Eur J Med Res (2008) 13: 173-178

GROWTH HORMONE AND BONE MINERAL DENSITIY IN HIV-1-INFECTED MALE SUBJECTS*

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Abstract
The aim of this study was to characterize the GH-IGF-I axis of patients with HIV-1-infection without any symptoms of AIDS-associated wasting. A special emphasis was placed on determine bone mineral density (BMD) and biochemical markers of bone metabolism. Therefore 42 male fasting HIV-1-infected outpatients were included and estimation of serum GH, IGF-I, IGFBP-1 and 3, osteocalcin, TNF-α, 1,25dihydroxycholecalciferol, and endocrine markers of the gonad function by commercially available RIA's performed. DEXA-measurements of the lumbar spine and the Ward's triangle of the left hip were done. The GH, IGF-1, IGFBP-1 and 3 serum levels were within the normal range Performing Spearman-correlation test, we established significance between IGF-I serum levels and BMD lumbar spine and Ward's triangle ($p < 0.01$, $p < 0.05$), CD4 cell-count ($p < 0.05$), 1,25dihydroxycholecalciferol ($p < 0.05$), osteocalcin ($p < 0.05$), TNF-α ($p < 0.05$), body mass index (BMI) ($p < 0.05$) and total testosterone ($p < 0.01$). IGFBP-1 correlates both inversely significantly with CD4 cell-count ($p < 0.05$) and serum -calcium ($p < 0.05$). The IGFBP-3 correlates with BMI ($p < 0.05$) and serum osteocalcin ($p < 0.05$). Correlation both with markers of bone metabolism and vitamin D metabolites showed the important role of GH/IGF-I axis in modulating the availability of calcium in chronic conditions. This axis may be in a part responsible for the manifestation of the HIV-associated osteopenia.

Key words: Bone metabolism, GH, IGF-I, IGFBP, HIV

INTRODUCTION

The GH-insulin-like growth factor (IGF) axis is thought to be an essential component of the endocrine system responsible for stimulating protein synthesis and maintaining lean body mass in adults [1,2]. Both GH and IGF-I, enhance nitrogen retention and influence muscle protein synthesis [3, 4, 5]. IGF-physiology is greatly influenced by IGF binding proteins (IGFBP) More than 90 % of IGF-I in serum is bound by IGFBP-3 as part of a high molecular weight complex. IGF-I has its greatest anabolic effects when present as part of this complex [6]. Since changes in the concentration and / or structure of IGFBPs dramatically influence the biological activity of the IGFs [7], the quantification of serum IGF-I alone may be an insufficient measure of the potential biological activity in the IGF's. However, IGF-I also affects the concentration and structure of IGFBPs [8, 9]. Abnormalities in the IGF-system have been found to be associated with various catabolic states [10, 11, 12], such as is seen in terminally ill AIDS patients [12]. GH and IGF-I have been proposed as pharmacological agents for treating AIDS associated wasting [13, 14]. However, information about the IGF-I system in HIV-1-infected patients without wasting syndrome are rare.

Alterations of bone metabolism have been observed in numerous studies of small groups of male patients infected with HIV, hypocalcemic phases [15, 16, 17] hypercalcemic phases [18, 19, 20] reduced serum osteocalcin levels [21, 22] and hypoparathyroidism [21, 23] However, in addition to the disease process itself , social and individual factors seem to bee of importance in the pathogenesis of potentially HIV-associated osteoporosis, for instance, a lack of sufficient and balanced diet including vitamins and minerals or the abuse of drugs or alcohol.

Moreover, patients with growth hormone deficiency has been identified as an additional risk factor of low bone mass. The purpose of the present study was to determine whether changes occur in the circulating levels of GH, IGF-I in AIDS patients without wasting and whether alterations in IGFBP's 1 and 3 could be partly responsible for these changes. Additionally, we report relations between markers of the growth-hormone/IGF-I axis and bone metabolism/bone mineral density. Lifestyle information was also recorded because factors such as smoking and physical exercise may also influence bone mass.

