Original Article

Comparison of the Bone Mineral Density between Acromegaly Patients and Healthy Individuals

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Abstract

Introduction: Acromegaly patients have high bone turnover and negative calcium balance. Different studies have also reported that acromegaly causes disrupted calcium homeostasis and bone remodeling. **Objective:** The aim of this study was to compare bone mineral density between acromegaly patients and healthy individuals. **Materials and Methods:** Twenty-nine acromegaly patients referred to Imam Reza Hospital of Tabriz University of Medical Sciences were enrolled in this case-control study. Eighty-eight sex-, age-, and body mass index-matched individuals without any endocrine diseases were also considered as the control group. Lumbar (L2-L4) and hip bones' densities were determined using a dual-energy x-ray absorptiometry (DEXA) scan. **Results:** Lumbar T-score was significantly lower in acromegaly patients compared to healthy controls (-0.76±0.21 versus -0.13±0.18, p=0.042, respectively). However, the incidence of osteopenia and osteoporosis were not different in the studied population (p=0.072). **Conclusion:** Regarding our data, T-scores can be considered as a marker for response to therapy monitoring in acromegaly patients.

Keywords: Acromegaly, Insulin-like growth factor-1, Growth hormone, dual-energy x-ray absorptiometry

Introduction

The pituitary adenoma is the second most common intracranial neoplasm comprising 15% of all primary intracranial neoplasms, most commonly in the age group of 20-34 [1]. The peak incidence of acromegaly is in the fourth to sixth decade of life. In a systematic review, pituitary adenoma prevalence was estimated to be 16.7% (14.4% in autopsy and 22.5% in radiologic studies) [1]. Two major methods for pituitary adenomas diagnosis are imaging (CT & MRI) and autopsy. Pituitary adenomas are usually benign; however, hormonal changes or pressure to surrounding tissues may cause serious clinical symptoms, so that 1/1000 in the general population has significant clinical symptoms of pituitary adenoma [2].

Pituitary adenoma progression compresses adjacent tissues such as optic as well as third, fourth, and fifth cranial nerves causing visual defects including bilateral blindness, visual field loss, and ocular motion disorders [2].

As previously reported, growth hormone (GH) increase leads to abnormal bone metabolism in the body. Decreased GH level also causes decreased bone metabolism leading to osteoporosis [3]. However, acromegaly patients have high bone turnover and negative calcium balance. Studies have shown acromegaly causes disrupted calcium homeostasis and bone remodeling. Additionally, they have shown that GH increase may stimulate bone turnover; however, skeletal fractures aftermaths in these patients are not known [3].

In fact, the results of bone mineral densitometry (BMD) are conflicting, so that some studies have reported BMD increase [4-6] or decrease [7-9] in acromegaly patients. As a matter of fact, some of these studies accept the hypothesis that GH increase can protect the bone system [10]. However, recent studies have reported skeletal and vertebral fractures with a high prevalence even in patients with normal BMD [11-14].

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How to cite this article: Mostafavi, Z., Houshyar, J., Aliasgarzadeh, A., Aghamohammadzadeh, N., Sadra, V., Khani, M., Najafipour, M., Najafipour, F. Comparison of the Bone Mineral Density between acromegaly patients and healthy individuals. Arch Pharma Pract 2019;10(4):15-20.

These findings are similar to those found in secondary osteoporosis patients [15]. In fact, relevant guidelines advise vertebral X-ray to diagnose fractures; whereas, routine BMD study in these patients is seriously criticized. In this regard, Scillitani et al. [16] in a study on 152 acromegaly patients (99 women and 53 men) reported active disease in 107 patients. In 87 patients, gonadal activity was normal and hypogonadism was observed in the remaining patients. L2-L4 spines bone densitometry also showed higher BMD in patients with normal gonadal activity compared to controls. Lower BMD was also observed in hypogonadal patients.

Additionally, Bolanowski et al. [17] evaluated the vertebral bone densitometry in 40 acromegaly patients. The results showed 36 normal Z-scores, two above normal, and 2 below normal. According to this study, no significant differences were observed in Z-scores between acromegaly patients and normal controls.

