

# Elevated blood pressure in subjects with lipodystrophy

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**Objectives:** To assess the prevalence of elevated blood pressure in patients with lipodystrophy.

**Design:** Case-control study.

**Participants:** Forty-two patients with abnormal body fat (100%) and serum lipids (86%) (HIV-positive cohort) were matched by age and sex to 42 HIV-positive controls without previously diagnosed lipodystrophy and to 13 HIV-negative controls.

**Setting:** Tertiary care, university-based, fully dedicated HIV clinic.

**Main outcome measures:** Frequency and magnitude of elevated blood pressure during highly active antiretroviral therapy.

**Results:** There were  $23 \pm 16$  and  $22 \pm 12$  blood pressure measurements recorded per subject over  $21 \pm 11$  and  $22 \pm 11$  months for the HIV-positive cohort and HIV-positive controls, respectively. Three or more elevated readings occurred in 74% of the cohort and in 48% of the HIV-positive controls ( $P = 0.01$ ) and accounted for  $38 \pm 25\%$  versus  $22 \pm 26\%$  ( $P = 0.01$ ) of the total readings, respectively. The average of the three highest systolic readings ( $153 \pm 17$  versus  $144 \pm 15$  mmHg;  $P = 0.01$ ) and diastolic readings ( $92 \pm 10$  versus  $87 \pm 9$  mmHg;  $P = 0.01$ ) was greater for the cohort than for the HIV-positive controls. Family history of hypertension was more common in the cohort than in the controls but accounted for only 13% of the log odds ratio value for elevated blood pressure in the cohort. Systolic blood pressure was correlated with waist-to-hip ratios in the cohort ( $r, 0.45$ ;  $P = 0.003$ ) but not in the HIV controls ( $r, 0.06$ ;  $P = 0.68$ ) and tended to be related to fasting triglycerides ( $r, 0.34$ ;  $P = 0.052$ ) in subjects with HIV.

**Conclusions:** Elevated blood pressure may be linked to the metabolic disorders occurring in patients with HIV, as in the dysmetabolic syndrome.

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**Keywords:** Abdominal obesity, elevated blood pressure, fat accumulation, hypertension, lipodystrophy, metabolism, serum lipids

## Introduction

In 1988, Reaven described a constellation of findings including abdominal obesity, hypertension, elevated serum triglycerides, and insulin resistance [1]. This group of abnormalities has since been referred to as syndrome X or the dysmetabolic syndrome. The

syndrome has been expanded to include abnormalities of cholesterol and lipoproteins [2,3] and is of great importance because it predicts an increased risk for developing diabetes mellitus and accelerated atherosclerosis with progression to myocardial infarction, stroke, and peripheral vascular disease [2–5]. In fact, the syndrome has been described as the ‘deadly quartet’

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because of the very high risk of premature mortality when these four complications are present together [5,6].

A similar constellation of findings with central accumulation of adipose tissue [7–11], insulin resistance [12–19], and abnormalities of serum lipids and triglycerides [8,9,12,13,15,19–21] has become commonly recognized in persons with HIV receiving highly active antiretroviral therapy (HAART). In fact, these findings (often referred to as peripheral lipodystrophy, fat redistribution syndrome, protease inhibitor (PI)-associated lipodystrophy) have been identified in a number of cross-sectional studies and may occur in up to 80% of HIV-positive subjects receiving HAART regimens [13]. The constellation was initially attributed to the PI used to treat HIV [22], but other reports suggest that individuals may develop these abnormalities despite never having received PI [7,8,9,10,23–26]. There is also reason to suspect that nucleoside reverse transcriptase inhibitors (NRTI) may contribute to certain components of the syndrome [16,17,27,28].

With the exception of one preliminary report [29], hypertension, a component of the dysmetabolic syndrome, has not been identified as part of the metabolic and body habitus abnormalities complicating HAART [30]. By 1999, we began to recognize increasing numbers of patients with disorders of clinical fat distribution and serum lipids who also had elevated blood pressure. Because hypertension has been the missing component of abnormalities simulating the dysmetabolic syndrome in persons with HIV, we now report on a cohort of subjects referred to a specialty clinic because of clinical fat maldistribution and abnormal serum lipids and who also had elevated blood pressure. We compare findings in these subjects to a matched group with HIV who previously had not been identified as having abnormalities of body fat or serum lipids and to HIV-negative controls.

## Methods

### Study design

This study was a retrospective review of HIV-positive subjects with clinically apparent abnormalities of body fat and serum lipids. These subjects were matched to HIV-positive and HIV-negative controls. For each HIV-positive case, the period of review for assessing elevated blood pressure was extended back to 6 months prior to the initiation of a regimen that contained either a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a PI. The Institutional Review Board of the University of Southern California-Los Angeles County (LAC-USC) Medical Center approved the study.

