Published in final edited form as:

Clin Endocrinol (Oxf). 2009 December ; 71(6): 815–822. doi:10.1111/j.1365-2265.2009.03603.x.

Relationship of peak growth hormone to cardiovascular parameters, waist circumference, lipids and glucose in HIV-infected patients and healthy adults

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SUMMARY

Objective: Relative growth hormone (GH) deficiency is highly prevalent in patients with HIV. The purpose of this study was to investigate relationships of GH to metabolic and anthropometric parameters in HIV patients and non-HIV controls.

Design: Peak GH and metabolic parameters were assessed in a cross-sectional study of 191 HIV patients and 62 age and BMI-matched healthy controls.

Methods: Peak GH was assessed by GHRH/arginine stimulation testing.

Results: HIV patients demonstrated similar BMI, but increased waist circumference (WC) and reduced peak GH to GHRH/arginine compared with control subjects (12.4 [6.3, 24.8] vs. 21.3 [8.8, 34.5] $\mu\text{g/l}$, $P=0.006$, HIV vs. control). Among HIV and non-HIV groups, peak GH was inversely associated with WC ($\rho=-0.44$, $p<0.0001$; $\rho=-0.63$, $p<0.0001$) (HIV patients and controls, respectively), blood pressure ($\rho=-0.17$, $p=0.02$; $\rho=-0.36$, $p=0.004$), triglycerides ($\rho=-0.37$, $p<0.0001$; $\rho=-0.43$, $p=0.001$), glucose ($\rho=-0.34$, $p<0.0001$; $\rho=-0.30$, $p=0.02$), insulin ($\rho=-0.43$, $p<0.0001$; $\rho=-0.60$, $p<0.0001$) and CRP ($\rho=-0.29$, $p<0.0001$; $\rho=-0.59$, $p<0.0001$). Among HIV patients, the inverse association between peak GH and fasting glucose remained significant ($\beta=-0.006\text{mmol/l}$ change in glucose per $\mu\text{g/l}$ change in GH, $p=0.004$) controlling for age, gender, race, BMI, WC, protease inhibitor (PI) and nucleoside reverse transcriptase inhibitors (NRTI). Similarly, the inverse association between peak GH and triglycerides remained significant ($\beta=-0.01\text{mmol/l}$ change in triglycerides per $\mu\text{g/l}$ change in GH, $p=0.02$) controlling for age, gender, race, BMI, WC, PI and lipid-lowering medications. HIV men with peak GH $<7.5\mu\text{g/l}$ demonstrated higher BMI, WC, SBP, triglycerides, glucose and CRP.

Conclusions: Reduced GH secretion is independently associated with dyslipidemia and higher glucose, among HIV patients with abdominal fat accumulation.

INTRODUCTION

Growth hormone (GH) is released in pulsatile manner from the anterior pituitary gland under the control of hypothalamic growth hormone releasing hormone (GHRH), ghrelin and somatostatin, and exerts important effects on body composition, glucose homeostasis, cholesterol metabolism and inflammation. Adults with GH excess have increased lean body mass and decreased body fat, whereas those with GH deficiency (GHD) have decreased lean

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Competing interests/financial disclosure

SG has served as a consultant for EMD Serono Inc. and Theratechnologies Inc., and has received research support from Theratechnologies Inc.'

body mass and increased fat mass especially visceral adipose tissue (VAT). GHD has also been associated with increased cardiovascular events and excess mortality¹, abnormal cholesterol^{2, 3}, and increased inflammatory markers associated with cardiovascular risk, including C-reactive protein (CRP) and interleukin-6 (IL-6)⁴.

Relative GHD has been described in obesity⁵⁻⁷ and in patients with HIV-associated central fat accumulation^{8, 9}. Among HIV-infected patients, reduced pulse height and overnight GH concentrations, are most strongly associated with increased visceral adiposity^{8, 10}. Randomized trials have shown that GH administration can reduce visceral adiposity and improve lipids in HIV patients with abdominal fat accumulation¹¹⁻¹⁴. However, it remains unknown whether other metabolic abnormalities are related to relative reductions in GH among HIV-infected patients and if these relationships are independent of central adiposity.

In the current cross-sectional study, we investigate the physiologic relationships of peak GH, as stimulated by GHRH/arginine, with cardiovascular risk markers, fasting glucose, insulin and lipids to further understand the inter-relationships of GH secretory capacity with these metabolic and cardiovascular parameters, both among HIV and non-HIV-infected individuals. We sought to assess whether relative GHD contributes to increased metabolic risk among HIV-infected patients.