The study by Zgliczynski et al. [18] on 121 patients with active acromegaly showed that Eugonadal acromegalics had higher L2-L4 and femur neck bone densitometry compared to hypogonadal acromegalics.

Also, Longobardi et al. [19] conducted a study on 11 patients with active acromegaly. Data revealed decreased BMD in vertebrae but not in the femur neck in the studied population. Studies have reported different numbers of BMD in acromegaly patients, and due to the lack of a similar study in our region, we have no precise figures on this issue. Therefore, this study aimed to compare BMD status in acromegaly patients in comparison to normal individuals.

Materials and Methods

Twenty-nine acromegaly patients referred to Imam Reza Hospital of Tabriz University of Medical Sciences were enrolled in this case-control study from September 2018 to September 2019. Eighty-eight sex-, age-, and body mass index-matched individuals without any endocrine diseases were also considered as the control group. Lumbar (L2-L4) and hip bones' densities were determined using dual-energy x-ray absorptiometry (DEXA) scan and according to the obtained scores patients were classified into 3 groups including normal density (T-score >-1.0), osteopenic (-2.5< T-score <-1.0) and osteoporotic (T-scores <-2.5). For asymptomatic fractures, the x-ray analysis of the backbone was also performed. Because of the limited number of acromegaly patients, all acromegaly patients were included in this study. Insulin-like growth factor 1 (IGF-1) levels were also evaluated in acromegaly patients by an electrochemiluminescence instrument (Elecsys, USA). The inclusion criteria were acromegaly diagnosis and willingness to participate in the study. The consumption of nutritional or intravenous supplements, chronic renal failure, hyperparathyroidism, hyperthyroidism, gastrointestinal diseases, connective tissue diseases and arthritis rheumatoid, pathologic fracture background, bisphosphonate consumption, and abnormal menopause in women were also considered as exclusion criteria. This study was approved by the Ethics Committee of Tabriz University of Medical Sciences (IR.TBZMED.REC.1397.157). Written informed consent was also obtained from all participants prior to any action.

Statistical analysis

Data analysis was performed using statistical package for social sciences version 22. The normality distribution of the data was evaluated by the Kolmogorov–Smirnov test. Independent t-Test and Chi-Square test were also used for quantitative and qualitative comparison of variables between the groups. P <0.05 was considered statistically significant.

Results

- ### General characteristics

As shown in Table 1, 19 (65.5%) and 41 (70.7%) of the acromegaly and healthy individuals were female, respectively. The average age of the acromegaly and healthy individuals was 45.89±13.13 and 46.25±12.28 years, respectively (p=0.9). The mean body mass index (BMI) of the patients and healthy individuals was calculated as 30.77±5.34 and 30.28±4.44 Kg/cm^2, respectively (p=0.625). Moreover, the mean levels of IGF-1 in acromegaly patients were evaluated as 377.06±308.5 µg/L.

- ### Comparison of hip and lumbar T and Z scores between acromegaly patients and healthy individuals

Table 2 shows the hip and lumbar bones T and Z scores in acromegaly patients and healthy controls. As it is presented, the lumbar T-score is significantly lower in acromegaly patients compared to the healthy controls (-0.76±0.21 versus -0.13±0.18, respectively p=0.042,). No statistically significant differences were observed in other parameters between groups.

- ### Bone situation in the studied groups

As shown in Table 3, the incidence of osteopenia and osteoporosis was not different in the studied population (p=0.072).

Discussion

GH and IGF-1 are two important anabolic bone hormones that lead to an increase in the osteoblast number and intensified bone formation. The decreased level of GH, as well as acromegaly, lead to impaired bone metabolism, so that hormone deficiency results in decreased bone formation and acromegaly leads to increased bone anabolism, which creates a negative calcium balance in patients [20-22]. After the first evidence stating that acromegaly may impair calcium homeostasis and bone remodeling, further research showed that excessive GH may also stimulate bone anabolism; however, increased bone fragility has not been confirmed. There are different conflicting results in research data. Some studies have shown that acromegaly increases bone density [5,

[6]. However, some others showed that acromegaly can decrease bone density [5, 23]. Some studies have also reported that acromegaly does not make any significant changes in bone density [7-9]. In other words, some authors proposed this hypothesis that extra GH in the human body can protect the skeletal system [10, 24]. However, in recent years, some studies showed that acromegaly can cause skeletal system fragility or increased vertebral fracture [11, 12, 25].

