Bulletin of Environment, Pharmacology and Life Sciences
Bull. Env. Pharmacol. Life Sci., Vol 12 [8] July2023 :49-55
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Online ISSN 2277-1808
Journal's URL:http://www.bepls.com
CODEN: BEPLAD

ORIGINAL ARTICLE **OPEN ACCESS**

Changes in BMD in Patients with Acromegaly Depending on The Gonadal Status and Activity of The Disease

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ABSTRACT
The article about the acromegaly is a severe neuroendocrine disease, which is based on chronic hypersecretion of growth hormone in individuals with complete physiological growth, which leads to pathological disproportionate growth of bones, cartilage, soft tissues, internal organs, as well as disorders of the functional state of the cardiovascular, pulmonary system, peripheral endocrine glands, which cause the development of severe systemic complications.
Keywords: *diagnosis, treatment, spinal, fracture, sex glands, patients, gonadal, status*

Received 16.04.2023 Revised 25.06.2023 Accepted 21.07.2023

INTRODUCTION

In 2019, an assessment of the epidemiological situation of acromegaly over the past 12 years was carried out for the first time in Uzbekistan based on the results of the national register. At the same time, the authors studied the frequency of not only the disease itself, but also its complications, the relationship of their development with gender, age and duration of hypersecretion of GR [2, 3,4].The latest consensus on the diagnosis and treatment of complications of acromegaly emphasizes that the diagnosis and treatment of complications of the disease are critical to ensure a favorable long-term outcome for this chronic disease [5,6,7]. At the same time, special importance is attached to musculoskeletal complications of acromegaly (ODO), which account for approximately 75% [8,9] and, as a cause of disability, can affect many aspects of everyday life [10,11,12,13]. ODO is one of the key complications of acromegaly, significantly impairing the quality of life in the active stage of the disease and in some cases persisting when acromegaly remission is achieved. Early diagnosis of acromegaly is necessary for early and aggressive treatment to reduce the risk of arthropathy, since changes in joints and cartilage are often irreversible [14, 15, 16].According to a meta-analysis of a number of studies, the activity of the disease, male gender and hypogonadism correlate with a higher frequency of spinal fracture than in other relevant comparison groups [17]. Despite the available studies, the effect of the state of the function of the gonads on BMD in patients with acromegaly remains unclear. In the course of several studies [18, 19], a positive effect of normally functioning gonads on BMD was shown, while the results of other studies [20, 21] were contradictory, and BMD was high regardless of the function of the gonads. According to Ueland T. Et al. [20], the relationship between the function of the sex glands and BMD was revealed through a single-factor analysis, and the multivariate analysis confirmed the importance of indicators such as age and gender. Taking into account the influence of the state of the gonads on BMD, we set out to study the changes in BMD in patients with acromegaly depending on the gonadal status and activity of the disease.

MATERIALS AND METHODS

The object of our research were 120 patients with acromegaly observed in the Endocrinology Center for the period from 2000 to 2020. The age of the patients ranged from 20 to 75 years and averaged 42 ± 9.7 years. Of these, 43 (42.6%) were men and 77 (57.4%) were women. At the same time, the duration of the disease ranged from 1 year to 26 years.

The diagnosis of acromegaly was established on the basis of clinical manifestations of the disease and was confirmed by high serum levels of GR, IGF-1 levels that were above the age limit. To determine them, radioimmune and enzyme immunoassay methods were used. Somatotropinoma was established on the basis of an MRI examination of the hypothalamic-pituitary region. To identify and monitor ODO acromegaly, we have developed a map that allows timely detection of complications of the bone system

and follow-up. This card was filled in for each patient. General clinical studies were conducted; dual-energy absorptiometry (DEXA), single-photon emission computed tomography (SPECT) using scintigraphy; hormonal studies (study of the basal level of pituitary and peripheral gland hormones); neuroimaging studies (magnetic resonance imaging of the hypothalamic-pituitary region); as well as neuro-ophthalmological studies (visual acuity, fundus and field of vision).

RESULTS

According to the levels of sex hormones, we divided patients into two groups: with hypogonadism (men – 12, women-20) and eugonadism (men – 35, women-53) and conducted a separate analysis between men and women. The average age of patients in the study groups was 44.4±12.2.

According to the results of the study of the spine BMD, both men (-2.6 SD vs. 0.2 SD, $p<0.05$) and women with hypogonadism (-2.5 SD vs. 1.15 SD, $p<0.001$) had osteoporosis (Fig.1).