Our results suggest that a relative reduction in GH secretion, as measured by the GHRH/arginine test, is independently associated with higher fasting glucose and triglycerides among HIV-infected patients, suggesting a physiological consequence of reductions in GH among HIV-infected patients with increased central fat accumulation receiving ART and the potential value of strategies to augment endogenous GH secretion in this population.

MATERIALS AND METHODS

Subjects

One hundred and sixty HIV-infected men, 35 healthy control men, 31 HIV-infected women, and 27 healthy control women were evaluated in this cross-sectional study. Subjects were recruited from October 2001 to March 2006. Recruitment was accomplished through community advertisement and primary care provider referral. HIV-infected subjects on stable antiretroviral therapy for at least 12 weeks were recruited to assess for changes in body composition and low peak GH stimulation for participation in a randomized trial administering physiologic doses of growth hormone¹³. HIV-infected subjects were assessed with a standard GHRH/arginine test, and had weight, anthropometrics and other lab tests performed. Non-HIV-infected control subjects were recruited for comparison with HIV-infected patients and were healthy men and women between 18 to 60 years of age, who denied a history of HIV disease. The same exclusion criteria were applied to both HIV and control participants: diabetes mellitus, renal failure, BMI <20 kg/m², use of GH, GHRH, oral or parenteral glucocorticoids, oral contraceptive estrogen, megestrol acetate, anabolic steroids or antidiabetic agents within 3 months prior to screening, or prior pituitary disease or radiation treatment. Patients with known untreated thyroid disease were excluded. Patients receiving chronic stable testosterone (n=32) were permitted to participate. Menopausal status was determined by clinical history.

Neither HIV patients nor control subjects were recruited based on specific anthropometric criteria, but a subset of the HIV patients reported in this manuscript with evidence of fat redistribution, based on a waist to hip ratio (WHR) > 0.90 and peak GH <7.5µg/l on GH stimulation testing (n=67) were invited to participate in a longitudinal study of GH administration previously reported¹³. Limited baseline analyses in HIV-infected patients of

relationships of peak GH to GHRH/arginine stimulation and metabolic parameters were previously published¹³.

The study was approved by the Massachusetts General Hospital (MGH) and Massachusetts Institute of Technology (MIT) institutional review committees and subjects provided written informed consent. Eligible subjects were seen at the general clinical research centers at the MIT and MGH.

GH assessment

After an overnight 12-hour fast, subjects received standardized stimulation testing with GHRH/arginine. GHRH 1-29 (Geref, Serono, Inc., Norwell, MA) 1ug/kg IV bolus along with simultaneous administration of arginine hydrochloride (0.5g/kg)(maximum dose, 30g) administered intravenously over 30min. GH concentrations were measured at -15, 0, 15, 30, 45, 60, 90, and 120 minutes after GHRH and arginine administration.

Biochemical indices

All blood testing were performed after an overnight 12-hour fast before any stimulation testing. GH concentration was measured by two-site RIA with an intra-assay coefficient of variation (CV) of 4.4% and inter-assay CV of 6.6% (Corning, Inc. Nichols Institute Diagnostics, San Juan Capistrano, CA). IGF-1 was measured by two-site RIA with an intra-assay CV of 4.9% and inter-assay CV of 5.1% (Diagnostic Systems Laboratories, Inc., Webster, TX). Insulin concentrations were measured by either radioimmunoassay (RIA; Siemens Medical Solutions Diagnostics, Deerfield, IL; intra-assay and interassay coefficients of variation from 3.1 to 9.3% and from 4.9 to 10.0%, respectively) or chemiluminescence immunoassay (Ultra-sensitive Beckman Access-2 Chemiluminescence platform; Beckman Coulter, Chaska, MN; sensitivity 0.03 IU/mL, precision 3-5.6%). The correlation between the two assays was $r = 0.99$, $p < 0.0001$.

Homeostasis model assessment (HOMA-IR) was calculated¹⁵. C-reactive protein (CRP) was measured by ELISA (DSL, Webster, TX) with intra-assay and inter-assay CVs ranging from 1.7%-3.9% and 2.8%-5.1% respectively. Low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald formula. Total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, and glucose were measured using standard techniques. CD4 count was determined by flow cytometry (Becton Dickinson Immunocytometry Systems, San Jose, CA) and the HIV viral load was determined by ultrasensitive assay (Amplicor HIV-1 Monitor Assay; Roche Molecular Systems, Indianapolis, IN), with limits of detection of 50-75,000 copies/ml.

