CLINICAL STUDY

GH treatment reduces trunkal adiposity in HIV-infected patients with lipodystrophy: a randomized placebo-controlled study

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Abstract

Objective: HIV lipodystrophy is a common complication of highly active anti-retroviral therapy, characterized by both metabolic and morphological features. The most feared morphological feature is body fat redistribution leading to HIV lipodystrophy. GH is known to induce reduction of visceral obesity and body fat redistribution in adults.

Design: A crossover, double-blind protocol of GH treatment (6 months of recombinant human GH (rhGH) at 0.2 IU/kg per week) vs placebo (6 months of placebo with a 2 month wash-out between periods) was performed.

Subjects and setting: Thirty HIV-infected patients with lipodystrophy were recruited in the Outpatient Clinic of the Division of Infectious Diseases of San Raffaele Scientific Institute in Milan, Italy.

Main outcome and results: Our data demonstrate an effect of low-dose rhGH administration in reducing trunk adiposity in HIV patients with lipodystrophy (Δ from basal: -394 ± 814 g, $P = 0.048$ with respect to placebo. Data are given as mean $\pm$ standard deviation). A trend to an increase of arm depots was also shown (Δ from basal: $+43 \pm 384$ g, $P = \text{NS}$ with respect to placebo). Interestingly, no detrimental metabolic effects on glucose tolerance and lipid levels were found following the administration of 0.2 IU/kg per week of rhGH for 6 months.

Conclusions: Low-dose GH administration is an effective treatment in reducing trunk obesity in HIV-infected patients with lipodystrophy.

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Introduction

The advent of highly active anti-retroviral treatment (HAART) caused a dramatic improvement of patient survival in HIV-related infection (1). Since the introduction of either protease inhibitors (PIs) or nucleoside and non-nucleoside reverse transcriptase inhibitors (NRTIs and NNRTIs respectively) in the therapy of AIDS, it was evident that these drugs were not devoid of important metabolic and morphological side-effects (2). Increases in blood lipid level (mainly triglycerides), uric acid concentration and glycemia were all reported with different incidences in populations of HIV-infected patients treated with PIs, NRTIs, NNRTIs or a combination of them (3–6). Along with metabolic alterations, many patients also show morphological changes in the distribution of body fat, with an increase in trunk adiposity and a reduction (or atrophy) of fat tissue in arms and legs being the most common form of lipodystrophy (2–6).

The common denominator of metabolic and morphological alterations of HIV-related lipodystrophy is

insulin resistance, namely a reduction of the ability of insulin to increase glucose uptake and metabolism (1–6). Three mechanisms for both PIs (2, 3, 5) or NRTIs (3, 6, 7) have been proposed to justify the manifestation of lipodystrophy: (i) the inhibition of the peroxisome proliferator-activated receptor- γ shown by PI (2); (ii) the resulting hypertriglyceridemia inducing insulin resistance by an indirect mechanism; and (iii) mitochondrial toxicity with inhibition of respiratory chain enzymes by NRTIs (6, 7). Interestingly, a number of hormone alterations have been described in HIV-infected patients: increased levels of fasting and post-prandial insulin and C-peptide concentrations (5), disrupted circadian rhythm of cortisol levels (with sporadic increased daily cortisoluria) (8), and, finally, a defect of growth hormone (GH) secretion following a combined arginine/GH-releasing hormone (GHRH) stimulus (9, 10). In adulthood there is evidence that a defective GH secretion is associated with abnormal fat distribution (11) and that GH administration normalizes the pattern of fat deposition. Therefore, a crossover, double-blind protocol of GH treatment (6 months

of GH at 0.2 IU/kg/week) vs placebo (with a 2 month wash-out between the two treatment periods) was performed. The aim of the study was to test whether GH administration is effective in reducing trunk obesity in HIV patients with lipodystrophy.

Methods

Population

The present protocol was evaluated and approved by the Institutional Ethical Committee of San Raffaele Scientific Institute. Written informed consent was obtained from all patients before entering the study protocol.

