

Early report

“Buffalo hump” in men with HIV-1 infection

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Summary

Background Enlargement of the dorsocervical fat pad (“buffalo hump”) has been reported in numerous HIV-1-infected patients. Some investigators have speculated that this finding is associated with protease-inhibitor treatment.

Methods Between June, 1995, and October, 1997, we studied eight HIV-1-infected men who had developed a buffalo hump while otherwise stable on antiretroviral therapy. Measurement of 24 h urinary free cortisol excretion and an overnight low-dose dexamethasone suppression test were done to screen for Cushing’s syndrome. In one patient, plasma cortisol concentrations were measured every 4 h for 24 h to assess the circadian rhythm of cortisol. Results of total and regional body-composition analysis by dual-energy X-ray absorptiometry, and glucose, cholesterol, triglyceride, and cortisol concentrations were compared with those obtained in a control population of 15 HIV-1-positive men whose age, body-mass index (BMI), and CD4-lymphocyte count were within the range of values in the eight study patients.

Findings The eight patients with a buffalo hump were clinically stable on various antiretroviral regimens, four of which included a protease inhibitor. No other signs of Cushing’s syndrome were observed, and plasma cortisol values did not differ significantly from those of controls. 24 h urinary free cortisol excretion was normal in seven patients and slightly raised in one (248 nmoles). In this patient, a repeat 24 h urinary free cortisol was 175 nmoles and plasma cortisol concentrations over 24 h showed a normal circadian pattern (nadir 83 nmol/L at 2400 h). All eight patients had normal suppression of cortisol values after dexamethasone 1 mg (plasma cortisol less than 83 nmol/L). When compared with HIV-1-positive controls, men with a buffalo hump had a significantly greater proportion of fat in the trunk region, suggesting central fat accumulation. Triglyceride but not cholesterol values were higher in the patients than in controls but this difference was not significant. Fasting glucose values did not differ significantly.

Interpretation The development of a buffalo hump cannot be attributed to hypercortisolism in these eight men. Furthermore, its occurrence is not unique to patients on protease inhibitors. Although the mechanism for

dorsocervical fat accumulation is unclear, we speculate that regional abnormalities in lipogenesis and lipolysis occur, possibly influenced by the hormonal and metabolic changes seen with HIV-1 infection and its treatment.

Lancet 1998; **351**: 867–70

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Introduction

The accumulation of adipose tissue in the dorsocervical region, commonly referred to as “buffalo hump”, is a typical finding in patients with glucocorticoid excess. Although benign, this disorder can lead to substantial disfigurement and so compromise quality of life. Recently, anecdotal reports of HIV-1-infected patients who developed a buffalo hump have appeared on the Internet (“Crix list”: <http://crix.pinkpage.com/>; accessed on March 9, 1998) and in the medical literature.^{1,2} The observation that enlargement of the dorsocervical fat pad occurred after initiation of combination antiretroviral therapy that included a protease inhibitor has led to the suggestion that the enlargement could be a consequence of protease-inhibitor therapy.

We report the results of studies done in eight HIV-1-positive men referred for investigation of a buffalo hump, four of whom were on triple antiretroviral regimens that included a protease inhibitor. Measurement of urinary free cortisol excretion and an overnight low-dose dexamethasone suppression test were done to screen for Cushing’s syndrome. In addition, total and regional body-composition analysis and measurements of lipids, glucose, and cortisol in these men were compared with those obtained in a control population of HIV-1-infected men without buffalo hump.

Methods*Patients*

We studied eight consecutive HIV-1-positive men referred to the Division of Endocrinology, San Francisco General Hospital, for investigation of dorsocervical-fat-pad enlargement between June, 1995, and October, 1997. 15 HIV-1-positive men without dorsocervical-fat-pad enlargement were selected as controls during the same period from a natural history cohort study conducted by our group. The controls were selected to be within the range of the age, body-mass index (BMI), and CD4-lymphocyte count of the eight study patients (table 1).

Measurements

All measurements were obtained under fasting conditions between 0800 h and 1100 h. Weight was measured on a calibrated scale with the participants wearing hospital gowns only. Total fat and lean body mass were measured by dual-energy X-ray absorptiometry (Lunar model DPX, Madison, WI, USA) with software version 3.6.³ In addition, estimates were made of the proportion of body fat in the trunk region. For this purpose, the trunk region was defined by an upper horizontal

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Patient	Age (years)	BMI (kg/m ²)	CD4 cell count (cells/ μ L)	Duration of buffalo hump (months)	Antiretroviral drugs
1	44	25.6	146	26	AZT, ddl
2	46	23.9	550	12	AZT, ddC
3	39	23.6	103	3	AZT
4	51	24.9	100	12	ddl
5	45	24.8	400	3	AZT, 3TC, IDV
6	61	24.6	288	1	AZT, ddl, IDV
7	43	22.4	460	1	3TC, DLV, NFV
8	40	28.0	190	1	ddl, 3TC, IDV

AZT= zidovudine; ddl= didanosine; ddC= zalcitabine; 3TC= lamivudine; IDV= indinavir; DLV= delavirdine; NFV= nelfinavir.