Anthropometric measurements

Weight and anthropometric measurements were determined in the morning, prior to breakfast. Waist circumference (WC) was measured at the level of the iliac crest. Anthropometric measurements were obtained using an inelastic tape measure by the bionutrition staff.

Statistical methods

Distributions of continuous outcome variables were examined for normality by the Wilk-Shapiro test and examination of the histogram distributions. For variables with normal distribution, comparisons between two groups were performed using Student's t-test. For variables with non-normal distribution, comparisons between two groups were performed using the Wilcoxon rank sum test. For dichotomous or categorical variables, comparisons were performed using the chi-square test. Race was dichotomized to Caucasian or other race. Statistical significance was assumed when a null hypothesis could be rejected at p -

value <0.05 . Spearman correlation coefficients (ρ) were assessed in the univariate analysis comparing peak stimulated GH to other covariates as peak GH was not normally distributed (Wilk-Shapiro $p<0.0001$). Univariate regression analyses were performed in both HIV and non-HIV groups. Using multivariate linear regression modeling, we sought to investigate whether the relationships of peak GH with fasting glucose, fasting insulin, triglycerides, blood pressure, and CRP remained significant after adjusting for potential relevant covariates, including indices of abdominal adiposity in both HIV and non-HIV groups. Multivariate models for glucose, triglycerides, insulin, blood pressure and CRP are shown in the text and tables. Additional sensitivity analyses were performed excluding HIV-infected men on stable testosterone treatment ($n=32$, 12.7%), and excluding 13 postmenopausal women in multivariate regression modeling, similarly controlling for the anthropometric and demographic variables used in the primary models. CRP outliers greater than 100mg/L were excluded from the analyses.

Metabolic and anthropometric variables were also compared among HIV-infected men with a peak GH of less than and greater than 7.5 $\mu\text{g/l}$ based on prior data from our group establishing this optimal cut-off to define relative growth hormone deficiency among HIV infected men^{9, 16}. All statistical analyses were performed using SAS JMP statistics software version 5.1 (SAS Institute Inc., Cary, NC). Results are reported as mean $\pm$ SD, unless otherwise indicated.

RESULTS

Characteristics of study participants

253 participants including 195 men (160 HIV-positive and 35 HIV-negative) and 58 women (31 HIV-positive and 27 HIV-negative) participated in the study. Demographic and body composition parameters are shown for HIV patients and controls in Table 1. HIV and control participants were similar for age, race and BMI. Although BMI was similar, WC and WHR were higher in the HIV patients. Systolic blood pressure (SBP), total cholesterol, LDL-cholesterol, triglycerides, insulin, HOMA-IR and CRP were higher in HIV patients while HDL-cholesterol was lower in HIV patients. Peak GH determined by GHRH/arginine stimulation was also lower in HIV patients (12.4 [6.3, 24.8] vs. 21.3 [8.8, 34.5] $\mu\text{g/l}$, $P=0.006$, HIV vs. control) (median [IQR]).

Among the women in the study, 74.5% were premenopausal and 25.5% were postmenopausal. Similar percentages of women in the HIV and non HIV groups were postmenopausal, 26% and 19%, respectively.

Despite having similar waist circumference (95.4 ± 14.1 cm for women and 96.4 ± 10.5 cm for men), women exhibited higher stimulated peak GH compared to men (25.5 [12.2, 41.2] $\mu\text{g/l}$ in women; 12.2 [6.5, 20.0] $\mu\text{g/l}$ in men)(median [IQR]).

Univariate analysis

In HIV and in control subjects, peak GH concentration was negatively related to age, BMI, WC, triglycerides, glucose, insulin, blood pressure and CRP as shown in Table 2. Among HIV patients, peak GH was also related to total cholesterol and IGF-1; and among controls, peak GH was also related to HDL-cholesterol (Data are shown in Table 2 and Figure 1).

Multivariate analysis

HIV-infected patients—Among HIV patients, peak GH remained negatively associated with fasting glucose even after adjusting for age, gender, race, BMI, WC, protease inhibitor (PI) use, and nucleoside reverse transcriptase inhibitor (NRTI) use ($\beta=-0.006\text{mmol/l}$ change

in glucose per $\mu\text{g/l}$ change in peak GH, $p=0.004$) (Table 3A). Peak GH also remained significantly inversely associated with triglyceride concentration after adjusting for age, gender, race, smoking, BMI, WC, use of lipid-lowering medications, and PI use ($\beta=-0.01$ mmol/l change in triglycerides per $\mu\text{g/l}$ change in peak GH, $p=0.02$) (Table 3B).