### Study cohort

The study cohort consisted of 42 consecutive patients who were referred to the HIV Metabolic Disorders Clinic at the LAC-USC Medical Center Rand Schrader HIV Clinic between March 1998 through August 1999 from the primary care section of this university-affiliated, public hospital-based clinic for evaluation of peripheral fat loss, central fat accumulation, or abnormalities of serum lipids. Each patient had a complete history, which included a query about hypertension in a first-degree relative and physical examination. Their antiretroviral regimens included one or two NRTI drugs plus at least one PI or NNRTI drug with or without a PI.

### Control populations

To assess whether elevated blood pressure was related to changes in body habitus or abnormalities in serum lipids, each subject in the cohort was randomly matched by sex and age within 3 years to an HIV-positive subject also receiving primary care in the Rand Schrader HIV Clinic. Medical providers who had referred the subjects included in the cohort were asked to identify potential cases for the control group. Subjects were considered eligible if they had not reported maldistribution of body fat, their medical providers had not identified such abnormalities, and prior serum lipids had not been determined or were within the normal range. Subjects identified for the HIV control group were scheduled to be evaluated and undergo the same testing as done for the study cohort. The controls were receiving the same types of antiretroviral regimens as the study cohort. In addition, 13 HIV-negative subjects were also selected at random from the clinic and research staff. The HIV-negative controls were matched by sex and age within 3 years to a member of the study cohort and also underwent a number of the same evaluations as the HIV-positive control group.

### Definitions and evaluation of subjects for elevated blood pressure

The HIV-positive subjects were defined as having elevated blood pressure if three or more readings recorded in their medical records showed diastolic blood pressure (DBP)  $\geq 90$  mmHg or systolic values  $\geq 140$  mmHg, or combination of three or more elevations of diastolic or systolic pressure. Medical records of the HIV subjects in the study cohort and control group were analyzed for all blood pressure readings prior to the last visit (referred to as the 'index visit') to the Metabolic Disorders Clinic. A single medical record is used for all primary care and specialty clinic visits to the Rand Schrader Clinic.

All vital signs, whether for primary care or specialty care clinic visits are taken in a single triage area by the same triage nurses, trained and reassessed periodically

for their skills to obtain vital signs. Patients generally sit in a waiting area for 20–30 min prior to being evaluated by their medical providers. During that time, they are called to the triage area and invariably sit quietly for 5 to 10 min before having their vital signs measured. HIV-negative controls had blood pressure measurements in both arms and readings were taken in triplicate on one occasion.

To assess further the magnitude and course of elevated blood pressure, the average of the three highest systolic and DBP measurements obtained during multiple clinic visits were determined for each individual HIV-positive subject. The mean values for the average of the three highest systolic and diastolic readings for the two HIV-positive groups were then determined.

### Body composition and laboratory definitions

Abnormal changes in body habitus included peripheral loss of adipose tissue (lipoatrophy) and/or accumulation of central fat. Lipoatrophy included new onset of sunken cheeks (loss of buccal fat), thin extremities with or without prominence of subcutaneous veins, or loss of buttock tissue in the subgluteal fat region. Accumulation of adipose tissue involved enlargement of abdominal girth without evidence of ascites, accumulation of fat in the dorsocervical (buffalo hump) or supraclavicular regions, multiple symmetric lipomas, or increase in breast size. Changes were considered abnormal if self-reported by subjects and confirmed by measurements and assessments carried out by one of the specialists in the Metabolic Disorders Clinic, or findings were identified by one of the specialists and verified by the subject as new, even if not initially self-reported by the subject.

Measurements of body circumference were taken by one of the investigators (F.R.S. or W.B.) using a non-stretchable tape measure and recorded to the nearest 0.1 cm. Circumferences were determined for the chest at the nipple line (evaluated in men only), ‘minimum waist’ (measured at the smallest visible diameter) between the lower rib margin and iliac crest, maximum diameter across the hip and buttocks, and mid thigh (boundary midway between the greater trochanter and superior border of the patella). Abdominal obesity was defined as a waist-to-hip ratio (WHR) of  $\geq 0.95$  for men or  $\geq 0.85$  for women or minimal waist circumference  $> 100$  cm for men and  $> 90$  cm for women. Subjects were not classified as having abdominal obesity if the WHR surpassed threshold values for sex, unless there was apparent abdominal enlargement, as loss of body mass at the hip without appreciable increase in abdominal girth may result in an increased WHR (pseudo-abdominal obesity).

