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Source / Izvornik: **Journal of Clinical Densitometry, 2007, 10, 327 - 331**

Journal article, Accepted version
Rad u časopisu, Završna verzija rukopisa prihvaćena za objavljivanje (postprint)

https://doi.org/10.1016/j.jocd.2007.03.103

Permanent link / Trajna poveznica: https://urn.nsk.hr/urn:nbn:hr:105:493659

Article title: Bone properties in patients with acromegaly: quantitative ultrasound of the heel

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Running title: Bone properties of acromegalic patients

Abstract

Growth hormone (GH) deficiency and acromegaly serve as good models for investigating the effects of GH on bone remodelling. However, the results from various studies are rather conflicting. The aim of our study was to estimate the potential role of gender, disease activity and duration on both calcaneus quantitative ultrasound (QUS) parameters and bone turnover markers in patients with acromegaly. Thirty-six acromegalic patients (17 men, 19 women) and three age and gender adjusted controls for every patient were included in the study. The disease was active in 22 patients, and was considered cured in 14 of them. In each subject, quantitative ultrasound of the heel and parameters of bone turnover (bone alkaline phosphatase, β-crosslaps, and osteocalcin) were measured. The results demonstrated lower QUS values in acromegalic patients compared with the controls. When stratified by gender, the differences in QUS parameters were significant in men, but not in women. Male patients with active disease had significantly lower QUS values than those in remission. Such differences were not observed among women. Multiple regression model indicated strong association between disease activity and the QUS parameters. The group of patients with active disease had a higher level of serum β-crosslaps, while osteocalcin concentration was significantly increased only in male patients with active disease. The results of our study suggest significantly lower QUS values and increased bone turnover in male patients with active acromegaly. The disease activity is the strongest predictor of the QUS parameters in acromeglic patients.

Keywords: acromegaly, bone, calcaneus, quantitative ultrasound

Introduction

Growth hormone (GH) and insulin-like growth factors (IGFs) are important regulators of bone remodelling process. Both GH and IGF-1 influence osteoblast differentiation and proliferation *(1, 2)*. Two distinctive clinical conditions, GH deficiency (GHD) and acromegaly, serve as good models for investigating the effects of GH on bone metabolism. Several studies revealed that patients with GHD have reduced bone mass and increased fracture risk *(3-5)*.

Although it is generally thought that chronic GH excess in acromegalic patients influences bone metabolism, the results from various studies are rather conflicting. It seems that other hormones, namely sex steroids as the most important ones, modulate the net GH/IGF-1 effect on bone *(6, 7)*. Some studies reported no differences in bone mineral density (BMD) at spine and femur between acromegalic patients and controls *(8, 9)*, while others reported lower *(10)* or even higher *(11)* values. The major limitations of these studies were a small size of the sample or a lack of analysis regarding gender or disease activity. Although acromegaly has often been associated with osteoporosis *(12)*, no study revealed increased fracture rate in acromegalic patients. Moreover, a recent study showed decreased fracture risk in acromegaly *(13)*. Several studies reported the anabolic effect of GH/IGF-1 axis on cortical bone, with either no effect or negative effect on the trabecular bone BMD *(7, 12, 14)*. All the studies were based on measurements of bone density by dual energy x-ray absorptiometry (DXA). However, as DXA provides no information on bone microarhitecture, the individual risk of fracture cannot be explained solely by BMD measured by DXA. This observation suggests that fracture risk prediction could be improved by the evaluation of other bone characteristics such as trabecular microstructure.

Quantitative ultrasound (QUS) has been extensively used in the last decade, due to some important advantages over DXA: it is inexpensive, ionisation-free and portable. The

speed of low-frequency ultrasound through bone depends on bone quality and density. QUS reveals physical properties of the bone determined by bone composition and structure. Thus, it provides useful information not only on bone mass, but also on bone tissue architecture and elasticity. Several studies confirmed the QUS as a good diagnostic tool for detecting individuals at risk of fragility fracture *(15-18)*. However, to our knowledge, only one study reported the influence of GH excess on calcaneus QUS parameters *(19)*. In this regard, the aim of the present study was to estimate the potential role of gender, disease activity and duration on calcaneus QUS values and bone markers concentration in patients with acromegaly.