After adjusting for BMI, the relationship between peak GH and fasting insulin trended to be inversely correlated but did not meet statistical significance ($\beta=-0.054$ $\mu\text{IU/ml}$ change in insulin per $\mu\text{g/l}$ change in peak GH, $p=0.08$). A similar trend was seen after adjusting for WC ($\beta=-0.054$ $\mu\text{IU/ml}$ change in insulin per $\mu\text{g/l}$ change in peak GH, $p=0.09$). After adjusting for BMI, the relationship between peak GH and CRP was no longer significant ($\beta=-0.040$ mg/l change in CRP per $\mu\text{g/l}$ change in peak GH, $p=0.25$). SBP and DBP remained significantly inversely associated with peak GH after adjustment for BMI ($\beta=-0.11$ mmHg change in SBP per $\mu\text{g/l}$ change in peak GH, $p=0.03$; $\beta=-0.061$ mmHg change in DBP per $\mu\text{g/l}$ change in peak GH, $p=0.04$), but not after adjustment for WC ($\beta=-0.085$ mmHg change in SBP per $\mu\text{g/l}$ change in peak GH, $p=0.09$; $\beta=-0.050$ mmHg change in DBP per $\mu\text{g/l}$ change in peak GH, $p=0.11$).

Similar results were seen in the HIV-infected group excluding men using testosterone ($n=159$). Adjusting for the same covariates as in the primary model (e.g. age, race, BMI, anthropometrics and medication use), peak GH remained significantly related to triglyceride ($\beta=-0.01$ mmol/l change in triglycerides per $\mu\text{g/l}$ change in peak GH, $p=0.02$) and glucose ($\beta=-0.006$ mmol/l change in glucose per $\mu\text{g/l}$ change in peak GH, $p=0.01$) in the subgroup not using testosterone.

Analyses in the HIV group excluding postmenopausal women yielded similar results. Peak GH remained significantly associated with triglycerides ($\beta=-0.02$ mmol/l change in triglycerides per $\mu\text{g/l}$ change in peak GH, $p=0.009$) and glucose ($\beta=-0.006$ mmol/l change in glucose per $\mu\text{g/l}$ change in peak GH, $p=0.008$) excluding postmenopausal women, adjusting for the same covariates as in the primary model.

Non-HIV-infected patients—Among the HIV-negative controls, peak GH response to GHRH/arginine was no longer significantly related to fasting glucose after adjusting for age, gender, race, BMI and WC, ($\beta=-0.00006$ mmol/l change in glucose per $\mu\text{g/l}$ change in peak GH, $p=0.99$) nor to triglyceride concentration after adjusting for age, gender, race, smoking, BMI, WC and use of lipid-lowering medications ($\beta=-0.004$ mmol/l change in triglycerides per $\mu\text{g/l}$ change in peak GH, $p=0.41$) (Tables 4A and 4B). Similar results were seen excluding postmenopausal women. After adjustment for age, gender, race, BMI, and waist circumference, the inverse relationship between peak GH and fasting insulin persisted in HIV negative controls ($\beta=-0.081$ $\mu\text{IU/ml}$ change in insulin per $\mu\text{g/l}$ change in peak GH, $p=0.02$).

Comparisons based on peak GH response to GHRH/arginine

HIV-infected patients—Demographic, body composition, hemodynamic, biochemical, and other characteristics are shown for HIV-infected men with response $>$ or ≥ 7.5 $\mu\text{g/l}$, the criterion previously shown to best identify HIV-infected men with relative GHD16 (Table 5). Among HIV infected men, those with relative growth hormone deficiency based on this criterion were older in age, had higher BMI, WC, waist to hip ratio, SBP, triglycerides, fasting glucose, fasting insulin, CRP, and lower IGF-1. After adjustment for age, parameters that remained significantly different between the groups for men were BMI, WC, waist to hip ratio, SBP, fasting glucose, fasting insulin and IGF-1. After adjustment for BMI and age, fasting glucose, fasting insulin and waist to hip ratio remained higher in HIV-infected men with peak GH < 7.5 $\mu\text{g/l}$, while IGF-1 remained lower. Smoking was more prevalent in HIV patients with peak GH < 7.5 $\mu\text{g/l}$ after adjusting for BMI and age. Thus, we adjusted for

smoking in multivariate modeling given the known potential effects of smoking on triglycerides.