Table 1: Characteristics of patients with buffalo hump

border at the lower edge of the chin, lateral borders formed by vertical lines that bisected each axilla and that were oriented obliquely to include the waist, hip, buttock, and thigh tissue, and a lower border formed by the intersection of oblique lines extending from the level of the superior aspect of the iliac crest and passing through the hip joint. These markings allowed more precise delineation of the trunk region than the default software settings, which are based on skeletal rather than soft-tissue landmarks.

Laboratory measurements included serum glucose, cholesterol, and triglyceride concentrations, CD4 count, and plasma cortisol concentration. A 24 h urine collection was done for measurement of cortisol and creatinine excretion in the eight patients, and plasma cortisol was measured at 0800 h after administration of dexamethasone (1 mg) at 2300 h the previous evening. One of the patients (patient 1) had a circadian study in which plasma cortisol was measured every 4 h for 24 h in the General Clinical Research Center at San Francisco General Hospital. Cortisol was measured by a competitive binding assay.[†] Urine samples were assayed after isolation of cortisol by high-performance liquid chromatography.

Differences between patients and controls were analysed with Student's *t* test. Because triglyceride values were not normally distributed, we did a non-parametric analysis using the Mann-Whitney rank-sum test. A two-sided *p* value of 0.05 was the criterion for statistical significance.

Results

The clinical characteristics of the eight men with buffalo hump are shown in table 1. The mean time from diagnosis of HIV-1 infection was 9.6 (SD 3.7; range 5–15) years. All eight patients were on stable nucleoside-analogue therapy; four of these (patients 5–8) had started treatment with a protease inhibitor 2–18 months (median 7.5) before development of a buffalo hump. Patients 1–6 reported stable bodyweights. Patient 7 reported 7 kg weight loss due to colitis 4 months before the development of a buffalo hump, followed by a gain in weight back to baseline values. This weight gain coincided with initiation of nelfinavir, which was started 2 months before development of the buffalo hump. Patient 8 gained 18 kg weight over the first 8 months of indinavir treatment, then had stable bodyweight for the 3 months before development of a buffalo hump.

No other signs of Cushing's syndrome were evident in the patients. No patient had a history of taking appetite stimulants, anabolic hormones, or systemic glucocorticoids, except for patient 8 who took megestrol acetate (for 6 months) and testosterone (for 12 months) 3 years before a buffalo hump developed. Patient 4 had occasionally used dexamethasone mouthwash in the past, and patient 7 had started fluticasone propionate nasal spray (200 μ g daily) 3 months before our investigation. Patient 3 reported a similar buffalo hump in his father. Hump size varied among the patients, with the largest

	Glucose (mmol/L)	Cholesterol (mmol/L)	Triglyceride (mmol/L)	Cortisol (nmol/L)	Urinary free cortisol (nmol/24 h)
Patients					
1	4.4	2.7	1.7	422	248, 175*
2	5.3	4.6	5.2	386	34
3	4.4	5.9	13.1	102	56
4	5.3	4.3	1.6	303	52
5	3.5	4.4	3.0	155	39
6	5.7	6.1	2.8	317	91
7	4.5	5.8	4.2	157	50
8	5.9	5.4	5.1	97	47
Group summary†					
Patients (n=8)	4.9 (0.8)	4.9 (1.1)	4.6 (3.7)‡	243 (130)	
Controls (n=15)	4.9 (0.7)	4.8 (1.1)	2.4 (1.4)	295 (99)	

*Two urinary free cortisol measurements were done. †Group summary values are mean (SD). ‡*p*=0.07 compared with controls.

Table 2: Laboratory data

measuring 18 × 12 cm in patient 7 (figure 1). Fine-needle aspiration of the buffalo hump in patient 7 confirmed the presence of benign fatty stroma. Patient 1 had surgical removal of 350 g adipose tissue, with no subsequent recurrence of the buffalo hump.