Serum for lipid analysis was collected within 6 weeks of the index visit. When complete lipid panels were done

in the fasted state, subjects were asked not to eat or drink anything other than water from 8:00 p.m. the evening before. Samples were drawn between 8:00 a.m. and 12:00 noon on the next day. Lipids were considered abnormal if the total cholesterol was  $\geq 200$  mg/dl, fasting low density lipoprotein (LDL)-cholesterol as calculated by the Friedewald equation was  $\geq 130$  mg/dl, high density lipoprotein (HDL)-cholesterol  $\leq 35$  mg/dl, or fasting triglycerides were  $\geq 200$  mg/dl. A random blood sugar  $\geq 200$  mg/dl was considered abnormal and fasting blood sugar  $\geq 126$  mg/dl was diagnostic of diabetes. Bioelectrical impedance analysis to assess total body lean tissue was performed after subjects rested quietly for at least 20 min, their bladders were empty, and electrodes placed according to the manufacturer’s guidelines (RJL Systems). The manufacturer’s Fluid and Nutrition Analysis software (version 3.1a) was used to determine fat-free mass.

### Statistical methods

Number (%) of subjects and mean values  $\pm 1$  SD were reported as descriptive results for all variables. Between-group comparisons were performed using McNemar’s exact test or paired t test (unless otherwise specified) for the HIV-positive cases and matched HIV-positive controls. Thirteen pairs of HIV-positive cases from the cohort were also matched to HIV-negative controls. For several outcomes (i.e., serum LDL-cholesterol, fasting triglycerides, chest and mid thigh circumference), a two-group t test was used to determine statistical significance, as missing data resulted in  $< 90\%$  of outcomes being paired between the two groups. Pearson correlation analysis was used to evaluate the relationship between blood pressure levels and lipids or WHR. Statistical significance was set at  $\alpha = 0.05$ .

To control for family history of hypertension, conditional logistic regression (CLR) was conducted using both the family history of hypertension and a number of parameters of blood pressure (proportions with elevations of diastolic or systolic values, mean pressures, etc. as shown in Table 4) as covariates in comparing the cohort and HIV-positive controls. The unadjusted analysis of paired data were analyzed using standard methods (i.e., paired t test for continuous outcomes and McNemar test for categorical outcomes) or CLR, which produced similar results. Since the analyses adjusted for family history of hypertension were performed using CLR, the results of unadjusted analyses were also reported using CLR as shown in Table 4.

## Results

### Body habitus and metabolic abnormalities in the study cohort

For the cohort of 42 subjects, the most common

abnormality in body habitus was loss of subcutaneous fat, which was demonstrable in 88% of the cohort (Table 1). More than half of the group had new onset of thin extremities with or without prominent veins and more than half had lost fat in the buccal or

**Table 1.** Abnormalities in the study cohort prompting referral for evaluation.

	HIV-positive cases (n = 42)
Body habitus changes	42 (100%)
Loss of subcutaneous adipose tissue	37 (88%)
Thin extremities with prominent veins	29 (69%)
Sunken cheeks	24 (57%)
Loss of subgluteal tissue	23 (55%)
Accumulation of adipose tissue	29 (69%)
Abdominal enlargement	24 (57%)
Buffalo hump	10 (24%)
Multiple lipomas	3 (7%)
Breast enlargement <sup>a</sup>	3 (7%)
Lipid or carbohydrate abnormalities <sup>b</sup>	36 (86%)
Total cholesterol $\geq$ 200 mg/dl (41)	26 (63%)
HDL cholesterol $\geq$ 35 mg/dl (41)	20 (48%)
Fasting triglycerides $\geq$ 200 mg/dl (23)	14 (33%)
Fasting LDL cholesterol $\geq$ 130 mg/dl (23)	9 (21%)
Random blood sugar $\geq$ 200 mg/dl (42)	4 (10%)
Fasting blood sugar $\geq$ 126 mg/dl (19)	2 (5%)

<sup>a</sup>Breast enlargement occurred in two men and the one woman in the study cohort. <sup>b</sup>Values in parentheses are the number of subjects who had test done at the index visit. All subjects had body habitus data. HDL, high density lipoprotein; LDL, low density lipoprotein.

subgluteal regions. Abdominal enlargement was the most frequent manifestation of fat accumulation and was demonstrable by anthropometric measurements in 69% of the subjects. Lipid or glucose abnormalities were also common and were present in 86% of subjects in the cohort. The most common of the metabolic abnormalities involved elevations of total cholesterol to  $\geq$  200 mg/dl, which occurred in 63% of the cohort while depression of HDL-cholesterol  $\leq$  35 mg/dl occurred in 48% of these subjects.