Increased bone resorption with direct effects of the excess hormone on kidney function, may be responsible for negative calcium balance by bone loss and fragility [20, 22]. Although, it should be mentioned that low bone density is not a common clinical finding in acromegaly patients [20]. Different factors may play a role in bone density in acromegaly patients. First, acromegaly patients suffer from osteoarthritis mainly due to osteophyte and joint hypertrophy in the vertebral column and this can cause bone density overestimation [26, 27]. Moreover, the BMD of the acromegaly patients should have been assessed less than normal due to increased growth hormone and bone enlargement [25]; however, in most acromegaly patients, despite broadened bones, normal or increased densitometry have been reported. This is in agreement with the statement that excess growth hormone can increase bone content more than that of bone area [6, 8, 11, 12]. It is noteworthy that these anabolic effects occur in cortical bones; while, smaller trabecular structures are negatively affected by excessive GH [14, 20, 25, 28]. However, bone densitometry cannot differentiate the cortical and trabeculate bones [24, 29].

In this study, 29 acromegaly patients were evaluated, of whom 65.5% were women. The average age of acromegaly patients was 45.89±0.13.3 years. Bolanowski et al. [30] conducted a study on 62 acromegaly patients (40 women and 22 men) and showed that 34 patients (54.83%) had active disease and the remaining 28 patients (45.17%) were treated. Reid et al. [31] conducted a study in this regard and assessed 138 acromegaly patients of whom, 77 patients had active disease and 61 had their disease controlled. Zhang et al. [32] in a study on 16 acromegaly patients and 19 healthy participants showed that acromegaly patients had difficult intubation. Accordingly, the IGF-1 level and hypoxia/apnea index were significantly higher than that of the controls. Tuzcu et al. [33] a study on 29 acromegaly patients and 42 healthy participants also reported a significantly higher GH and IGF-1 levels in acromegaly patients compared to the controls. Moreover, the total hip T-score was significantly lower in acromegaly patients.

In Bolanowski et al. [30] study, IGF-1 serum level in acromegaly women and men was 772.9 and 847.3 ng/ml, respectively and in the control group it was 214.8 and 146.3 ng/ml in women and men, respectively. In the study by Subbarayan et al. [34], the average IGF-1 level in acromegaly patients was 228 ng/ml. In another study by Reid et al. [31], the average IGF-1 in patients with active acromegaly was 595 ng/ml and in treated patients, it was 173 ng/ml. Zhang et al. [32] demonstrated that the IGF-1 level in acromegaly patients and healthy controls was 994 and 198.26 ng/ml, respectively. In Tuzcu et al. [33] study, the average IGF-1 level in acromegaly and control groups was reported as 676.47 and 178.17 ng/ml, respectively. In our study, the average IGF-1 level in acromegaly patients was lower than that of previous studies, probably due to disease control in our patients.

We observed that the average hip T-score in two acromegaly and control groups had no statistically significant difference, but the lumbar T-score in acromegaly patients was significantly lower than that of the healthy controls. Bonadonna et al. [11] also reported a significant difference in T-score in acromegaly patients and healthy controls (-1.3 and -2.4, respectively, $p < 0.05$). Moreover, Mazziotti et al. [12] in 2008 reported a significant difference in the average T-scores in acromegaly and healthy controls (-0.7 and -1.2, respectively, $p<0.05$). However, this research group in 2013 reported that the average T-scores in acromegaly and healthy were not statistically significant (-0.5 and -0.2, respectively, $p<0.05$) [35]. In Sucunza et al. study [36] the average lumbar T-scores in acromegaly and healthy groups were 1.2 and 1.1, respectively, which were statistically significant. Many studies have also assessed femur neck. In Kaji et al. [6] study it was observed that acromegaly patients show significantly increased femoral head density. In another study by Mazziotti et al. [35] the average femoral head density scores showed an increased femoral head density in acromegaly patients compared to the healthy controls (OR=1.18). However, in the studies of Longobardi et al. [19], Bolanowski et al. [30], and Ueland et al. [25], no significant effects on femur T-score were reported in acromegaly patients compared to the healthy controls. In contrast, Mazziotti et al. [35] reported significant increased average hip T-scores in acromegaly patients compared to the healthy controls (0.25 and -0.25, respectively, OR=0.57). These results show that acromegaly has different effects on different bones. Besides, the patients under treatment and those with active phase disease can have different scores.