Thirty HIV-infected patients with lipodystrophy (with both the adipose tissue redistribution and the metabolic changes of the syndrome) were enrolled in this study. All patients were in a stable clinical condition and on the same anti-retroviral treatment for at least 3 months prior to their enrollment in the study. All patients were taking PIs along with NRTIs or NNRTIs. Patients with a body mass index (BMI) $> 32 \text{ kg/m}^2$, diabetes mellitus, epilepsy, CD_4 count $< 200 \text{ cells/ml}^3$,

Kaposi sarcoma or other major lung, heart, liver and nervous system disease were excluded from the present study. Table 1 shows the main biochemical and clinical data of study subjects. Table 5 contains the main metabolic parameter characteristics of lipodystrophy. Only 23 patients (out of 30 initially enrolled) completed the study.

Study protocol

Twenty-three patients completed the study. After being enrolled in the study patients were randomized either to Arm A (recombinant human GH (rhGH) first, then placebo) or to Arm B (placebo first, then rhGH). The first treatment was continued for 6 months. The second treatment was also given for 6 months after a 2 month interruption to allow pharmacological wash-out. The entire protocol lasted 14 months. The dose of rhGH (Genotropin, Pfizer) was given daily s.c. (0.028 IU/kg per day corresponding to 0.2 IU/kg per week).

Anthropometrics, dual-energy X-ray absorptiometry (DXA), oral glucose tolerance tests (OGTTs) and GH secretion by GHRH plus arginine tests were performed four times: (i) at the beginning of the study; (ii) at the

Table 1 Demographic and anthropometric characteristics of the study groups. Data are given as mean $\pm$ standard deviation (s.d.).

	ALL	Arm A (sequence Genotropin/placebo)	Arm B (sequence placebo/Genotropin)
PERIOD 1			
BASAL			
Patients (n)	30	15	15
Sex ratio (M/F)	13/17	5/10	8/7
Age (years)	39.63 $\pm$ 8.54	38.07 $\pm$ 8.48	41.20 $\pm$ 8.59
Weight (kg)	64.50 $\pm$ 10.75	61.47 $\pm$ 10.59	67.53 $\pm$ 10.38
BMI (kg/m ²)	22.36 $\pm$ 2.45	21.61 $\pm$ 2.41	23.12 $\pm$ 2.29
END			
Patients (n)	25	13	12
Sex ratio (M/F)	10/15	4/9	6/6
Weight (kg)	64.42 $\pm$ 11.74	61.12 $\pm$ 11.64	68.00 $\pm$ 11.23
Δ WEIGHT	—	+0.04 $\pm$ 1.59	−0.75 $\pm$ 2.83
Δ Waist	−0.57 $\pm$ 3.54	+0.62 $\pm$ 3.71	−2.1 $\pm$ 3.54
Δ Hip	−1.11 $\pm$ 2.48	−0.38 $\pm$ 2.18	−2.05 $\pm$ 2.63
Δ Trunk	−1.00 $\pm$ 3.11	−1.38 $\pm$ 2.9	−0.50 $\pm$ 3.45
Δ Thigh	+1.07 $\pm$ 2.51	+0.77 $\pm$ 2.83	+1.45 $\pm$ 2.11
Δ Biceps	+0.10 $\pm$ 2.39	−0.77 $\pm$ 2.58	+1.22 $\pm$ 1.63
Δ Triceps	+0.40 $\pm$ 3.06	+0.13 $\pm$ 3.91	+0.76 $\pm$ 1.5
PERIOD 2			
BASAL			
Patients (n)	23	11	12
Sex ratio (M/F)	9/14	3/8	6/6
Weight (kg)	64.09 $\pm$ 10.69	59.36 $\pm$ 8.46	68.42 $\pm$ 10.97
END			
Patients (n)	20	10	10
Sex ratio (M/F)	9/11	3/7	6/4
Weight (kg)	65.15 $\pm$ 11.82	61.71 $\pm$ 11.29	68.58 $\pm$ 11.88
Δ WEIGHT	—	+1.71 $\pm$ 3.75	−0.62 $\pm$ 3.34
Δ Waist	+0.39 $\pm$ 4.68	+3.05 $\pm$ 5.19	−1.83 $\pm$ 2.82
Δ Hip	−0.07 $\pm$ 7.00	−1.95 $\pm$ 7.18	+1.50 $\pm$ 6.74
Δ Trunk	−0.07 $\pm$ 4.40	+1.75 $\pm$ 4.10	+1.50 $\pm$ 6.74
Δ Thigh	+1.25 $\pm$ 2.55	+1.20 $\pm$ 1.87	+1.29 $\pm$ 3.09
Δ Biceps	−0.05 $\pm$ 1.32	+0.22 $\pm$ 1.18	−0.28 $\pm$ 1.44
Δ Triceps	−0.82 $\pm$ 2.98	−0.78 $\pm$ 3.69	−0.86 $\pm$ 2.40