### Comparison of the study cohort with the HIV-positive and negative control groups

Table 2 provides a comparison of the demography, clinical features, and laboratory results for the study cohort and two control groups. With a few exceptions, the three groups were comparable. First, the cohort was an average of 2 years older than the controls ( $42.8 \pm 7.9$  versus  $40.8 \pm 8.8$  years;  $P = 0.001$ ). Second, there were significantly fewer subjects who were Hispanic in the study cohort compared to the HIV-positive control group (43% versus 79%  $P = 0.001$ ). The proportion of Hispanics in the HIV control group is in keeping with the prevalence of Hispanics in the Rand Schrader HIV Clinic, which has ranged from 56% to 74% since the Clinic first opened in 1985. Third, those in the cohort more often reported family histories of hypertension than the HIV-positive con-

**Table 2.** Characteristics of subjects in study groups at index visit.

	HIV-positive cases (n = 42)	HIV-positive controls (n = 42) <sup>a</sup>	HIV-negative controls (n = 13) <sup>a</sup>
Age (years) (mean $\pm$ SD)	42.8 $\pm$ 7.9	40.8 $\pm$ 8.8**	43.2 $\pm$ 7.3
Men [n (%)]	41 (98%)	41 (98%)	12 (92%)
Ethnicity			
Hispanics [n (%)]	18 (43%)	33 (79%)**	4 (31%)
Non-Hispanic Caucasians [n (%)]	15 (36%)	4 (10%)	5 (38%)
Non-Hispanic Blacks [n (%)]	9 (21%)	3 (7%)	1 (8%)
Asian Pacific Islanders [n (%)]	0	1 (2%)	3 (23%)
Duration of HAART (months) (mean $\pm$ SD)	21.9 $\pm$ 10.2	24.6 $\pm$ 11.5	NA
Current smoking [n (%)]	11 (26%)	13 (31%)	1 (8%)
Previous smoking [n (%)]	25 (60%)	23 (55%)	4 (31%)
Diabetes [n (%)]	4 (10%)	3 (7%)	0
Family history of diabetes <sup>b</sup> [n (%)]	12 (29%)	12 (29%)	6 (46%)
Family history of hypertension [n (%)]	26 (62%)	15 (36%)*	7 (54%)
Treatment for hypertension <sup>c</sup> [n (%)]	5 (12%)	4 (10%)	0
Systolic blood pressure (mmHg) [n (%)]	129 $\pm$ 15	129 $\pm$ 15	119 $\pm$ 13
Diastolic blood pressure (mmHg) [n (%)]	77 $\pm$ 11	77 $\pm$ 8	72 $\pm$ 10
HIV RNA undetectable [n (%)]	25 (60%)	30 (71%)	NA
< 50 HIV RNA copies/ml [n (%)]	12 (29%)	26 (62%)	NA
< 400 HIV RNA copies/ml [n (%)]	13 (31%)	4 (10%)	NA
HIV RNA detectable [n (%)]	17 (40%)	12 (29%)	NA
Log <sub>10</sub> (RNA copies/ml) [median (range)]	3.95 (1.98–5.83)	4.70 (2.36–5.88)	NA
CD4 lymphocyte counts ( $\times 10^6$ /l) (mean $\pm$ SD)	407 $\pm$ 292	320 $\pm$ 208*	NA
Hemoglobin (g/dl) (mean $\pm$ SD)	13.9 $\pm$ 2.0	14.4 $\pm$ 1.3	NA
Alanine aminotransferase (U/L) (mean $\pm$ SD)	65.3 $\pm$ 57.6	55.5 $\pm$ 32.7	NA
Creatinine (mg/dl) (mean $\pm$ SD)	1.05 $\pm$ 0.98	0.89 $\pm$ 0.28	NA

<sup>a</sup>Comparisons were performed on 42 matched pairs of HIV-positive cases and controls and in 13 matched pairs of HIV-positive cases and HIV-negative controls, using McNemar's exact test or paired t test. Significant  $P$  values: \* $0.01 \leq P < 0.05$ ; \*\* $0.001 \leq P < 0.01$ . Pairs with unknown data were excluded from the significance test. <sup>b</sup>Patients with a family history of diabetes had one first-degree or two second-degree relatives with diabetes. <sup>c</sup>Received treatment for hypertension during the observation period. NA, Data not available.

trols (62% versus 36%  $P=0.04$ ). Finally, the CD4 lymphocyte counts were greater in the cohort versus the HIV-positive control group ( $407 \pm 292$  versus  $320 \pm 208 \times 10^6$  cells/l;  $P=0.04$ ).

### Comparison of body habitus and metabolic abnormalities in the three groups

Despite the fact that the HIV-positive control group was selected based on the absence of apparent changes in body habitus and lack of previous testing of serum lipids, the three groups were remarkably similar as shown in Table 3. There was no difference in total cholesterol or HDL cholesterol across the three groups, whereas, fasting serum triglycerides were significantly higher in the two HIV-positive groups when compared to the HIV-negative control subjects. However, fasting triglycerides were only obtained in a subset of HIV-positive subjects, and the difference in levels for the cohort ( $308 \pm 226$  mg/dl) versus the HIV-positive controls ( $208 \pm 125$  mg/dl) did not reach statistical significance ( $P=0.09$ ). The lack of statistical difference may have been related to fewer fasting specimens in the HIV-positive controls. It is also noteworthy that the average WHR which was significantly increased in subjects with HIV compared to HIV-negative controls, was almost identical between the study cohort and HIV-positive controls ( $0.94 \pm 0.08$  versus  $0.92 \pm 0.05$ , respectively). This finding was unexpected as subjects in the HIV-positive control group had not complained of increasing abdominal girth and it had not been recognized by their primary care givers.