Non HIV-infected patients—Insufficient numbers (n=11) of non HIV-infected patients with peak GH<7.5 µg/l were available to perform this comparison among non-HIV patients.

DISCUSSION

In the present study, we investigated the physiologic relationships of stimulated GH secretion to metabolic and cardiovascular risk markers in HIV patients and control subjects. Our data suggest reduced peak GH response to GHRH/arginine in HIV compared to non HIV-infected patients, despite similar BMI. The differences in peak GH between the HIV and non HIV groups may well be due at least in part to the increased WC among the HIV-infected patients. Increased abdominal fat accumulation is common among HIV-infected patients receiving highly active antiretroviral therapy (HAART), and we and others have shown that increased abdominal adiposity contributes to reduced GH in the HIV group 16. The purpose of the current study was to investigate the relationships of metabolic indices (lipids, CRP, glucose, insulin, blood pressure) to GH responses to GHRH/arginine within the HIV and non HIV groups.

Our data demonstrate that peak GH stimulation by GHRH/arginine was negatively associated with age, BMI and WC in both HIV and control subjects. Interestingly, peak GH was also negatively associated with triglycerides, fasting glucose, fasting insulin, SBP, DBP, and CRP in HIV and in control subjects. We adjusted for body composition in linear regression modeling to assess whether body composition mediated in part the relationship between GH and metabolic variables. In HIV patients, after controlling for BMI and WC, peak GH remained significantly inversely associated with triglycerides and fasting glucose, but not with blood pressure or CRP. The inverse relationship of peak GH and insulin was abrogated somewhat by controlling for BMI or for waist circumference in HIV patients, but an independent relationship between peak GH and insulin persisted in HIV negative controls after adjusting for potential covariates. With further adjustment for age, race, gender, PI and NRTI use, the inverse relationship between peak GH and fasting blood glucose remained significant in HIV patients. Peak GH also remained significantly inversely associated with triglyceride concentration after controlling for age, race, gender, BMI, WC, smoking, PI and lipid lowering medications in the HIV group.

The significant relationships between peak GH and glucose and between peak GH and triglycerides after inclusion of BMI and WC into the models demonstrate these relationships are not simply a function of abdominal adiposity in the HIV group. Taken together, the data suggest that increased abdominal adiposity may be strongly associated with reduced GH in HIV, but low GH is itself associated with dyslipidemia and increased fasting glucose independent of central adiposity.

In contrast, the relationship between peak GH and triglycerides and between peak GH and glucose seen in univariate regression analyses did not persist in the non HIV patients after controlling for BMI and WC. These data suggest there may be differences between HIV and non HIV groups in the relationship of GH secretion to critical metabolic variables. One potential explanation for the differential effect we observed might be that GH secretion was reduced to a greater degree in the HIV subjects.

Patients with true GHD have known alterations in lipid metabolism and glucose homeostasis, including abnormal serum lipoprotein patterns² and impaired insulin sensitivity¹⁷. GH facilitates lipolysis and stimulates glycerol release in adipose tissue¹⁸ and

inhibits lipoprotein lipase activity in adipose tissue¹⁹. Among HIV patients in the current study, peak GH remained significantly associated with triglycerides even after adjusting for potential covariates (age, gender, race, BMI, WC, smoking, PI and lipid-lowering medication use), suggesting an independent inverse relationship between GH secretory capacity and triglycerides. Consistent with this finding, GH administration to obese patients²⁰ and to HIV patients with central fat accumulation has been shown to decrease triglyceride levels^{13, 21}.

We also found peak GH remained significantly associated with fasting glucose after adjusting for potential covariates (age, gender, race, BMI, WC, PI and NRTI use). The importance of GH in glucose homeostasis has long been recognized in conditions of GH excess and deficiency; glucose is increased at low and high concentrations of GH^{17, 22-25}. Increased release of free fatty acids from excess visceral fat may link GHD to increased glucose.

The association between peak GH and CRP seen in this study may be mediated in part through body composition changes linked to deficient GH secretion. Reduced GH may contribute to excess visceral adiposity, which in turn may mediate increased inflammation. Indeed, we demonstrate that adjustment for BMI or WC significantly attenuates the significant relationship between GH and CRP. Evidence in support of this hypothesis can be seen in studies in which GH treatment reduces inflammatory cardiovascular risk markers, including CRP and IL-6 in GHD patients²⁶, but it remains unknown if this effect is due to the changes seen in abdominal fat.