conclusion of 6 months of Genotropin (rhGH)/placebo or placebo/Genotropin; (iii) after 2 months of wash-out period; and (iv) at the conclusion of 6 months of Genotropin/placebo or placebo/Genotropin.

Anthropometrics

Weight, height and waist/hip ratio were recorded four times during the experimental protocol.

Body composition

DXA was performed four times during the experimental protocol.

OGTT

A 75 g OGTT was performed in all patients four times during the experimental protocol. The 1997 American Diabetes Association criteria were used to classify patients into; diabetics, those having impaired glucose tolerance or normal, based on basal, 1st hour and 2nd hour glycemia (12).

GH secretion

Combined GHRH (50 µg) and arginine hydrochloride (15 g) infusions were performed four times: (i) at the beginning of the study; (ii) at the conclusion of 6 months of Genotropin/placebo or placebo/Genotropin; (iii) after 2 months of wash-out period; and (iv) at the conclusion of 6 months of Genotropin/placebo or placebo/Genotropin.

Analytical determinations

All analytical determinations were performed in the core laboratory of San Raffaele Scientific Institute. Blood cells count, CD₄ count, virus concentration, alanine aminotransferase and aspartate aminotransferase, free triiodothyronine and free thyroxine, thyrotropin, plasma glucose, total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides and uric acid were measured by standard techniques as previously described (13). Glycosylated hemoglobin (HbA1c) was measured by HPLC as previously described (13). Plasma insulin, C-peptide, GH, insulin-like growth factor-I (IGF-I) and tumor necrosis factor-α (TNF-α) were measured by RIA as previously described (13).

Statistical analysis

For the recorded variables, descriptive statistics have been calculated. In particular, the mean, s.d., minimum and maximum with the median, if the case, for the quantitative variables and absolute and relative frequencies for the qualitative ones. The statistical

analysis was by means of ANOVA, according to the two-period and two-treatment crossover design.

Results

Patients were randomly assigned to the two different therapeutic sequences (Arm A: 6 months of rhGH/placebo, 2 months of wash-out; Arm B: 6 months of placebo/rhGH) and were homogeneous for age, sex distribution, body weight and BMI. Only 23 (73%) patients started the second treatment period and only 20 (67%) performed all the planned tests. Drop-outs were due to pregnancy (one case), hepatitis A (one case) and withdrawal of consent (two cases) during rhGH treatment, and increase of transaminase levels (one case), wrong randomization (one case) and withdrawal of consent (one case) during the placebo period.

The effects on body composition are presented in Table 2. Data are given as mean ± standard deviation (s.d.). Independently from the sequence of the treatment (Arm A or Arm B) the total tissue percentage fat did not change significantly. Arm tissue percentage fat increased by $0.47 \pm 3.84\%$ during rhGH treatment and decreased by $1.26 \pm 2.81\%$ during placebo (Table 2). Leg tissue percentage fat decreased during rhGH (Arm A: -0.68 ± 2.05 ; Arm B: -0.67 ± 1.67 , $P = 0.0248$) without any modification of lean tissue (-16.2 ± 739 vs -22.3 ± 671 , $P = \text{NS}$). Trunk tissue fat mass also decreased clearly in patients on rhGH (-394.1 ± 814.3 g), $P = 0.0483$ with respect to placebo (-16 ± 1555). This effect was not coupled to an evident increase in lean tissue (trunk lean g: rhGH $+480.5 \pm 1398$; placebo $+679.9 \pm 1105$). The data on the measurement of waist/hip ratio confirmed a decrease of the ratio in patients of Arm A, while no change was shown in patients of Arm B. No statistically significant differences were noted when results were analyzed by sex (data not shown).

