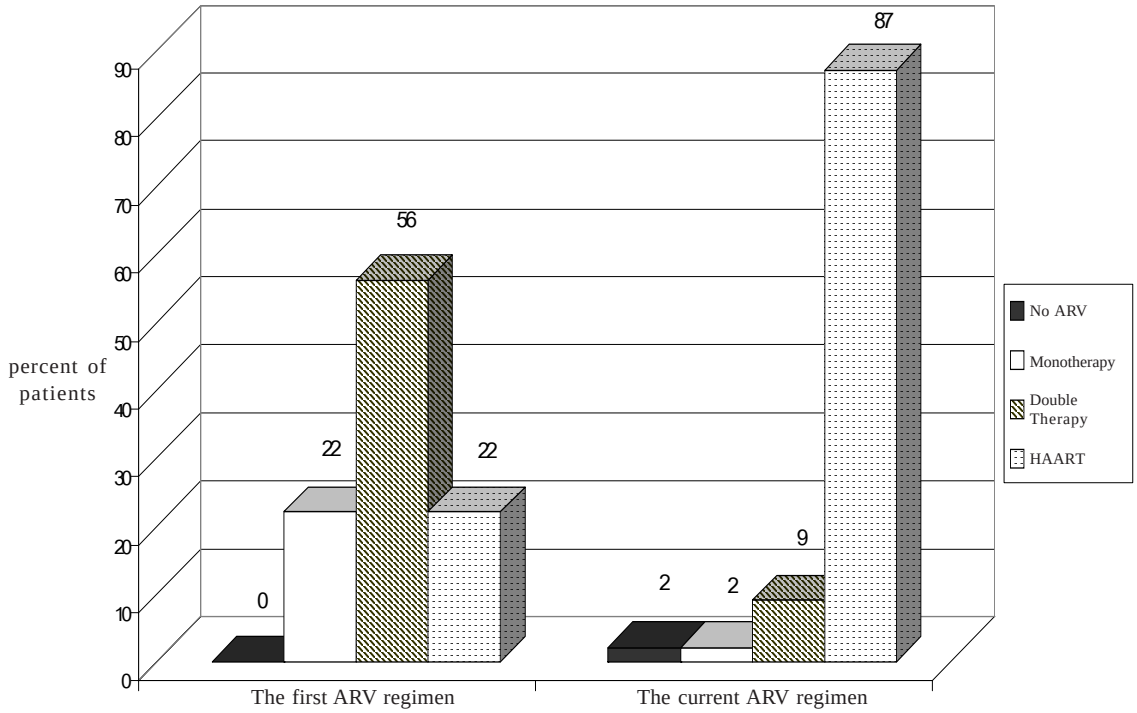

Fig. 1 Initial and current ARV regimens used in lipodystrophic patients

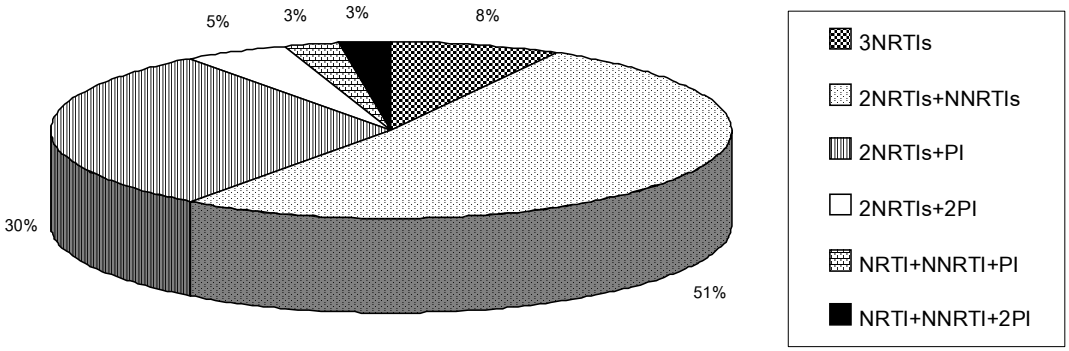

Fig. 2 HAART regimen in lipodystrophic patients

lipodystrophic patients evaluated themselves as having a mixed syndrome while the remainder found only fat wasting.