Adjustment for WC also attenuated the significant association between peak GH and blood pressure. Therefore, the inverse relationship of GH and blood pressure may also be related to effects of abdominal adiposity. GH treatment has been shown to reduce diastolic blood pressure in non HIV-infected men with abdominal obesity²⁰ and among HIV-infected patients with central fat accumulation who experienced reduction in visceral fat in response to low dose physiological GH¹³.

Our group has previously shown the prevalence of relative GHD in HIV-infected men with lipodystrophy and abdominal fat accumulation to be 38.5% using an optimal cut-off of 7.5 µg/l peak response to arginine GHRH testing¹⁶. In the current study, we show that HIV-infected men with relative GHD (peak GH < 7.5 µg/l) have higher waist circumference, SBP, triglycerides, fasting glucose and insulin, consistent with similar observations in hypopituitary patients with GHD or familial isolated GHD^{4, 27, 28}. Long-term treatment with physiologic GH in HIV-infected patients with relative GHD using the cut-off of 7.5 µg/l was shown to have beneficial effects on VAT, triglycerides and blood pressure, providing further evidence of a physiological consequence of relative GHD and potential clinical benefit to its treatment¹³.

This study has a number of limitations. Prior data on GH responses to GHRH-arginine and expected normal values in healthy controls are limited. Although the study was large (n=253), the healthy control group included only 62 patients which may have limited our ability to detect significant covariates in multivariate regression analysis. Testosterone use may confound results of the GHRH/arginine test, but we repeated the analysis among patients not receiving testosterone and recapitulated the results of the primary analysis. We also performed additional analyses to eliminate potential confounding by menopausal status and similar relationships were recapitulated. Antiretroviral and lipid lowering medication use were controlled for in the models as well.

Our results suggest that reduced GH secretory capacity is associated with abdominal adiposity, triglycerides, fasting blood glucose, blood pressure, and inflammation among

HIV-infected patients. These data suggest physiological consequences of reduced GH in the HIV population. Although the direction of causality cannot be determined in this cross-sectional study, our data strongly suggest that relative GHD appears to be significantly and independently associated with metabolic dysregulation and increased cardiovascular risk indices, particularly increased glucose and triglycerides among HIV-infected patients receiving HAART and with increased WC. The relationships between peak GH and triglycerides and between peak GH and glucose remained significant, even after controlling for potential covariates. Although less robust relationships might be seen among HIV-infected patients with more normal WC, as we show in the controls, HIV-infected patients on HAART commonly exhibit increased WC, so this is a relevant and large subpopulation to study. Further investigation is needed to determine the long-term metabolic and cardiovascular effects of strategies to physiologically augment GH concentrations in relatively GH deficient HIV-infected patients with abdominal fat accumulation.

Acknowledgments

The authors wish to thank the nursing and bionutrition staff of the Clinical Research Centers of MGH and MIT, Jeff Breu, and all of the participants in this study.

Supported in part by NIH RO1 DK063639, NIH M01 RR01066-25S1 and NIH K23 HL092792.

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Figure 1. Relationships to GHRH/Arginine Stimulated GH

Solid circles denote patients with HIV, and open circles denote uninfected controls. Solid line indicates regression line for HIV patients and broken line indicates regression line for controls. *P*-values shown for simple linear regression.