Table 3 reports the results of the 75 g OGTT performed at the beginning and at the end of every treatment period. The data of the area under the curve for glucose (AUC 0-120 min) are corrected by subtraction of the basal glucose level. rhGH did not induce a statistically significant decrease of glucose AUC vs placebo. Plasma insulin and C-peptide levels were higher in the two basal periods with respect to the normal range of our laboratory, and did not vary after rhGH treatment. The homeostasis model assessment of insulin resistance (HOMA IR) index (calculated according to Matthews *et al.* (14)) did not change following rhGH treatment. In Table 3 are reported the total numbers of patients showing abnormal values of glycemia, HbA1c and fructosamine during rhGH and placebo administration (no difference between rhGH and placebo).

In Table 4 are summarized the results of the maximal GH stimulation test performed by combined infusion of GHRH (50 µg) and arginine hydrochloride (15 g).

Table 2 The effect of treatment on body composition (Δ from basal). Data are given as mean $\pm$ s.d.

	ALL Genotropin (22 patients)	ALL placebo (21 patients)	Arm A (sequence Genotropin/placebo) (Period 1)	Arm A (sequence placebo/Genotropin) (Period 2)	Arm B (sequence Genotropin/placebo) (Period 1)	Arm B (sequence placebo/Genotropin) (Period 2)
Arm tissue lean (g)	-47.9227 ± 473.799	-171.895 ± 796.383	-6.391 ± 445.319	-30.155 ± 239.228	-278.200 ± 1040.550	-96.230 ± 525.861
Arm tissue fat (g)	$+43.885 \pm 384.339$	-97.933 ± 227.480	$+26.033 \pm 487.373$	-114.455 ± 210.430	-85.541 ± 239.584	$+65.240 \pm 231.133$
Arm tissue (% fat)	$+0.47 \pm 3.84$	-1.26 ± 2.81	$+0.547 \pm 4.658$	-1.738 ± 3.835	-0.909 ± 1.822	-0.375 ± 2.791
Leg tissue lean (g)	$+16.264 \pm 739.915$	$+22.314 \pm 671.569$	-248.191 ± 764.770	$+84.644 \pm 721.433$	-24.433 ± 660.248	$+333.610 \pm 625.060$
Leg tissue fat (g)	-69.841 ± 315.670	-73.619 ± 408.133	-136.100 ± 389.271	$+88.422 \pm 237.349$	-195.150 ± 473.596	$+9.670 \pm 185.547$
Leg tissue (% fat)	-0.394 ± 1.594	-0.221 ± 1.451	-0.676 ± 2.046	-0.383 ± 0.845	-0.674 ± 1.669	-0.055 ± 0.753
Trunk tissue lean (g)	$+480.423 \pm 1398.18$	$+679.914 \pm 1105.33$	$+219.391 \pm 955.280$	$+912.344 \pm 1370.26$	$+505.591 \pm 882.318$	$+793.880 \pm 1802.77$
Trunk tissue fat (g)	-394.1 ± 814.3	-16.4 ± 1455.7	-236.866 ± 738.435	$+770.355 \pm 829.910$	-606.491 ± 1570.27	-582.780 ± 899.056
Trunk tissue (% fat)	-0.993 ± 1.905	-0.925 ± 3.277	-0.754 ± 2.151	$+0.788 \pm 2.249$	-2.210 ± 3.412	-1.280 ± 1.626
Total tissue lean (%)	$+552.600 \pm 1722.48$	$+667.805 \pm 1591.62$	$+114.358 \pm 1438.65$	$+991.221 \pm 1941.24$	$+425.250 \pm 1309.78$	$+1078.49 \pm 1957.00$
Total tissue fat (g)	-330.077 ± 1152.25	-221.052 ± 1731.05	-238.400 ± 1214.40	$+761.911 \pm 1112.51$	-958.275 ± 1778.95	-440.090 ± 1127.28
Total tissue (% fat)	-0.544 ± 1.554	-0.467 ± 2.080	-0.439 ± 1.756	0.544 ± 1.561	-1.225 ± 2.150	-0.670 ± 1.352

Table 3 Glucose tolerance test (75 g oral glucose): the AUC (glucose mg/dl 120 min) was corrected by subtracting the basal area. Data are given as mean $\pm$ s.d.