The controls were similar to the patients with buffalo hump with respect to age (patients *vs* controls mean 46 [SD 7] *vs* 44 [5] years), BMI (24.7 [1.6] *vs* 25.0 [1.7] kg/m²), and CD4 count (280 [173] *vs* 261 [141] cells/ μ L). The mean time from diagnosis of HIV-1 infection was 10.9 (4.5; 3.5–17.5) years. Of the 15 controls, seven were on nucleoside-analogue therapy and eight were on combination antiretroviral regimens that included a protease inhibitor. Median duration of protease-inhibitor treatment in the control group was 4 months (range 1.5–12 months).

Fasting glucose values were similar in the two groups (table 2). Fasting triglyceride values were higher in the patients than in the controls but this difference was not



Figure 1: Enlargement of dorsocervical fat pad ("buffalo hump") in patient 7

The mass measured 18 x 12 cm and consisted of benign fatty stroma.

	Lean body mass/height (kg/m)	Total fat (%)	Trunk fat (%)
Patients			
1	33.3	22.3	57.0
2	30.5	17.5	60.8
3	32.0	16.4	68.2
4	34.0	21.4	55.9
5	35.7	13.7	66.7
6	32.3	16.9	73.9
7	31.7	13.5	70.1
8	38.4	19.7	69.9
Group summary*			
Patients (n=8)	33.5 (2.5)	17.7 (3.3)	65.3 (6.6)†
Controls (n=15)	34.0 (2.6)	18.0 (5.5)	56.8 (8.7)

Trunk fat is expressed as percentage of total fat.

*Group summary values are mean (SD).

†p=0.03 compared with controls.

Table 3: **Body composition data**

significant ($p=0.07$). Cholesterol values did not differ significantly between the groups.

The percentage of total body fat was similar in the two groups (table 3). Lean body mass was also similar in the two groups and did not differ significantly from the mean value in HIV-1-negative men (32.5 [3.4] kg/m) previously studied by our group with the same methods.⁵ Trunk fat, expressed as a percentage of total fat, was significantly greater in patients than in controls ($p=0.03$).

Basal morning cortisol values were within the normal range and did not differ significantly between the two groups (table 2). In the patients with buffalo hump, 24 h urinary free cortisol excretion was within the normal range (<166 nmoles) in seven of eight patients and raised in one patient (248 nmoles). In the latter patient, a repeat 24 h urinary free cortisol was 175 nmoles and measurement of plasma cortisol over 24 h confirmed normal circadian rhythmicity with a peak value of 422 nmol/L at 0800 h and nadir of 83 nmol/L at 2400 h. All patients had suppression of cortisol values to less than 83 nmol/L after administration of dexamethasone 1 mg (figure 2).

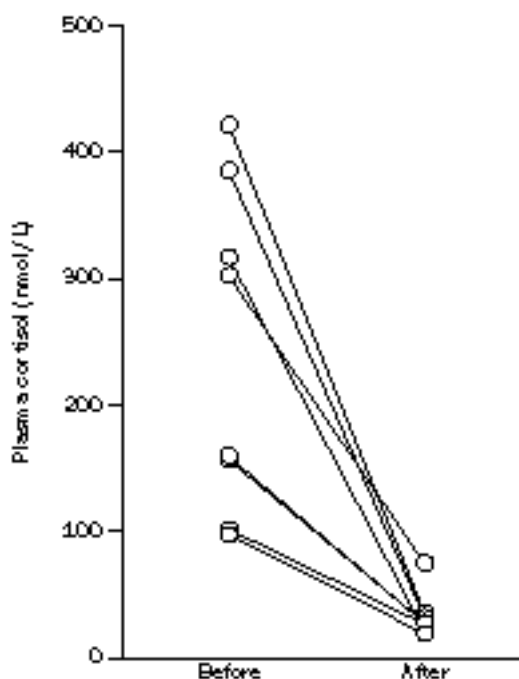


Figure 2: **Low-dose dexamethasone suppression test**
Plasma cortisol values before and after administration of dexamethasone 1 mg in eight patients with buffalo hump.

Discussion

We have excluded Cushing's syndrome as the cause of dorsocervical-fat-pad enlargement in the eight HIV-1-positive men reported here. All patients had a normal response to a low dose of dexamethasone, with suppression of plasma cortisol values to less than 83 nmol/L. These findings exclude Cushing's syndrome with more than 95% certainty.⁶⁻⁸ 24 h urinary free cortisol excretion, which is higher than normal in more than 90% of patients with Cushing's syndrome,⁹⁻¹¹ was within the normal range in seven patients and slightly raised in one patient. This patient had an appropriate diurnal variation in plasma cortisol. Loss of diurnal variation of plasma cortisol is another characteristic finding in Cushing's syndrome.¹⁰ The absence in these men of other features associated with Cushing's syndrome further supports our suggestion that the atypical pattern of fat distribution described here is not related to hypercortisolism per se. However, the tendency for central fat accumulation suggested by regional fat analysis is intriguing and may reflect an underlying metabolic abnormality similar to hypercortisolism—central obesity is one of the classic features of Cushing's syndrome.