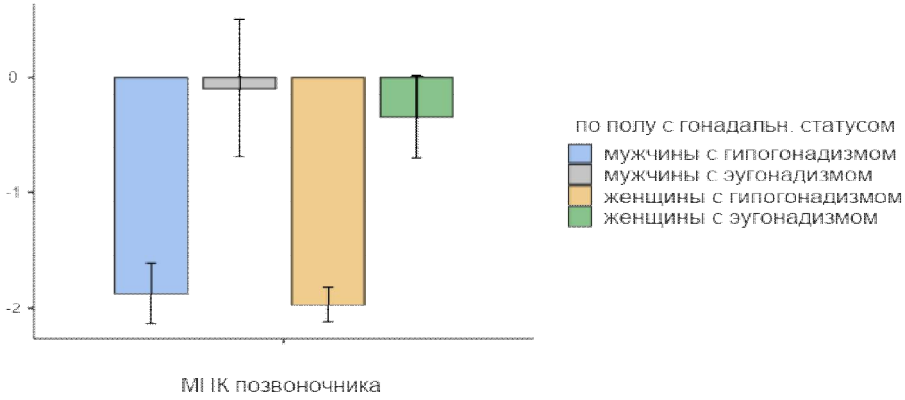

Fig.1. BMD L1-L4 of the spine in patients with acromegaly, depending on the gonadal status.

Studies of hip neck BMD have shown low BMD in both men and women suffering from hypogonadism, while men have osteopenia (-1.8 SD, $p<0.01$), and women have osteoporosis (-2.5 SD, $p<0.001$) (Fig. 2).

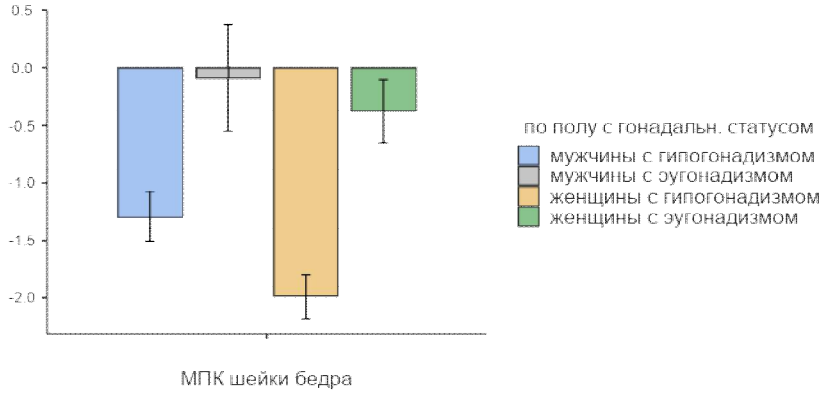

Fig.2. Hip neck BMD in patients with acromegaly depending on gonadal status.

At the same time, the BMD indicators in patients with eugonadism were within the normal range (0.4 SD in men, -0.25 SD in women).

Densitometric indicators of hip condition in patients with acromegaly with different gonadal status showed the following (Fig.3.)

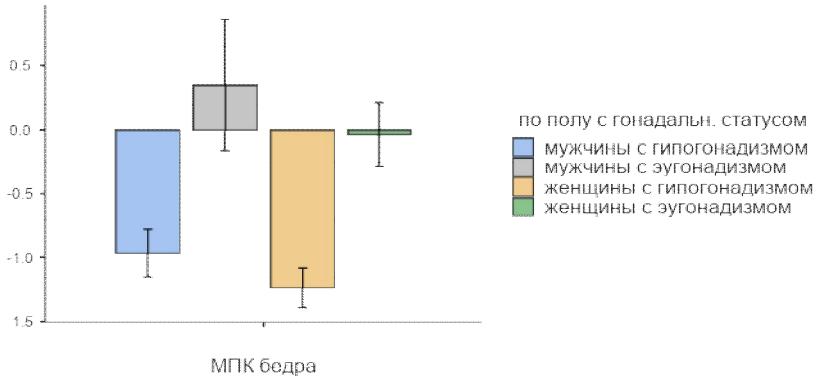

Fig.3. Hip BMD in patients with acromegaly depending on gonadal status.

According to the results obtained, both men (-1.2 SD vs. 0.7 SD, p<0.05) and women with hypogonadism (-1.6 SD vs. 0.65 SD, p<0.05) had osteopenia of the femur according to the results of densitometry.

Next, we studied the presence of a correlation between the development of hypogonadism and bone mineral density (Fig. 4).