### Comparison of blood pressure in the HIV-positive subjects and controls

The total duration of observations for blood pressure

for the study cohort and HIV-positive controls from the index visit back to 6 months prior to the institution of HAART was comparable ( $21.1 \pm 11.0$  versus  $22.0 \pm 10.9$  months, respectively;  $P=0.23$ ) as was the total number of blood pressure readings during this same period ( $23.0 \pm 15.6$  versus  $21.8 \pm 12.3$  values, respectively;  $P=0.55$ ). Three or more elevations in either the DBP ( $\geq 90$  mmHg) or systolic blood pressure (SDP;  $\geq 140$  mmHg) occurred in 74% of the study cohort and 48% of the HIV controls ( $P=0.01$ ) during this period of time. Elevations of SBP (71% versus 43% and elevations of DBP (43% versus 21% occurred more frequently in the cohort than in the controls ( $P=0.01$  and  $P=0.02$ , respectively). The proportion of elevated blood pressure (either diastolic or systolic) and SBP readings was significantly higher in the study cohort ( $38 \pm 25\%$  versus  $22 \pm 26\%$   $P=0.01$  and  $33 \pm 24\%$  versus  $20 \pm 26\%$   $P=0.02$ , respectively), but there was no difference in the proportion of elevated diastolic readings in the two groups. However, both the average SBP and DBP in the study cohort were significantly higher than for the HIV controls ( $P=0.02$  for each).

To assess further the magnitude and course of elevated blood pressure, the average values for the three highest systolic and DBP measurements for each individual HIV-positive subject across their respective clinic visits were determined. The mean values for the three highest systolic and diastolic measurements for all of the individuals in the cohort ( $153 \pm 17$  and  $92 \pm 10$  mmHg, respectively) were significantly higher than the respective values in the HIV controls ( $144 \pm 15$  and  $87 \pm 9$  mmHg,  $P=0.01$  for each comparison; Table 4). After three elevated readings, the proportion

**Table 3.** Metabolic and body composition parameters for subjects in the study groups (mean  $\pm$  SD).

	HIV-positive cases (n = 42)	HIV-positive controls (n = 42) <sup>a</sup>	HIV-negative controls (n = 13) <sup>a</sup>
Metabolic parameters (mg/dl)			
Total serum cholesterol (41,41,12) <sup>b,c</sup>	221 $\pm$ 52	229 $\pm$ 71	193 $\pm$ 40
Serum HDL-cholesterol (41,40,12)	40.0 $\pm$ 13.9	40.1 $\pm$ 12.6	44.1 $\pm$ 11.1
Fasting triglycerides (23,9,12)	308 $\pm$ 226	208 $\pm$ 125	92 $\pm$ 44**
Random blood sugar (42,42,0)	119 $\pm$ 68	100 $\pm$ 27	NA
Body composition parameters			
Weight (pounds) (42,42,13)	163 $\pm$ 33	164 $\pm$ 27	164 $\pm$ 20
Height (inches) (42,42,13)	68.4 $\pm$ 3.4	67.3 $\pm$ 3.1	69.3 $\pm$ 3.2
BMI (kg/m <sup>2</sup> ) (42,42,13)	24.5 $\pm$ 4.0	25.4 $\pm$ 3.2	24.0 $\pm$ 2.0
Fat-free mass (kg) (41,41,13)	59.6 $\pm$ 9.0	61.5 $\pm$ 11.2	61.3 $\pm$ 7.2
Chest circumference (cm) (18,40,12)	98.5 $\pm$ 7.9	98.5 $\pm$ 9.0	96.1 $\pm$ 5.9
Waist circumference (cm) (41,41,13)	85.2 $\pm$ 12.5	87.6 $\pm$ 5.8	83.0 $\pm$ 7.1
Waist-to-hip ratio (41,41,13)	0.94 $\pm$ 0.08	0.92 $\pm$ 0.05	0.84 $\pm$ 0.06**
Mid thigh circumference (cm) (37,41,13)	48.6 $\pm$ 10.5	50.1 $\pm$ 4.3	52.9 $\pm$ 2.3

<sup>a</sup>A paired t test was used to compare each group with the HIV-positive cases when paired data contained  $> 90\%$  data points. Otherwise, a two-group t test was used. Significant  $P$  values: \* $0.01 \leq P < 0.05$ ; \*\* $0.001 \leq P < 0.01$ .

<sup>b</sup>Values in parentheses are the number of subjects who had test done at the index visit. <sup>c</sup>Serum for lipid and blood glucose determinations was obtained within 6 weeks of the index visit.