The physical features typical of Cushing's syndrome include violaceous striae, muscle wasting, central obesity, and substantial fat deposition in the face, supraclavicular, and dorsocervical areas. Fat deposition in these areas is seldom found in individuals with normal cortisol values, whether they are obese or of normal weight.¹² The mechanism for dorsocervical-fat-pad enlargement in Cushing's syndrome remains unclear. Redistribution of body fat in such patients could be mediated by the lipid-accumulating effect of cortisol on adipocytes.¹³⁻¹⁵ Accordingly, regional variation in glucocorticoid-receptor density¹⁶ or differential metabolism of cortisol to cortisone in certain adipocytes¹⁷ could alter body-fat distribution, although the dorsocervical region has not been studied specifically. Glucocorticoid-mediated changes in insulin, sex-steroid, and growth-hormone concentrations may also have a role, because these hormones are known to affect adipocyte function.^{14,15,18} Alternatively, fat accumulation may simply reflect an increased number of fat cells by an as yet unknown mechanism.

The aetiology of buffalo hump in these HIV-1-infected individuals is unclear. Subclinical changes in endocrine and metabolic function could be occurring, which would affect regional lipogenesis and lipolysis. Subtle alterations in adrenocortical and gonadal function are frequently observed in HIV-1 infection, with mild increases in plasma cortisol values and decreases in sex steroid concentrations.¹⁹ These changes may contribute to abnormal body-fat topography, and further hormonal assessment, including the measurement of androgen concentrations, may be warranted in patients with buffalo hump. Whether the atypical accumulation of fatty tissue is directly related to HIV-1 infection or is a consequence of HIV-1-related therapy is also unknown. The fact that four of our patients with a buffalo hump had no history of protease-inhibitor use, however, indicates that the development of a buffalo hump is not unique to protease-inhibitor therapy.

Hypertriglyceridaemia has been reported previously in patients with HIV-1 infection and has been attributed both to a decrease in triglyceride clearance and increase in de-novo hepatic lipogenesis.^{20,21} The 15 HIV-1-positive controls in our study had a mean triglyceride

concentration of 2.4 mmol/L, which is roughly twice the normal mean value. The mechanism of the further increase in triglyceride values in patients with a buffalo hump is not certain, although a possible relation between increased triglyceride concentration and atypical body-fat distribution should be considered. For example, central fat accumulation may lead to the metabolic syndrome of insulin resistance, hypertriglyceridaemia, and hypertension, if the major component gained is visceral fat.^{22,23} Further studies are needed to clarify the hormonal and metabolic changes in these patients, with consideration of specific imaging to quantify the relative distribution of visceral and subcutaneous adipose tissue in the abdominal region.

In conclusion, we report the development of a buffalo hump in eight HIV-1-infected men. Although there are several natural history cohort studies and large trials of antiretroviral treatments, to our knowledge, the recognition of dorsocervical-fat-pad enlargement has been limited to anecdotal reports.^{1,2} The incidence and prevalence of this disorder are not known and cannot be inferred from these reports or from our limited data. Further studies are needed to define the epidemiology, pathophysiology, associated metabolic abnormalities, and potential treatment of dorsocervical-fat-pad enlargement in patients with HIV-1 infection.

Contributors

All researchers participated in the clinical investigation of the study participants, data collection, and analysis. Joan Lo and Morris Schambelan conducted the endocrinological assessment of the patients. Kathleen Mulligan, Viva Tai, and Heather Algren managed the natural history cohort and did the analyses of body composition. Kathleen Mulligan and Joan Lo did the statistical analyses. Joan Lo, Kathleen Mulligan, and Morris Schambelan prepared the paper. All investigators reviewed and approved the final version before submission.

Acknowledgments

The study was supported by a grant from the US National Institute of Diabetes and Digestive and Kidney Diseases (DK45833) and was conducted in the General Clinical Research Center (RR-83) at San Francisco General Hospital with support by the Division of Research Resources of the National Institutes of Health.

We thank S Deeks, J Engelman, J Lalezari, M Lippe, P McGraw, W Owen Jr, M Poscher, and M Roland for their referral of patients with buffalo hump.

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