Table 1

Characteristics of HIV patients vs. uninfected controls

Variable	HIV (n=191)	Controls (n=62)	P
Age (yr)	44.6 ± 7.2	44.3 ± 8.0	0.81
Race (%)			0.09
White	142 (74%)	39 (63%)	
Black	29 (15%)	17 (27%)	
Asian	2 (1%)	3 (5%)	
Hispanic	18 (9%)	3 (5%)	
Ever smoked (%)	93 (49%)	12 (19%)	<0.0001
PI use (%)	97 (52%)		
NRTI use (%)	170 (90%)		
CD4 count (cells/mm ³)	566 ± 313		
Viral load (copies/ml)	4389 ± 19411		
BMI (kg/m ²)	26.6 ± 4.4	26.2 ± 4.2	0.58
Waist circumference (cm)	97.4 ± 11.5	92.8 ± 10.6	0.006
Waist to hip ratio	0.98 ± 0.07	0.88 ± 0.07	<0.0001
Systolic BP (mm Hg)	119 ± 17	113 ± 14	0.02
Diastolic BP (mm Hg)	75 ± 10	73 ± 10	0.20
Total cholesterol (mmol/l)	4.9 ± 1.1	4.5 ± 0.9	0.02
HDL-cholesterol (mmol/l)	1.1 ± 0.4	1.4 ± 0.4	<0.0001
LDL-cholesterol (mmol/l)	2.8 ± 0.9	2.6 ± 0.8	0.13
Triglycerides (mmol/l)	1.9 [1.2, 2.7]	1.0 [0.7, 1.5]	<0.0001 *
Fasting glucose (mmol/l)	5.1 ± 0.7	4.9 ± 0.5	0.10
Fasting insulin (μIU/ml)	5.9 [3.5, 11.1]	3.8 [2.6, 6.8]	0.0003 *
HOMA-IR	1.3 [0.8, 2.5]	0.8 [0.5, 1.6]	0.0005 *
CRP (mg/l) [†]	3.1 [1.4, 7.7]	1.7 [0.7, 5.1]	0.006 *
Peak GH to GHRH-Arg (μg/l)	12.4 [6.3, 24.8]	21.3 [8.8, 34.5]	0.006 *

Results are reported as mean ± SD except for variables with non-normal distributions where they are reported as median [interquartile range].

* For variables with non-normal distributions, groups are compared by Wilcoxon rank-sum test as indicated, otherwise by Student's t test.

[†] Outliers with CRP > 100 mg/l were excluded. Analysis including all data was also significant. $p=0.02$. PI=Protease inhibitor; NRTI=Nucleoside reverse transcriptase inhibitor

Table 2

Variables associated with peak GH concentration on GHRH/arginine testing

Variable	HIV		Controls	
	Spearman Correlation Coefficient (rho)	P-value	Spearman Correlation Coefficient (rho)	P-value
Age	−0.20	0.005	−0.34	0.007
BMI	−0.42	<0.0001	−0.56	<0.0001
Waist Circumference	−0.44	<0.0001	−0.63	<0.0001
Total cholesterol	−0.22	0.004	−0.012	0.93
Triglycerides	−0.37	<0.0001	−0.43	0.001
HDL-cholesterol	0.039	0.62	0.39	0.003
LDL-cholesterol	−0.13	0.11	−0.076	0.58
Fasting Glucose	−0.34	<0.0001	−0.30	0.02
Fasting Insulin	−0.43	<0.0001	−0.60	<0.0001
SBP	−0.23	0.002	−0.37	0.003
DBP	−0.17	0.02	−0.36	0.004
CRP	−0.29	<0.0001	−0.59	<0.0001
IGF-1	0.43	<0.0001	0.090	0.52

Table 3A

Relationships between adjusted covariates and fasting glucose (mmol/l) in multivariable regression modeling for HIV+ patients

Parameter	Estimate (β)	Standard Error	P-value
Age (years)	0.01	0.006	0.09
Gender	0.08	0.07	0.25
Race	-0.01	0.06	0.80
BMI (kg/m ²)	0.01	0.02	0.52
Waist Circumference (cm)	0.002	0.008	0.84
Peak GH to GHRH/arginine (μ g/l)	-0.006	0.002	0.004
PI Use	-0.22	0.09	0.02
NRTI Use	0.35	0.16	0.03

Table 3B

Relationships between adjusted covariates and triglycerides (mmol/l) in multivariable regression modeling for HIV+ patients

Parameter	Estimate (β)	Standard Error	P-value
Age (years)	-0.008	0.02	0.68
Gender	0.29	0.20	0.14
Race	0.39	0.16	0.02
Smoking	-0.15	0.13	0.26
BMI (kg/m ²)	0.11	0.06	0.08
Waist Circumference (cm)	-0.04	0.02	0.09
Lipid-Lowering Medication Use	-0.07	0.15	0.62
Peak GH to GHRH/arginine (μ g/l)	-0.01	0.006	0.02
PI Use	0.81	0.26	0.003

Table 4A

Relationships between adjusted covariates and fasting glucose (mmol/l) in multivariable regression modeling for controls

Parameter	Estimate (β)	Standard Error	P-value
Age (years)	0.01	0.008	0.09
Gender	0.07	0.07	0.33
Race	0.04	0.06	0.51
BMI (kg/m ²)	0.01	0.03	0.71
Waist Circumference (cm)	0.01	0.01	0.28
Peak GH to GHRH/arginine (μ g/l)	−0.00006	0.004	0.99

Table 4B

Relationships between adjusted covariates and triglycerides (mmol/l) in multivariable regression modeling for controls