Anthropometric data, body fat composition and metabolic data were compared between fat wasting and the mixed syndrome group. Patients in the fat wasting group had less total body fat than the mixed syndrome group (10.87% and 19.03%, respectively; p = 0.003). No other statistically significant differences were found.

Ninety-three percent of lipodystrophic patients had at least one metabolic alteration as illustrated in Table 1. Lipid metabolism abnormalities occurred more frequently than did glucose abnormalities (88% and 52%, respectively). Lipid metabolism abnormalities were classified as elevated total cholesterol (56%), elevated triglyceride (67%), and decreased high density lipoprotein cholesterol (37%). Glucose abnormalities were categorized as impaired fasting glucose (12%), impaired glucose tolerance (21%), hyperinsulinemia (27%), insulin resistance (30%) and diabetes mellitus (27%).

Discussion

The prevalence of lipodystrophy in the present study was within the range of previous reports[3,5,14,18]. Estimates vary, possibly because of variation in methodology, lipodistrophy defining criteria, and patient populations. It is also probably due to the authors' inclusion of patients who either did or did not receive antiretroviral treatment and due to several patterns of antiretroviral combination given to these patients. Moreover, most patients did not observe the alterations or realize the importance of this syndrome because of lacking either knowledge or awareness of the syndrome. For example, some cases just found out they had buffalo hump at the time of interview.

Defining criteria of lipodystrophy vary among different studies[3,12,14,27,28]. Some defined lipodystrophy as metabolic and body shape changes, while others defined the term as only fat maldistribution. For HIV-infected Thai patients, subjective assessment and objective assessment as anthropometry are a suitable means for evaluating lipodystrophy in routine follow-up because other objective reference methods including computed tomography,

Table 1. Glucose and lipid metabolism abmormalities in lipodystrophic patients

Metabolic Abnormalities	No of patients (%)
Glucose abnormality	
FPG ≥ 110 mg/dl	14/42 (33%)
110 – 125 mg/dl (IFG)	5/42 (12%)
≥ 126 mg/dl (DM)	9/42 (21%)
2-hr PG > 140 mg/dl	14/34 (41%)
140-199 mg/dl (IGT)	7/34 (21%)
> 200 mg/dl (DM)	7/34 (21%)
Fasting insulin > 15 μIU/ml	10/37 (27%)
HOMA Index > 4 (IR)	11/37 (30%)
* At least 1 glucose abnormality	22/42 (52%)
Lipid abnormality	
Total cholesterol level ≥ 214 mg/dl	24/43 (56%)
≥ 200 mg/dl	29/43 (67%)
Triglyceride level ≥ 174 mg/dl	29/43 (67%)
≥ 200 mg/dl	28/43 (65%)
HDL cholesterol level < 40 mg/dl	16/43 (37%)
Total Chol ≥ 214 mg/dl and TG ≥ 174 mg/dl	19/43 (44%)
**At least 1 lipid abnormality	38/43 (88%)
> 1 metabolic abnormalities	40/43 (93%)

* At least 1 glucose abnormality: FPG ≥ 110 mg/dl or 2-hr-PG ≥ 140 mg/dl or fasting insulin > 15 μIU/ml or HOMA Index > 4

** At least 1 lipid abnormality: total cholesterol level ≥ 214 mg/dl or triglyceride level ≥ 174 mg/dl or HDL cholesterol level < 40 mg/dl 3

nuclear magnetic imaging and dual-energy X-ray absorption, are too expensive. In Australia, Carter VM et al determined the prevalence of lipodystrophy in a single population by using various criteria[12]. When objective assessments for determining body shape changes were applied, the prevalence of lipodystrophy in their patients was comparable to the present study.

In the present study, 2NRTIs plus NNRTI was the HAART regimen that had been used the most in lipodystrophic patients. It is a PI-sparing regimen that has advantages over PI therapy in some aspects. Adverse reactions and number of pills needed per day for this regimen are less than those of PI therapy. In addition, NNRTIs have been shown to have equivalent efficacy to PIs in randomized studies of treatment-na ve patients[19,20]. GPOvir®, A new local antiretroviral combination of three antiretroviral agents (d4T + 3TC + NVP) has been recently available in a tablet formulation. None of the presented patients used this combined medication because the product had not been launched into the market during the study period.