In our study, in the acromegaly group, 41.4 % had osteopenia and 10.3% osteoporosis, and in the control group, 24.1% had osteopenia and 3.4% osteoporosis; the two groups had no statistically significant difference. Osteopenia and osteoporosis incidences in acromegaly patients are different in various studies; whereas, in Diamond et al. [29] and Longobardi et al. [39] studies on acromegaly patients, densitometry of peripheral and vertebral bones showed lower densitometry scores in acromegaly patients. Moreover, the study by Longobardi et al. [19] showed that probably elevated cytokine levels are responsible for this phenomenon. In contrast, Kaji et al. [6], Kotzmann et al [8], Bonadonna et al. [11], Mazziotti et al. [35], Scillitani et al. [16], and Sucunza et al. [36] reported much lower osteopenia incidence and higher average bone densitometry of similar bones in acromegaly patients compared to the healthy controls. On the other hand, many studies have reported no statistically significant differences regarding bone densitometry. Bolanowski et al. [30], Matsuyama et al. [37], Mazziotti et al. [35] in 2013, and Ueland et

al. [25], reported no significant differences in bone densitometry, and osteopenia and osteoporosis incidence in acromegaly patients. This finding may be due to treated patients entering the study, evaluation of only trabeculate bones but not cortical ones, and not omitting confounding factors such as age and gender. In other studies, the results on various bones were different. For instance, Tuzcu et al. [33] reported that although GH and IGF-1 serum levels were higher in acromegaly patients compared to the healthy people, no differences were observed between groups regarding the vertebral bone densitometry. Only hip T-score was reported to be lower in acromegaly patients than that of the healthy controls, but it was not so much to qualify them for osteopenia.

Conclusion

In acromegaly patients, due to the IGF-1 increase, the elevated BMD is expected. However, this increase is not observed after treatment and resultant GH and IGF-1 decrease. On the other hand, acromegaly-dependent hypogonadism leads to BMD decrease. In the present study, patients were under treatment, t-scores were in a normal range, and this parameter may be considered as a marker for therapy response efficiency monitoring.

Acknowledgments

This work was conducted as part of the specialty Dissertation for Dr. Zahra Mostafavi. This study was supported by the Endocrine Research Center in Tabriz University of Medical Sciences, Tabriz, Iran [Grant No.:59374]. The authors would like to acknowledge the Department of Internal Medicine at Tabriz University of Medical Sciences (Iran) for their great help.

Conflict of interests

The authors declare no conflict of interest.

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Table 1. General characteristics of individuals.

Parameters	Acromegaly patients	Healthy individuals	p
Sex (female, n, %)	19 (65.5)	41 (70.7)	-
Age (year)	45.89±13.13	46.25±12.28	0.9
BMI (Kg/Cm^2)	30.77±5.34	30.28±4.44	0.625
IGF-1 (µg/L)	377.06±308.5	-	-

Data are presented as mean±standard division (SD). p<0.05 was considered as statistically significant. BMI: body mass index; IGF-1: insulin-like growth factor-1.

Table 2. Hip and lumbar bones T and Z scores in studied groups.

Bone	Parameters	Acromegaly patients	Healthy individuals	p
Hip	T-Score	0.18±0.23	0.38±0.18	0.518
	Z-score	0.64±0.2	0.51±0.18	0.670
Lumbar	T-Score	-0.76±0.21	-0.13±0.18	0.042*
	Z-score	0.2±0.18	-0.14±0.17	0.834

Data are presented as mean±standard division (SD). p<0.05 was considered as statistically significant.

Table 3. The bone situation in studied groups

Groups	Acromegaly patients		Healthy individuals		p
	Frequency	(%)	Frequency	(%)	
Normal	14	48.3	42	72.4	
Osteopenic	12	41.4	14	24.1	0.0
Osteoporotic	3	10.3	2	3.4	72

Data are presented as frequency or percent. p<0.05 was considered as statistically significant.