PATIENTS AND METHODS

PATIENTS

42 male patients with a confirmed serological diagnosis (including Western blot analysis) of HIV-1 infection participated in the study. They were examined as

* In honour of the 80th birthday of Prof. Dr.med. Drs. h.c. Konrad Federlin, Justus-Liebig-University Giessen, Germany

outpatients. (age range 19 to 51 years) At the time of examination none of the patients had concomitant opportunistic infections; acute or chronic hepatitis with increased transaminase activities; alterations of the liver parenchyma under sonomorphic criteria; wasting symptoms; gastrointestinal disorders such as pancreatic insufficiency or malabsorption syndrome, or chronic diarrhea. The patients did not take any drugs known to influence the characteristics of bone metabolism or the endocrine system, but the necessary medication including antiretroviral therapy was continued. The recruitment of the patients was performed before our patients received protease inhibitors for additional antiretroviral therapy. Patients with a CD4 cell count below 250 got a daily treatment with Cotrimoxazol- therapy (Trimethoprim 80 mg/Sulfamethoxazol 400 mg) for prevention of the pneumocystis carinii pneumonia. Four subjects suffered from a previous mycobacterium infection, were treated daily with Rifambutin 900 mg, Isoniazid 120 mg, and Ethambutol-HCL 200mg. A soor mycosis resulting from infection with candida species was treated locally with Amphothericin B containing drugs. Patients with cytomegaly-associated chorioretinitis were excluded from the study, since treatment with Foscarnet or Gangcyclovir is known to affect calcium level. Clinical data are shown in Table 1. Fasting blood samples were obtained by puncture of a cubital vein. The serum was frozen and stored at –30°C until analysis. 24-h urine samples were collected after a gelatin-free diet and stored without additives at –30°C.

Methods

The lymphocyte subpopulations (CD4) were determined using monoclonal antibodies and the FACscan autoanalyzer (both from Becton-Dickinson). Total pyridinolines were measured using RIA kit from Biermann, Bad Nauheim, Germany. The reference value for this kit was set at values lower than 50 nmol/pyd/nmol crea. Serum calcium, phosphate, creatinine and albumin as well as the urinary excretion of calcium, phosphate, and creatinine were measured by standardized laboratory methods. Plasma PTH (1-84) was determined by radioimmunoassay (RIA) from the Nichols Institutes, Wijchen, The Netherlands. Serum osteocalcin was measured using a commercial RIA kit from Incestar, Stillwater, Minnesota, USA. The inter-

Table 1. Descriptive characteristics and biochemical markers of 42 HIV-1-infected male subjects.

Item	N	Minimum	Maximum	mean	Standard deviation	Equal variance
weight [kg]	42	51	106	73.29	13.82	+
Body Maß Index [kg/m^2]	42	18.1	29.1	22.755	2.556	+
age [years]	42	19	51	34.79	7.61	+
CD 4 cells [total]	42	10	410	166.71	130.51	no (p=0.056)
Serum Ca [mmol/L]	42	1.78	2.73	2.2740	0.2236	+
Serum D3 [pg/mL] 1,25(OH)2D	42	6	92	28.45	18.16	no (p=0.053)
Serum D3 [ng/mL] 25OHD	42	9	64	30.14	15.04	no (p=0.083)
PTH [pg/mL]	42	7	42	20.12	8.55	+
Prokollagen-1-Peptid [ng/mL]	42	41.9	225.0	94.543	36.129	+
Osteocalcin [ng/L]	42	5.1	24.7	13.893	5.683	no (p=0.061)
Calcitonin [ng/L]	42	1	15	7.81	3.80	no (p=0.088)
Albumin[g/L]	42	26	53	38.86	7.06	+
Cross-Links [nmol Pyd/mmol Krea]	42	13	132	64.45	31.91	no (p=0.092)
Urin Ca2+ [mmol/24h]	42	0.9	11.4	4.324	2.689	no (p=0,002)
BMD [LWS a.p.] [% of age related means]	42	81	103	93.33	6.88	no (p=0.016)
BMD [WARD] [% of age related means]	42	84	105	95.26	5.57	no (p=0.045)
Testosteron [ng/dL]	42	68	710	335.76	161.31	+
Prolactin [mU/L]	42	3	29	12.92	6.78	no (p<0.005)
FSH [mU/mL]	42	0.6	4.2	2.079	0.953	+
LH [mU/mL]	42	0	4	1.85	0.85	+
STH [ng/mL]	42	0.1	3.7	1.455	0.976	no (p=0.041)
IGF 1 [ng/mL]	42	68	319	163.95	67.01	no (p=0.062)
IGFBP 1 [ng/mL]	42	9	181	57.64	44.63	no (p=0.002)
IGFBP 3 [ng/mL]	41	1.3	5.9	3.582	1.158	no (p=0.012)
TNF-α	35	13	167	77.89	47.01	+