Parameter	Estimate (β)	Standard Error	P-value
Age (years)	0.005	0.01	0.58
Gender	0.005	0.09	0.96
Race	0.11	0.08	0.18
Smoking	0.04	0.10	0.66
BMI (kg/m ²)	-0.03	0.04	0.42
Waist Circumference (cm)	0.03	0.01	0.09
Lipid-Lowering Medication Use	-0.18	0.20	0.39
Peak GH to GHRH/arginine (μ g/l)	-0.004	0.005	0.41

Table 5

Baseline demographic and clinical characteristics in HIV-infected men by relative growth hormone deficiency categories

	GHD*+/HIV+ (n = 59)	GHD-/HIV+ (n = 101)	p	Age-adjusted p	Age and BMI-adjusted p
Demographics					
Age (yr)	46.7 ± 6.9	43.3 ± 7.4	0.005		
Race (%)			0.31	0.42	0.31
Caucasian	50 (85)	79 (78)			
African American	4 (7)	12 (12)			
Asian	0 (0)	2 (2)			
Hispanic	5 (8)	8 (8)			
Ever Smoked (%)	33 (56)	41 (41)	0.07	0.07	0.006
Body composition					
Body mass index (kg/m ²)	28.2 ± 3.9	25.3 ± 3.8	<0.0001	<0.0001	
Iliac waist (cm)	102.1 ± 10.5	94.1 ± 9.5	<0.0001	<0.0001	0.09
Waist to hip ratio	1.02 ± 0.06	0.97 ± 0.06	<0.0001	<0.0001	0.0005
Hemodynamic parameters					
Systolic blood pressure (mmHg)	125 ± 17	117 ± 16	0.007	0.03	0.05
Diastolic blood pressure (mmHg)	76 ± 10	75 ± 10	0.36	0.64	0.72
Blood chemistry and lipids					
Total cholesterol (mmol/l)	5.1 ± 1.1	4.8 ± 1.1	0.11	0.24	0.72
HDL-cholesterol (mmol/l)	1.1 ± 0.4	1.0 ± 0.4	0.17	0.33	0.55
LDL-cholesterol (mmol/l)	2.9 ± 0.8	2.8 ± 0.9	0.47	0.65	0.76
Triglycerides (mmol/l)	2.2 [1.7, 3.2]	1.8 [1.2, 2.9]	0.04 [†]	0.12	0.17
Fasting glucose (mmol/l)	5.3 ± 0.8	5.00 ± 0.6	0.0008	0.003	0.01
Fasting insulin (μIU/ml)	4.4 [3.1, 8.2]	8.9 [5.5, 17.8]	<0.0001	<0.0001	<0.0001
Peak GH to GHRH/arginine (μg/l)	4.9 [3.2, 6.4]	20.3 [12.4, 34.4]	<0.0001 [†]	<0.0001	<0.0001
CRP (mg/liter)	5.6 [2.0, 11.9]	2.4 [1.3, 5.1]	0.0002 [†]	0.09	0.13
IGF-1 (μg/l)	152 [112, 202]	365 [264, 463]	<0.0001 [†]	<0.0001	<0.0001
Immune function					
CD4 count (cells/mm ³)	607 ± 296	555 ± 326	0.35	0.25	0.26

	GHD ⁺ /HIV ⁺ (n = 59)	GHD ⁻ /HIV ⁺ (n = 101)	p	Age-adjusted p	Age and BMI-adjusted p
Viral Load (copies/ml)	994 ± 6657	5872 ± 22089	0.04 [‡]	0.16	0.37
Current medication use (%)					
PI use	30 (52)	51 (50.5)	0.88	0.98	0.87
NRTI use	55 (95)	90 (89)	0.20	0.33	0.39
Lipid drug use	26 (44)	24 (24)	0.009	0.08	0.10
Anti-Hypertensive drug use	18 (31)	13 (13)	0.008	0.04	0.18

Outliers with CRP > 100mg/l were excluded. Analysis including all data also significant. $p=0.0002$.

For continuous variables, results are reported as mean ± SD except for variables with non-normal distributions where they are reported as median [interquartile range]. For categorical variables, results are reported as number (%).

* Relative growth hormone deficiency (GHD) based on peak growth hormone (GH) to growth hormone releasing hormone-arginine (GHRH-Arg) < 7 µg/l

[‡] Comparison of two groups by Wilcoxon rank-sum test for non-normally distributed variables as indicated, otherwise by Student's T-Test.