**Table 4.** Blood pressure data in HIV-positive subjects during the entire study period.

	HIV-positive cases (n = 42)	HIV-positive controls (n = 42)	P value 1 <sup>a</sup>	P value 2 <sup>a</sup>
Number of readings (mean ± SD)	23.0 ± 15.6	21.8 ± 12.3	0.55	NT
Duration of blood pressure data (months) (mean ± SD)	21.1 ± 11.0	22.0 ± 10.9	0.23	NT
At least three elevated blood pressure values [n (%)]	31 (74%)	20 (48%)	0.01	0.04
At least three elevated SBP values [n (%)]	30 (71%)	18 (43%)	0.01	0.04
At least three elevated DBP values [n (%)]	18 (43%)	9 (21%)	0.02	0.02
Proportion of readings elevated (mean ± SD)	0.38 ± 0.25	0.22 ± 0.26	0.01	0.04
Proportion of systolic readings elevated (mean ± SD)	0.33 ± 0.24	0.20 ± 0.26	0.02	0.09
Proportion of diastolic readings elevated (mean ± SD)	0.15 ± 0.16	0.10 ± 0.17	0.17	0.31
Mean SBP in all readings (mmHg) (mean ± SD)	134 ± 10	128 ± 12	0.02	0.08
Mean DBP in all readings (mmHg) (mean ± SD)	80 ± 6	76 ± 7	0.02	0.07
Mean of three highest SBP readings (mmHg) (mean ± SD)	153 ± 17	144 ± 15	0.01	0.06
Mean of three highest DBP readings (mmHg) (mean ± SD)	92 ± 10	87 ± 9	0.01	0.03

<sup>a</sup>Both P value 1 and P value 2 were obtained from conditional logistic regression analysis, with P value 2 adjusted for family history of hypertension. SDP, Systolic blood pressure; DBP, diastolic blood pressure.

of elevated values ( $50 \pm 23\%$  versus  $49 \pm 37\%$  respectively) in these subjects with elevated values was similar ( $P > 0.05$ ). Similarly, the three highest systolic and diastolic readings ( $160 \pm 13$  and  $96 \pm 9$  mmHg versus  $156 \pm 11$  and  $93 \pm 8$  mmHg, respectively) were similar in these two subsets with sustained elevations in blood pressure ( $P > 0.05$ ).

#### Treatment for hypertension

Five patients in the cohort were receiving antihypertensive therapy. Three of these patients had begun therapy more than 6 months prior to initiating HAART; one of the three contributed no elevated blood pressure readings during the study period. Two other subjects in the cohort started treatment for hypertension during the first 6 months of the study period. Four patients in the HIV-positive control group had antihypertensive therapy initiated at various times during the study period. Inclusion of these nine subjects did not affect appreciably the magnitude of differences in blood pressure between the two groups (data not shown).

#### Effect of ethnicity on blood pressure

Because the proportion of Hispanics in the two HIV-positive groups was different, the effect of ethnicity on

the occurrence of elevated blood pressure was evaluated further. Table 5 shows that elevated blood pressure was similar in Hispanics (61%) and non-Hispanics (63%). When blood pressure in the groups was analyzed by conditional logistic regression, the difference in the proportion of patients with elevated blood pressure in the cohort and HIV-positive controls were similar by univariate and multivariate analysis after adjustment for the effect of ethnicity ( $P = 0.02$  and  $P = 0.04$ , respectively). This analysis thus indicated that Hispanic ethnicity had little effect on blood pressure.

#### Effect of family history on blood pressure

A history of hypertension in a first-degree relative occurred in 26 (62%) of the cohort and 15 (36%) of the HIV-positive controls ( $P = 0.04$ , McNemar's exact test; Table 2). When the data were controlled for family history of hypertension, the difference in blood pressure measures between the two groups tended to diminish ( $P$  values in last column of Table 4). However, the number of subjects with at least three elevated systolic or DBP measurements, proportion of readings that were elevated, and mean of the highest three readings of DBP were still significantly different between the two HIV groups ( $P < 0.05$ ;  $P$ -value 2; Table 4). In fact, in the unadjusted analysis, the odds

**Table 5.** Effects of ethnicity and family history on elevated blood pressure.

Effect of ethnicity	HIV-positive cases (n = 42)	HIV-positive controls (n = 42)	Total (n = 84)	OR (95% CI) <sup>a</sup>	P
Hispanic patients	18 (43%)	33 (79%)			
Elevated blood pressure	14 (77%)	17 (52%)	31/51 (61%)		
Non-Hispanic patients	24 (57%)	8 (21%)			
Elevated blood pressure	17 (71%)	3 (38%)	20/32 (63%)		
Effect of family history of hypertension					
Unadjusted for family history				4.7 (1.5–20.2)	0.01
Adjusted for family history				3.8 (1.2–16.9)	0.04

<sup>a</sup>Odds ratio (OR) and 95% confidence interval (95% CI) for at least three elevated blood pressure readings in subjects in the cohort versus the HIV-positive controls were estimated by conditional logistic regression analysis.