Materials and methods

Subjects

Thirty-six patients (17 men, aged 48.5±10.6 and 19 women, aged 52.5±10.8) with acromegaly referred to the Department of Endocrinology, University Hospital of Zagreb, in the period between July 2003 and October 2005 were included in the study. Two female patients were excluded from the study as they had been treated with agents affecting bone metabolism (one alendronate, one high dose corticosteroids). Three age and gender adjusted controls for every patient were obtained from a dataset used to create the Croatian general population ultrasound measurements standards *(20)*. Each patient signed an informed consent before entering the study. The Local Ethics Committee approved the study.

The diagnosis of acromegaly was based on characteristic clinical features, failure to suppress serum GH level below 1 μg/l after oral glucose tolerance test and high serum IGF-1 level. Acromegaly cure was defined by normal IGF-1 level for age, and suppression of GH level below 1ug/l after glucose load. The disease was active in 22 patients (10 recently diagnosed, 12 previously unsuccessfully treated by surgery or radiotherapy) and 14 had been

considered cured. Among female patients, 11 had an active disease, and 8 were considered cured, while among male patients, 11 had an active disease and 6 were considered cured. The average duration of remission was 82.0±15.02 months.

Females with regular menstrual cycles were considered as having normal gonadal function. Similarly, normal testosterone concentration and the absence of clinical symptoms of hypogonadism were considered proof of normal gonadal function in males. Ten female patients (7 with active disease (63%) and 3 cured (38%)) were postmenopausal. One cured female patient was postoperatively given estrogen replacement. Six male patients (4 with active disease (36%) and 2 cured (33%)) were hypogonadal. Four male patients (1 with active disease, 3 cured) were postoperatively given testosterone. Seven male (4 with active disease, 3 cured) and 8 female patients (5 with active disease, 3 cured) were given replacement of other hormones (levothyroxine, hydrocortisone, or both).

Height and weight were measured without shoes using a portable stadiometer and a digital scale.

Serum IGF-1 was measured by enzyme-linked immunosorbent assay (ELISA; Biocode-Hycel, Belgium) and GH level was assayed by radioimmunoassay (RIA; IBL Germany). Bone alkaline phosphatase, osteocalcin and β-crosslaps levels were measured by ELISA (Nordic Bioscience Diagnostics) and the level of free testosterone was measured by RIA (DPC).

Quantitative ultrasound

In each subject, a broadband ultrasound attenuation (BUA) and speed of sound (SOS) of the heel were measured using the Sahara ultrasound (Hologic). The left foot was examined if there was no history of fracture or other relevant foot disease (in such cases the right foot

was measured). Before the first measurement on the respective day, quality assurance was performed using the calibrating phantom. The quantitative ultrasound index (QUI) was calculated by the device software. Coefficients of variations were 6.5% for BUA, 0.2 % for SOS and 2.8% for QUI.

Statistical analysis

The ultrasound measurements were expressed as the mean and standard deviation. We used an independent sample t-test to compare ultrasound measurements between patients with acromegaly and controls, and between patients with active disease and those in remission. Correlations were assessed using Pearson's test. The effect of disease activity on QUS parameters was assessed in the multiple regression model, which was adjusted for gender, body mass index and gonadal status effects. The analysis was performed in the SPSS statistical package, version 12.0.0 (SPSS Inc, Chicago, IL, USA), with statistical significance set at $P<0.05$.

Results

The final sample consisted of 17 male patients and 19 female patients, with 51 male and 57 female controls. The initial analysis revealed higher ultrasound values among controls, with the difference being more pronounced among males (Table 1). The statistical analysis revealed significant differences between the patients and controls in males, and no differences in females, except for the borderline in significant finding in the case of BUA (Table 1). Further analysis among patients with acromegaly revealed significant differences in ultrasound measurements among male patients in the active disease stage and in remission,

and the absence of such a difference among females (Table 2). Multiple regression model indicated strong association between disease activity and the QUS parameters (Table 3).