Findings in the present study are consistent with previous studies showing that NRTI may play a role in the occurrence of lipodystrophy and abnormalities can develop after cessation of antiviral therapy[21-25]. The authors found that some patients who had this syndrome had been receiving only NRTI in mono- or double- antiretroviral therapy. One patient developed lipodystrophy after discontinuation of NRTI therapy.

Facial fat wasting is one of the early signs of lipodystrophy that was observed in lipodystrophic patients in the present study. This was obvious when the authors compared the patients' faces before and after they started antiretroviral therapy, with their identity card or driving license photo. In contrast to previous researches[14,18], there were only two types of lipodystrophy found in the present study: fat wasting and mixed syndrome. None of the patients had isolated fat accumulation. The patients assessed their severity of fat maldistribution as being more severe than their doctors did.

Limitations of the present study are its cross-sectional design, use of subjective morphologic assessment of which the sensitivity of measurement is unknown, and potential for different evaluations among the four physicians.

Finally, evidence of fat maldistribution during antiretroviral treatment suggests abnormalities of glucose and lipid which are risk factors of coronary heart disease. Therefore, serum lipid and glucose monitoring should be performed every three to six months after a HAART regimen is started. More frequent monitoring may be needed in patients who have metabolic abnormalities prior to antiviral therapy.

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ความชุกของภาวะไขมันกระจายตัวผิดปกติในร่างกายผู้ป่วยไทยที่ติดเชื้อเอชไอวี

สุจิตรา พุทธวงศ์, วิศิษฏ์ ประสิทธิศิริกุล, สมฤทัย วัชราวิวัฒน์

การวิจัยนี้เป็นการศึกษา ณ จุดเวลาใดเวลาหนึ่งเพื่อหาความชุก และศึกษาลักษณะทางคลินิกของการเกิดความผิดปกติของการกระจายของไขมันในร่างกายผู้ป่วยไทยที่ติดเชื้อเอชไอวีจำนวน 278 ราย ณ สถาบันบำราศนราดูร โดยผู้ป่วยที่เกิดความผิดปกติของการกระจายของไขมันในร่างกายจะได้รับการตรวจวัดทางห้องปฏิบัติการที่เกี่ยวข้องกับเมตะบอลิสมของน้ำตาลและไขมัน ตลอดจนรวบรวมข้อมูลประวัติการติดเชื้อและการใช้ยาต้านเชื้อเอชไอวี ผลการศึกษาพบว่าร้อยละ 17 ของผู้ป่วยไทยที่ติดเชื้อ เอชไอวีมีความผิดปกติของการกระจายของไขมันในร่างกาย อวัยวะที่มีการกระจายของไขมันผิดปกติได้บ่อยที่สุด ได้แก่ ใบหน้า ก้น ขา แขน และท้อง ตามลำดับ พบผู้ป่วยที่มีลักษณะของการเกิดความผิดปกติของการกระจายของไขมันเป็นแบบ mixed syndrome เป็นสัดส่วน 2 ใน 3 ของผู้ป่วยที่เกิดความผิดปกติของการกระจายของไขมันทั้งหมด ส่วนที่เหลือมีลักษณะเป็นแบบ fat wasting พบว่าผู้ป่วยที่มีความผิดปกติของการกระจายของไขมันในร่างกายส่วนใหญ่ (ร้อยละ 93) มีความผิดปกติของเมตะบอลิสมของไขมันหรือน้ำตาลอย่างน้อย 1 อย่าง โดยพบว่า ร้อยละ 83 ของผู้ป่วยเหล่านี้ มีความผิดปกติของระดับไขมันในเลือด ร้อยละ 21 มีความผิดปกติของความคงทนต่อกลูโคส ร้อยละ 30 มีภาวะดื้อต่อการออกฤทธิ์ของอินสุลิน และร้อยละ 27 เป็นเบาหวาน แสดงให้เห็นว่าผู้ป่วยเหล่านี้มีอัตราการเกิดความผิดปกติของ เมตะบอลิสมของน้ำตาลและไขมันซึ่งเป็นปัจจัยเสี่ยงที่สำคัญของการเกิดโรคหลอดเลือดหัวใจสูงกว่าคนปกติ