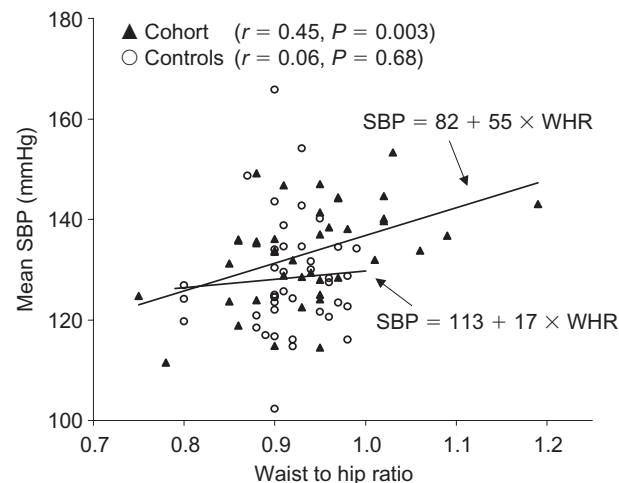
ratio (OR) for at least three elevated blood pressure measurements in the cohort versus the HIV-positive controls was 4.7 [95% confidence interval (CI), 1.5–20.2; Table 5]. Whereas the OR was 3.8 (95% CI, 1.2–16.9) when the analysis was adjusted for a family history of hypertension. Family history accounted for only 13% of the log OR value for at least three elevated blood pressure readings or 0–22% of the log OR values between various measures of blood pressure assessed in Table 4.

#### Risk factors for elevated blood pressure

Among the 84 total HIV-positive subjects, 51 had three or more elevated blood pressure readings and 33 did not have elevated blood pressure. There was a relationship ( $r$ , 0.34) between triglycerides and SBP in the 34 subjects who had this test done in the fasted state, but the difference did not quite reach significance ( $P = 0.052$ ). However, WHR was significantly correlated with SBP ( $r$ , 0.31;  $P = 0.01$ ). Similarly, increased WHR ( $\geq 0.85$  for women  $\geq 0.95$  for men) tended to occur more often in those with elevated blood pressure ( $n = 17$ , 34% than in subjects with normal blood pressure ( $n = 5$ ; 16%  $P = 0.08$ ). Fig. 1 shows that the WHR was correlated significantly with SBP in the cohort ( $r$ , 0.45;  $P = 0.003$ ) but not in the HIV-positive controls ( $r$ , 0.06;  $P = 0.68$ ).

## Discussion

Results of this study suggest that HIV-positive subjects with metabolic dysregulation may be at increased risk for hypertension. In the cohort of 42 consecutive



**Fig. 1.** Relationship of average SBP over the entire course of the study and WHR for subjects in the HIV-positive cohort and the HIV-positive controls. Triangles represent individual subjects in the cohort and open circles represent individual subjects in the control group.

subjects referred to a specialty clinic for evaluation of fat maldistribution or lipid abnormalities, 38% of blood pressure measurements (average of  $23 \pm 16$  readings per subject) during the prior 2 years were elevated. Overall, 31 (74%) of these patients had three or more blood pressure readings that were in the hypertensive range. In 42 age-matched controls, only 22% of a similar number of blood pressure readings recorded over the same time frame were elevated ( $P = 0.01$  versus the cohort), and only 20 (48%) of the controls had three or more elevated readings ( $P = 0.01$  versus the cohort). In addition, the average systolic and DBP readings in the cohort were greater than for controls ( $P = 0.02$  for each comparison). Finally, the average of the three highest systolic and DBP measurements ( $153 \pm 17$  and  $92 \pm 10$  mmHg, respectively) for individuals in the cohort were greater than the average of the three highest values in the controls ( $144 \pm 15$  and  $87 \pm 9$ , respectively;  $P = 0.01$  for each comparison).

It is unlikely that the frequency of elevated blood pressure values in the HIV subjects was due solely to 'white coat hypertension'. First, 'white coat hypertension' should have occurred randomly in both groups who had their blood pressure measured in the same triage area. It is possible, however, that some persons with abnormalities of body habitus may have had more concern and anxiety about their body image resulting in higher blood pressure readings. Second, for individuals who had at least three elevated values, the proportion of subsequent high measurements increased from 38 to 50% in the cohort and 22 to 49% in the HIV-positive controls, suggesting that the elevated readings were more sustained in these individuals and probably represented true abnormalities.