QUS values in patients with the cured disease did not significantly differ from those observed in the control groups.

In both males and females, patients with active disease had a higher serum level of β-crosslaps while the osteocalcin concentration was significantly increased only in males (Table 2).

We did not find a significant correlation between the IGF-1 and GH with the QUI (r=-0.11, *P*=0.622; r=0.19, *P* =0.445, respectively) among the patients in the active disease stage. Similarly, no significant correlation was found between the QUI and disease duration (disease duration-QUI r=-0.25, *P* =0.270).

Discussion

The present study supports the important role of chronic GH excess on bone properties, and its dependence on gender and disease activity. A study that previously analysed calcaneus QUS parameters in acromegalic patients *(19)* used a different QUS device (Achilles, Lunar). The main advantage of the current study was the representativeness of the control group, obtained from the database used to create normative data for QUS measurements in the general population of Croatia. The results demonstrated decreased QUS measurements in acromegalic patients compared to control subjects, suggesting impaired bone quality. In a similar manner, lower SOS, BUA and QUI values were observed in patients with active disease in comparison with the cured ones. Moreover, QUS results in the cured patients did not significantly differ from those in healthy subjects matched for age and sex, which

suggests that the QUS parameters changes are completely reversible after acromegaly has been cured.

Increased bone turnover has previously been documented in patients with acromegaly *(21, 22, 23)*. Moreover, growth hormone treatment in elderly osteoporotic women has been shown to increase both bone resorption and bone formation markers *(24)*. In accordance with those reports, this study revealed higher β-crosslaps and osteocalcin levels in subjects with active disease.

However, differences in the QUS measurements between patients and controls were significant in males while the same outcome was not observed in females, which means that the disease affects men more severely than women. In the multiple regression model the association between gender and QUS parameters was significant in the case of QUI, and borderline significant for the BUA and SOS, which speaks in favour of the above hypothesis. A similar finding was reported by Bolanowski et al. *(19)*. Based on these data it seems that the effect of the GH/IGF-1 axis on bone metabolism is stronger in men than in women, but the reason for the observed gender discrepancy is not quite clear. It is known that the GH/IGF-1 axis is involved in the pathogenesis of hyperandrogenism in polycystic ovarian syndrome *(25)*. In a similar manner, the gender discrepancy in bone metabolism between male and female acromegalic patients could be attributed to the androgenic effect of GH/IGF-1 excess on bone *(26)*. Tütüncü et al. hypothesized that this androgenic effect is more important in females, than in males, who already have maximal androgen influence on bone *(27)*. Another possible explanation can be that in female patients, in contrast to males, the impact of estrogen on bone metabolism could possibly overcome the GH/IGF-1 effect. However, in the present study the female patient group was more heterogeneous than the male group, with 10 out of 19 patients being postmenopausal at the time of the observation. This also has to be considered when looking into gender discrepancy in the QUS parameters and bone markers.

When dealing with the results of the present study we should not discard the possibility that the local conditions of the bone and surrounding heel tissue may introduce bias, as well as possible different calcaneal architecture between male and female patients with acromegaly. Changes of joint morphology may be associated with the GH excess. Osteoarthritis and secondary degenerative changes were described as a common feature in acromegaly (28, 29). A recent study reported increased thickness of articular cartilages of shoulder, wrist and knees, as well as the heel tendon size, in patients with acromegaly *(30)*. Moreover, hypertrophy of periarticular soft tissue was also found in those patients *(31)*. All the mentioned changes could influence the calcaneal QUS measurements. Moreover, lower BUA and SOS values could be the result of soft tissue swelling *(32)*. However, no ankle oedema was observed in the patients included in the study.

The absence of the correlation between the IGF-1 and GH levels with the QUI is not in line with the previous study reporting an inverse correlation of the QUS indices with GH, but not with IGF-1 *(19)*. Studies that evaluated the effects of acromegaly on bone density measured by DXA observed a significant correlation of IGF-1 with femoral neck BMD mainly containing cortical bone, but not with lumbar spine BMD which is prevalently composed of trabecular bone *(7, 14)*.