	Arm A (sequence Genotropin/placebo)	Arm A (sequence placebo/Genotropin)
PERIOD 1		
BASAL		
Patients (n)	15	15
Corrected AUC	3760 $\pm$ 2496	2864 $\pm$ 1990
Plasma IRI	13.6 $\pm$ 6.16	17.00 $\pm$ 9.57
Plasma C-peptide	2.67 $\pm$ 0.85	2.95 $\pm$ 0.94
END		
Patients (n)	12	12
Corrected AUC	2484 $\pm$ 2174	2076 $\pm$ 2308
AUC Δ^*	-1276 $\pm$ 1830	+788 $\pm$ 2586
Plasma IRI	13.50 $\pm$ 5.28	12.17 $\pm$ 4.76
Plasma C-peptide	2.99 $\pm$ 1.25	3.18 $\pm$ 0.75
PERIOD 2		
BASAL		
Patients (n)	11	12
Corrected AUC	2116 $\pm$ 2073	2754 $\pm$ 2355
Plasma IRI	13.27 $\pm$ 5.33	13.03 $\pm$ 5.38
Plasma C-peptide	2.98 $\pm$ 1.16	4.18 $\pm$ 3.80
END		
Patients (n)	9	11
Corrected AUC	1934 $\pm$ 2343	1436 $\pm$ 1533
AUC Δ^*	-182 $\pm$ 2821	-1318 $\pm$ 1735
Plasma IRI	16.67 $\pm$ 10.20	12.27 $\pm$ 5.37
Plasma C-peptide	3.79 $\pm$ 2.79	3.24 $\pm$ 0.89
No difference was evident between treatments.		
Glycemia: Genotropin, 3 patients showed abnormal glycemia; placebo, 3 patients showed abnormal glycemia (2 patients, 1 twice).		
HbA1c: Genotropin, 2 patients showed abnormal HbA1c; placebo, 1 patient showed abnormal HbA1c.		
Fructosamine: Genotropin, 5 patients showed abnormalities; placebo, 8 patients showed abnormalities.		

IRI (immunoreactive insulin), μ U/ml; C-peptide, ng/ml.**P* ns (vs basal period).

In each group the GH level obtained after maximal stimulation is widely variable (as the results of the s.d. analysis show), without any consistent relation to the different treatment. Increase of IGF-I in both Arm A (from 178 $\pm$ 49 to 227 $\pm$ 81 mg/dl) and Arm B (from 163 $\pm$ 59 to 187 $\pm$ 96 mg/dl) during rhGH treatment proves efficiency of GH stimulation during rhGH administration ($P = 0.0204$ between rhGH and placebo).

The pattern of plasma lipids is given in Table 5. In both Arms, treatment with rhGH induced a moderate decrease of total cholesterol and triglyceride plasma levels, a decrease which did not reach statistical significance when differences between the basal and the treatment period's data are considered. A statistically significant difference ($P = 0.0531$) of total cholesterol between treatments was observed (total cholesterol: Arm A from 213 to 205; Arm B from 211 to 202 mg/dl. Triglycerides: Arm A from 223 to 184; Arm B from 227 to 208 mg/dl).

Statistical analysis of plasma and urinary cortisol, plasma uric acid and plasma TNF- α showed no differences.

It was documented that there was only a trend to a decrease of plasma cortisol after rhGH treatment.

Discussion

GH continues to have important metabolic actions throughout the lifespan. In adulthood, GH deficit causes a distinct syndrome, which alters body composition and includes increased total visceral fat, decreased muscle mass and abnormal lipids pattern (15). All the symptoms are improved by GH replacement (16–18). The physiological dosage of GH recommended in the adult is much lower than that used in pediatric practice; consequently, hormonal side-effects are minimized. Furthermore, a reduced GH response to a variety of stimuli is a characteristic of obesity in adults (19, 20). Successful treatment with rhGH was performed both in adult obesity (21) and in subjects affected by the metabolic syndrome (22, 23). GH treatment is effective in reducing fat

Table 4 GH (ng/ml) peak secretion after GHRH and arginine infusion and plasma IGF-I (ng/ml) values. Data are given as mean $\pm$ s.d.