• Results of the Kolmogorov-Smirnov-Test with Lilliefors-correctur. „+“ means the p-niveau greater than 0.200.

Table 2. Correlation betwen the characteristics and the markers of the GH/IGF-I axis.

Correlationsmatrix (Spearman's Rankcorrelation r)			
	Item 1		
Item2	**IGF 1 [ng/mL]**	**IGFBP 1 [ng/mL]**	**IGFBP 3 [ng/mL]**
Gewicht [kg]	0.311* (42)	-0.248 (42)	0.204 (42)
Body Maß Index [kg/m^2]	0.381* (42)	-0.143 (42)	0.339* (42)
Alter [Jahre]	0.146 (42)	-0.079 (42)	-0.072 (42)
CD 4 cells [total]	0.311* (42)	-0.334* (42)	0.278 (42)
Serum Ca [mmol/L]	0.458** (42)	-0.357* (42)	0.122 (42)
Serum D3 [pg/mL] 1,25(OH)2D	0.313* (42)	-0.288* (42)	0.223 (42)
Serum D3 [ng/mL] 25OHD	0.389* (42)	-0.363* (42)	0.238 (42)
PTH [pg/mL]	0.304 (42)	-0.096 (42)	0.076 (42)
Procollagen-1-peptid [ng/mL]	0.136 (42)	0.056 (42)	0.191 (42)
Osteocalcin [ng/L]	0.531** (42)	-0.235 (42)	0.36* (42)
BMC [%]	0.067 (42)	0.13 (42)	0.063 (42)
BMD [LWS a.p.] [%of age related means]	0.411** (42)	-0.15 (42)	0.283 (42)
BMD [WARD] [%of age related means]	0.357* (42)	-0.041 (42)	0.201 (42)
TNF-α	-0.438* (35)	0.286 (35)	-0.200 (35)
Testosteron [ng/dL]	0.400** (42)	-0.203 (42)	0.221 (42)

* p-level of the tests r = 0 lower than 0.05; ** p-level of the test r = 0 lower than 0.01

and intra-assay coefficients of variation were 5% and 10%, respectively (reference 2.0 to 6.5 pg/ml). Calcitonin was measured using a RIA kit from Biermann, Bad Nauheim, Germany (normal values 5-15 pg/ml). Vitamin D concentration: 1,25-dihydroxycholecalciferol, (1,25 (OH)2D3) in serum was determined using a RIA from Nichols Diagnostics, Wijchen, The Netherlands (detection limit 5.0 ng/ml); 25 (OH)D3 was determined using a RIA from Nichols Diagnostics, Wijchen, The Netherlands (normal values 8-80 ng/ml). Prior to the assay the serum was absorbed on a C18OH column to remove the lipid components. The markers of the gonadal axis were measured by means of commercially available kits: FSH and LH RIA, (Biermann, Germany); prolactin and total testosterone RIA, (BYK, Germany).