Other factors, such as the duration and activity of the disease could also influence the bone metabolism in acromegalic patients. We did not find significant correlation between the disease duration and the QUS parameters. However, the estimation of the duration of the disease was based on the patients' recall. The unreliable accuracy of the data collected in such a way could compromise the validity of the results.

The shortcomings of this study primarily include the small size of the sample. Nevertheless, most of the previously published studies were also based on small sample sizes. A possible solution to this issue could be the development of a joined dataset, which would

enable a cross-comparison and meta-analysis of the available data. In such a manner, more reliable results of the acromegalic effects on the bone properties could be obtained.

In conclusion, besides bone density, calcaneus ultrasound can provide additional information on bone properties in acromegalic patients. Our data indicated lower levels of BUA, SOS and QUI in patients with acromegaly compared to healthy controls, suggesting impaired bone quality. Similarly, decreased QUS values and increased bone turnover markers were observed in patients with active acromegaly in comparison with the cured ones. The differences were more pronounced in males probably due to the androgenic effect of GH/IGF-1, which seems to be more important in females than in males. Multiple regression model indicated strong association between disease activity and the QUS parameters.

TABLES:

Table 1. Calcaneus quantitative ultrasound parameters in male and female patients with acromegaly and in controls

Table 2. Calcaneus quantitative ultrasound parameters and markers of bone turnover in male and female acromegalic patients with active and controlled disease

Table 3. Multiple regression model of the QUS parameters

Table 1.

	Males			Females		
Variable	**Patients (n=17)**	**Controls (n=51)**	***P***	**Patients (n=19)**	**Controls (n=57)**	***P***
Age (y)	48.5±10.6	48.3±10.2	*NS*	52.5±10.8	51.9±10.3	*NS*
BMI (kg/m^2)	29.9±4.8	27.3±3.8	*<0.05*	28.6±5.9	27.7±5.7	*NS*
QUI	77.2±23.7	100.7±21.8	*<0.001*	84.5±15.4	90.8±17.9	*NS*
SOS	1526.8±33.0	1555.3±34.9	*<0.05*	1534.0±27.9	1539.9±28.3	*NS*
BUA	56.9±29.1	83.1±20.3	*<0.05*	64.8±12.4	72.6±16.2	*0.06*

Table 2.

	Males			**Females**		
Variable	**Active disease (n=11)**	**Cured (n=6)**	***P***	**Active disease (n=11)**	**Cured (n=8)**	***P***
Age (y)	49.5±13.2	47.3±3.1	*NS*	49.4±7.8	55.2±13.8	*NS*
BMI (kg/m^2)	29.2±3.3	31.2±7.0	*NS*	29.1±3.6	27.9±8.3	*NS*
Basal GH	31.8±44.9	0.5±0.3	*<0.001*	25.7±54.5	1.6±1.8	*<0.001*
IGF-1	116.7±47.8	34.7±14.7	*<0.001*	110±41.7	47.2±21.9	*<0.001*
BAP	9.8±5.9	8.0±1.2	*NS*	13.8±11.8	12.5±8.6	*NS*
Osteocalcin	16.1±4.9	9.7±3.0	*<0.05*	25.8±18.5	18.3±17.8	*NS*
β-Crosslaps	0.5±0.2	0.3±0.2	*<0.05*	0.8±0.4	0.4±0.4	*<0.05*
QUI	66.7±17.2	96.3±22.7	*<0.05*	79.3±9.1	88.2±18.2	*NS*
SOS	1510.1±21.4	1557.2±29.0	*<0.05*	1523.6±16.6	1540.2±32.5	*NS*
BUA	45.3±24.0	78.2±26.5	*<0.05*	62.6±9.5	66.4±14.4	*NS*

Table 3.

	P (QUI)	P (BUA)	P (SOS)
Hypogonadism	0.436	0.235	0.441
Active disease	0.020	0.007	0.014
Gender	0.012	0.051	0.060
Body mass index	0.071	0.111	0.123

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