	Arm A (sequence Genotropin/placebo)	Arm B (sequence placebo/Genotropin)	Arm A (sequence Genotropin/placebo; males)	Arm A (sequence Genotropin/placebo; females)	Arm B (sequence placebo/Genotropin; males)	Arm B (sequence placebo/Genotropin; females)
PERIOD 1						
BASAL						
Patients (n)	15	15	5	10	8	7
GH	31.41 $\pm$ 28.57	24.24 $\pm$ 16.35	15.12 $\pm$ 6.74	39.56 $\pm$ 32.07	24.29 $\pm$ 17.70	24.19 $\pm$ 16.06
IGF-I	178.41 $\pm$ 49.47	160.73 $\pm$ 50.15	165.14 $\pm$ 33.87	185.05 $\pm$ 56.12	166.49 $\pm$ 51.52	154.14 $\pm$ 51.73
END						
Patients (n)	12	12	4	8	6	6
GH	36.81 $\pm$ 37.38	19.55 $\pm$ 12.26	11.78 $\pm$ 4.76	49.33 $\pm$ 40.61	17.62 $\pm$ 11.59	21.48 $\pm$ 13.68
IGF-I	227.81 $\pm$ 96.66	146.58 $\pm$ 43.09	267.45 $\pm$ 100.92	207.99 $\pm$ 94.71	139.52 $\pm$ 42.69	153.63 $\pm$ 46.29
PERIOD 2						
BASAL						
Patients (n)	11	12	3	8	6	6
GH	29.48 $\pm$ 18.22	21.89 $\pm$ 16.39	20.13 $\pm$ 14.67	32.99 $\pm$ 19.01	15.40 $\pm$ 13.07	28.38 $\pm$ 17.86
IGF-I	206.44 $\pm$ 82.61	163.33 $\pm$ 59.00	231.90 $\pm$ 90.90	196.89 $\pm$ 83.71	155.40 $\pm$ 74.01	171.25 $\pm$ 45.04
END						
Patients (n)	10	9	3	7	5	4
GH	30.32 $\pm$ 29.51	13.06 $\pm$ 12.53	9.70 $\pm$ 10.60	39.16 $\pm$ 31.07	13.80 $\pm$ 14.41	12.13 $\pm$ 11.83
IGF-I	229.16 $\pm$ 83.54	187.66 $\pm$ 94.96	255.27 $\pm$ 92.02	216.10 $\pm$ 84.66	184.25 $\pm$ 84.18	191.76 $\pm$ 116.82

GH peak secretion; $P = \text{NS}$ between treatments.IGF-I; $P = \text{NS}$ between periods, $P = 0.020$ between treatments.

Table 5 Plasma lipids (mg/dl). Data are given as mean $\pm$ S.D.

	Arm A (sequence Genotropin/placebo)	Arm B (sequence placebo/Genotropin)
PERIOD 1		
BASAL		
Cholesterol (total)	213.7 $\pm$ 25.3	216.9 $\pm$ 55.9
HDL	49.1 $\pm$ 17.8	39.5 $\pm$ 10.7
LDL	122.9 $\pm$ 22.3	126.5 $\pm$ 45.4
Triglyceride	223.4 $\pm$ 156.7	254.3 $\pm$ 118.9
END		
Cholesterol (total)	205.6 $\pm$ 25.3	238.3 $\pm$ 92.0
HDL	44.8 $\pm$ 12.2	38.5 $\pm$ 11.6
LDL	124.4 $\pm$ 23.3	136.6 $\pm$ 39.4
Triglyceride	184.8 $\pm$ 92.6	316.2 $\pm$ 512.4
PERIOD 2		
BASAL		
Cholesterol (total)	215.6 $\pm$ 40.1	211.1 $\pm$ 35.8
HDL	51.9 $\pm$ 13.5	39.0 $\pm$ 12.8
LDL	133.9 $\pm$ 40.5	127.1 $\pm$ 34.2
Triglyceride	190.5 $\pm$ 147.7	227.4 $\pm$ 83.9
END		
Cholesterol (total)	242.3 $\pm$ 61.5	202.2 $\pm$ 42.9
HDL	48.0 $\pm$ 17.1	34.3 $\pm$ 8.6
LDL	144.0 $\pm$ 38.0	135.4 $\pm$ 35.4
Triglyceride	269.4 $\pm$ 223.9	208.8 $\pm$ 88.6

$P = 0.05$ comparing the effect of Genotropin and placebo on total cholesterol and triglycerides.

mass, especially visceral fat mass, and in maintaining lean body mass. Reduction of the visceral fat following GH administration has a pivotal role in the positive modulation of insulin sensitivity (24).