The estimation of STH was performed using a RIA of FA Nichals Institute Wijchen, The Netherlands. Serum - IGF-I was estimated using a commercially available RIA of Nichals Institute Wijchen, The Netherlands. The IGF-binding proteins 1 and 3 were estimated by both RIA of the Wijchen, The Netherlands, Tumor necrosis-Factor-a [TNF-α] (IRMA, Fa Medgenix, Amersfoort, Netherlands) normal minimal demonstrable 5 pg/ml.

BMD Measurements

The measurement of the bone mineral density (BMD) was performed using the dual-energy X-ray absorptiometry (DEXA) of the LUNAR Radiation Corporation, Madison, Wisconsin, United States. Measurements were taken at the lumbar spine (L 1 to L 4 a.p.) and Ward's triangle of the left hip. Low BMD was defined according to World Health Organization (WHO) guidelines as T scores less than –2.5 SD's below the mean of young healthy adults.

Statistical Analysis

Normal distribution of data was analyzed by the Lillifors-modified Kolmogorow-Smirnov normality test (Table 1). Since most of the means were not normally distributed, non-parametric test were necessary to test the value of statistical significance. Data that showed unequal variance or abnormal distribution were analyzed by Mann-Whitney rank sum test. Correlation analysis with determination of Spearman-rank-correlation coefficient was performed to examine the degree of relationship between the variable "marker of GH/ IGF-I" and other variable. Statistical analysis was performed using Statistical Package for Social Science (SPSS) [25].

Results

None of our patients had an acute experienced weight loss of more than 10 % of their ideal body mass. We recorded lifestyle information and physical characteristics both in Table 1 and Table 3. There were no differences between the characteristics and the markers of GH/IGF-I axis. The descriptions of the binär named variables were presented in Table 4. In the HIV-1 infected patients there were considerable variation in the levels of serum IGF-I. Reduced serum IGF-I was associated with lowered body mass index and the reduced number of CD4 content. There were significant correlation between the IGF-1-levels and both the BMD of the lumbar spine and the WARD`s triangle of the left hip. However, patients with lowered IGF-I also presents decreased levels of total testosterone. Therefore, we are not able to exclude the additional influence of hypogonadism on the reduced bone mineral density of the lumbar spine and the Ward's triangle. The TNF-α -levels were inversely correlated with

Table 3. Means and p-levels of the Mann-Whitney-U-Tests.

Variable to test				
Variable of the group		**IGF 1 [ng/mL]**	**IGFBP 1 [ng/mL]**	**IGFBP 3 [ng/mL]**
smoker	yes (N=30)	22.08	20.87	23.22
	No (N=12)	20.04	23.08	15.63
p-level		0.631	0.611	0.064
Drug addicts	Yes (N=14)	19.04	24.36	16.71
	No (N=28)	22.73	20.07	23.22
p-level		0.362	0.296	0.102
Hepatitis C infection	yes (N=7)	17.43	25.43	17.36
	no (N=35)	22.31	20.71	21.75
p-level		0.353	0.370	0.385

Table 4. Descriptive statistical analysis of the binary named variables

Item	**number "yes"**	**number "no"**
smoker	30	12
unemployment	23	19
Drug addicts	14	28
Hepatitis C Inf.	7	35
Pneumocystis carinii Inf.	32	10
Tuberculose Inf.	3	39

the IGF-I-levels ($p < 0.05$). The reduced rate of bone formation is presented by the lowered serum osteocalcin. Decreased IGF-I and its binding protein 3 correlate significantly with the serum osteocalcin ($p < 0.05$).