That 48% of the HIV-positive controls, previously not identified as having abnormalities of body habitus or serum lipids, also had multiple elevations of blood pressure was not expected. Although the controls had a higher portion of Hispanic patients, this did not affect the risk for elevated blood pressure when analyzed by conditional logistical regression (Table 5). It is possible that metabolic dysregulation was already present in the controls, but was not as advanced as in the cohort as the controls were somewhat younger and age appears to be a risk factor for lipodystrophy [28,31]. Despite a trend for higher triglyceride levels in the cohort, other lipids were similarly abnormal in the controls and cohort. Likewise, although WHR, an indirect measure of abdominal adipose tissue [32–37], was significantly greater in the cohort, the average WHR in the controls was 0.92, indicating that almost half of the controls met criteria for abdominal obesity. If increased blood pressure is related to dysregulation of lipid metabolism or central adiposity in HIV, as with the dysmetabolic syndrome, this could also explain the unexpected, relatively high frequency of blood pressure readings in the HIV-positive controls.

In both HIV-positive groups, the proportion of patients with elevated SBP was greater than the proportion with elevated DBP. This is consistent with data from the Framingham Study involving untreated subjects, in which 31.6% were classified as hypertensive based on isolated elevation of SBP compared to 3.8% who were classified as having hypertension based on isolated elevation in DBP [38]. Of importance, isolated elevation of SBP is an independent risk factor for cardiovascular complications [39–43].

Unless the blood pressure is elevated over multiple clinic visits, a strict diagnosis of hypertension is not warranted, making it difficult to know when to initiate antihypertensive therapy. However, as 22–38% of readings in individual cases in the two groups were elevated over almost 2 years, their risk for cardiovascular complications was likely to be increased, because it is the average level of blood pressure to which the systemic circulation is exposed over prolonged periods which probably results in excess morbidity and mortality [44]. Because non-pharmacological modifications such as caloric restriction for obesity, exercise, decreased dietary sodium, and reduction in alcohol consumption have beneficial effects on blood pressure [45–47], we advocate that such measures be instituted in HIV patients with three or more SBP readings in the range of stage I hypertension (140–159 mmHg). Sustained values in this range that do not respond to non-pharmacological interventions, higher values of SBP, and elevations in DBP should prompt consideration for early drug therapy.

We can only speculate about possible reasons for the high proportion of patients in our study with elevated blood pressure readings. Hypertension [48], abdominal obesity [49,50], severe lipoatrophy [51], and lipid abnormalities [52] are each individually associated with insulin resistance in populations without HIV. Although we did not measure insulin sensitivity, evidence of insulin resistance (elevations of fasting insulin, C-peptide, etc) has been reported in several HIV cohorts with lipodystrophy [12–15,18,21,53]. Although, insulin resistance may occur early after initiating PI therapy [21,53], insulin resistance occurs in HIV-positive women and men not using PI who develop abnormalities of body fat and lipids [54,55]. Moreover, the greater frequency of hypertension in family members of the cohort than controls (62% versus 36% could have predisposed the cohort to greater risk of insulin resistance [56–59]. Prospective studies will be necessary to determine whether insulin resistance is a common denominator that links hypertension to abnormalities of body fat and lipid disorders in persons with HIV.

There are several limitations to this study. First, there is no commonly accepted case-definition for HIV associated 'lipodystrophy'. Thus, the diagnosis is often

based, as in our study, on patient report of change in body habitus and physician ascent that such changes have occurred. Moreover, metabolic abnormalities may be different in subjects with predominantly lipoatrophy or fat accumulation or a combination of the two. Without objective criteria to diagnose lipoatrophy and fat accumulation (e.g. imaging procedures), any relationship between blood pressure and body habitus will be tentative. Second, the HIV-positive controls were not selected at random but were identified by their medical providers as not having changes in body fat and not having known lipid abnormalities. Regardless, the controls also had evidence of disordered fat metabolism when examined more carefully. Thus, differences in blood pressure between the cohort and controls cannot be used to establish that there was relationship between fat maldistribution or abnormalities of serum lipids and elevated blood pressure. However, there was a high tendency for correlation between fasting triglycerides and SBP in subjects with HIV. In addition, WHR, which were greater in the cohort than in control subjects, were correlated significantly with SBP in the cohort but not in the HIV-positive controls. Finally, because our cohort included only one woman, it is uncertain how our findings apply to women. Regardless, these data together provide supportive evidence that disordered fat metabolism was contributing to the risk for elevated blood pressure.

In summary, our observations suggest that elevated blood pressure may be associated with abnormalities in fat distribution and serum lipids in subjects also expected to have insulin resistance. Together, these complications, as in the dysmetabolic syndrome, portend an increased risk for accelerated atherosclerosis. The occurrence of hypertension *per se* also portends an increased risk for myocardial infarction, stroke, renal failure, and peripheral arterial disease [60–65]. Thus, subjects such as we have described have several risk factors for serious morbidity and premature mortality not directly due to HIV. These risk factors should be identified early and managed by appropriate interventions, particularly in patients who have responded well to their antiretroviral therapy.

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