Alterations of body composition, common in HIV infections, are increasingly reported after HAART, creating the new syndrome of HIV lipodystrophy. Investigations intended to clarify the dynamics of these alterations have pointed to an impaired GH secretion and GH pulse amplitude. As in obesity, visceral fat is the best predictor of reduced GH concentrations (25–28).

Successful treatment with recombinant GH at different doses has already been reported. The main positive outcome was a reduction in visceral adipose tissue. Subcutaneous adipose tissue also decreased, but proportionally less, and skeletal muscle mass increased (29–31). A relationship between the dose of GH administered and therapeutic effects was shown. The dose of rhGH employed in this study, even if lower than the dose previously used in HIV-infected patients, is still quite high, being indeed situated in the high range of GH replacement therapy for adult GH deficiency (32, 33). Low-dose GH administration (0.07–0.10 IU/kg body weight) was proved effective in increasing lipolysis (by approximately 25%) in 1 week, without affecting glucose and protein kinetics and without altering insulin sensitivity (23). Therefore, in our trial we chose to administer a very low dose of GH (0.028 IU/kg body weight), low enough to minimize adverse effects but still efficient in inducing morphological changes in HIV adults. In fact, HIV patients are certainly more complicated than 'simply obese' men and their lipodystrophy may be more 'resistant' to the lipolytic action of GH. It is noteworthy that the effect on body composition was

achieved at a dose devoid of detrimental metabolic and hormonal side-effects.

We analyzed the two groups of patients all together (22 patients on GH treatment, 21 patients on placebo) and summarize the results of body composition in Table 2. The data of body composition, obtained by DXA scan, show that rhGH induced a selective decrease of trunk tissue fat. There is also evident a change in composition of leg tissues with a decrease in percentage fat (rhGH -0.394 ± 1.594 ; placebo -0.221 ± 1.451). Overall the effect on body composition is almost exclusively on trunk tissue fat mass, without any statistically significant effect on leg and arm fat depots. We speculate that increasing the dose of GH injected or/and the length of GH treatment may also induce an effect on limbs (Fig. 1).

The low-dose GH replacement was sufficient to determine the effect on body fat distribution, without causing

Figure 1 Variation of district tissue fat (g) from the basal following rhGH or placebo. * $P = 0.048$.

an increment of muscle mass, or a detrimental effect on metabolic parameters. In detail: (i) the maximal stimulated GH peak after rhGH administration is comparable with the basal level; (ii) increased levels of plasma IGF-I in the treated group (rhGH administration vs placebo) confirmed the effectiveness of GH treatment with respect to the GH–IGF-I axis; and (iii) GH did not show any effect on glucose metabolism (data from OGTT) or on insulin sensitivity (data from HOMA IR). In contrast, there was evident a positive effect on lipid metabolism, with a modification of the pattern of plasma lipids, due to a decrease in total cholesterol and triglyceride levels. HAART was previously shown to modify the GH–IGF-I axis. For this reason we repeated the rhGH plus arginine stimulation tests at the beginning and at the end of each treatment/placebo period. Our data indicate that a 6 month period of rhGH treatment plus HAART does not modify the GH–IGF-I axis.

The present results are relevant since a low-dose GH treatment improves body fat distribution and is devoid of metabolic side-effects. The question, which is still open, is the duration of the GH treatment effects. Previous work suggests the reversal of effects on fat distribution after cessation of GH treatment. For this reason, even in the light of the results of previous studies (32–34), we foresee the possibility of proposing short periods of low-dose GH treatment (6 months as in the present work) combined with a program of physical training (to be performed continuously both during the treatment and the wash-out periods). In fact, physical exercise is known to be a powerful physiological stimulus for GH release in humans (35, 36) and can be utilized to perpetuate the effects of exogenously administered GH in patients with HIV lipodystrophy. Finally, the present results may also be relevant for future studies aimed at assessing the effect of low-dose GH treatment in clinical conditions (other than HIV lipodystrophy) characterized by visceral obesity. The known metabolic effects of higher doses of rhGH on glucose and lipid metabolism should always be taken into consideration (37, 38).

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