Discussion

The reduction of bone mineral density in HIV-1 infected patients is documented in some studies with a small number of subjects. Carr et al. present the data of DEXA in 221 HIV-infected men which were treated with protease inhibitors or reverse transcriptase inhibitors. Osteoporosis was found in 3% and osteopenia in 44 % of the patients [25]. There was no independent association with other parameters including type or duration of antiretroviral therapy and lip dystrophy at any site. Lower BMD was associated with lower weight prior to commencing antiretroviral therapy, whereas low spinal BMD was associated mostly with higher lactate values [25]. Reduced BMD of lumbar spine and Ward's triangle in our male HIV-infected subjects showed a higher progression of BMD loss related with loss of CD4 cells and lower IGF-I-levels. Because both GH-deficiency and normal aging are associated with decreases in bone density, it has been hypothesized that reduced GH secretion may account in part for age related loss of bone. However, the age range of our subjects was not so extreme distributed.

Disturbances in the growth hormone and IGF-I have also been described in HIV infection. Decreased levels of IGF-I have been noted in some malnourished individuals with HIV-infection [26, 27], but normal levels of IGF-I were reported in two other groups of patients with prior weight loss [13, 14]. Our subjects were examined during period of relative clinical and weight stability and differ therefore from the propositions with malnutrition and decreased IGF-I-levels [26, 27]. GH levels of our subjects were within the normal range. These findings were in contrast to the report of Frost et al. [27], in which a pattern of increased GH levels, coupled with decreased IGF-1 levels in 3 of 11 patients with HIV-associated wasting, were noted. Evidence of growth hormone resistance has been presented in several studies [1]. When weight-stable HIV-infected patients with normal levels of IGF-I were given pharmacological doses of rhGH, circulating levels increased to a lesser extent than was seen in healthy control subjects [13, 14]. The cross-sectional nature of our study led us to determine whether the GH/IGF-1 axis is normal in prolonged periods of time in AIDS patients. Longitudinal data might exclude the possibility that we were observing only transient changes in the GH/IGF-I axis that occur with episodes of infection or malnutrition [26, 27, 28]. Frost et al. suggested, that mechanisms exist that prevent restoration of IGF-I levels to normal. These might include abnormal expression and post-translational modification of IGFBPs [27]. In wasting patients with AIDS Frost et al. [27] estimated reduced levels of circulating IGF-I, IGF-II, and IGFBP-3 and an inability of high concentrations of GH to maintain normal levels of IGF-I. IGFBP-3 levels were decreased in severely wasted AIDS patients. In contrast to the Frost' data we observed IGFBP-3 within the normal range, but our patients have stable weight and body mass indices.

HIV-infected patients with reduced CD4helper-cell-count showed increased levels of IGFBP-1. This correlation was significantly. IGFBP-1 is present as a phosphoprotein in two other catabolic states, trauma and uncontrolled diabetes mellitus [11]. High levels of IGFBP-1 may be a result of elevated serum cortisol. A hypermetabolic condition is observed in HIV-patients,

too. Therefore, elevated IGFBP-1 levels in AIDS patients with wasting were expected [27]. TNF-α increased rapidly circulating levels of IGFBP-1 in vivo and stimulates hepatocellular production IGFBP-1 at the level of IGFBP-1-mRNA abundance in cell culture [29].

GH may also influence bone density trough effects on vitamin D metabolism. Hypophysectomy eliminates increases in plasma levels of 1,25 dihydroxyvitamin D as well as in vitro production of the vitamin by kidney slices ex vivo normally seen with phosphate deprivation. GH treatment of these animals restores normal 1a-hydroxylase activity [30, 31]. Such effects on vitamin D metabolism could theoretically mediate increases in bone density trough increased calcium absorption or local effects on bone mineralization. From these background we present significant correlation between 1,25(OH)2D3 levels and the IGF-I secretion.

In conclusion, we have found that in HIV-1infected male subjects' serum GH, IGF-1 levels and IGFBP-1 and 3 were within the normal range. However, correlation both with markers of bone metabolism and vitamin D metabolites showed the important role of GH/IGF-I axis in modulating the availability of Calcium in chronic conditions. This axis may be in a part responsible for the manifestation of the HIV-associated osteoporosis.

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Received: November 7, 2007 / Accepted: January 30, 2008

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