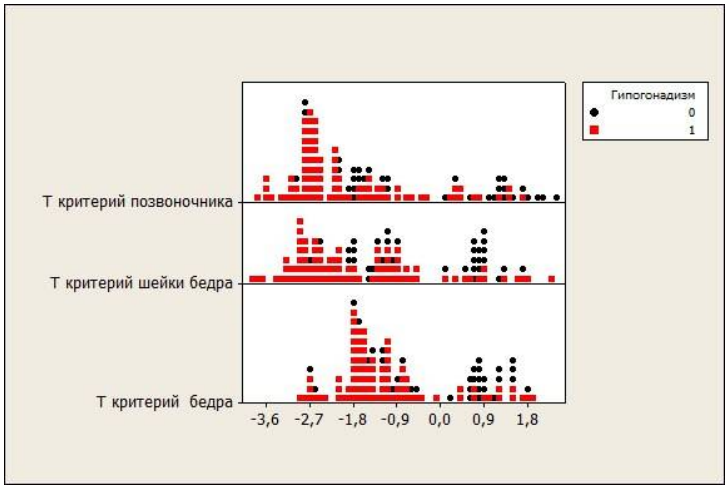

Fig.4. Correlation between hypogonadism and BMD: spine ; hip neck; hip.

The analysis of the obtained results showed the presence of a negative correlation between the development of hypogonazdism and the BMD of the spine (R=- 0.46, p<0.01), hip neck (R= -0.41, p<0.01), hip (R= -0.37, p<0.01).

Our next task was to conduct a comparative analysis of the BMD condition of patients with acromegaly depending on the activity of the disease (Table 1).

Table1.BMD indicators in patients with active and inactive acromegaly (T-criterion)

Indicator	Active(n=62)	Inactive(n=58)	P
Age, years	49±12,2	46,2±10,7	0,183
BMI kg/m2	30,3±4,07	31,1±5,72	0,4
Spine L1-L4, SD	–2,5 (–2,7–1,63)	–1,5 (–2,68-0,2)	0,04*
Hip, SD	–1,35 (–1,7–0,7)	–1 (–1,6-0,675)	0,038*
Hipneck, SD	–2,25 (–2,9–1)	–1,3 (–2,08-0,45)	0,043*

Analysis of the results of densitometry in patients with acromegaly with various stages of activity showed a decrease in BMD in almost all the bones studied at various stages of the disease. At the same time, more severe BMD disorders in the form of spinal osteoporosis (-2.5 SD vs. -1.5 SD, p<0.05) and femoral neck (-2.25 SD vs. - 1.3 SD, p<0.05) were detected in patients in the active stage of the disease.

Next, we analyzed the effect of disease activity on BMD in patients with acromegaly with different gonadal status. According to the results obtained, the study of the spine BMD at the L1-L4 level revealed the development of osteoporosis in patients with hypogonadism in the active stage of the disease compared with patients with inactive acromegaly (-2.55 SD vs. -1.6 SD, p<0.05). At the same time, patients with inactive acromegaly with eugonadal status have the development of osteopenia (-0.2 SD vs. - 0.1 SD),

which more often developed in patients who had a longer active stage before the onset of disease control (Fig.5).

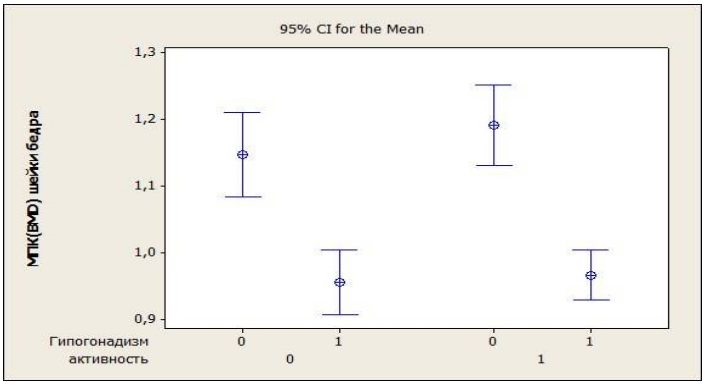

Fig. 5. Changes in the BMD of the spine at the L1-L4 level in patients with acromegaly, depending on the activity of the disease and gonadal status.

Assessment of hip neck BMD in the active stage of the process showed the development of osteoporosis in patients with hypogonadism, compared with patients with normal gonadal function (-2.6 SD vs. 0.75 SD, $p<0.001$). In patients with hypogonadism in the inactive stage of the disease, there is also a decrease in BMD, but already in the form of osteopenia (-1.3 SD vs. -0.95 SD) (Fig.6).

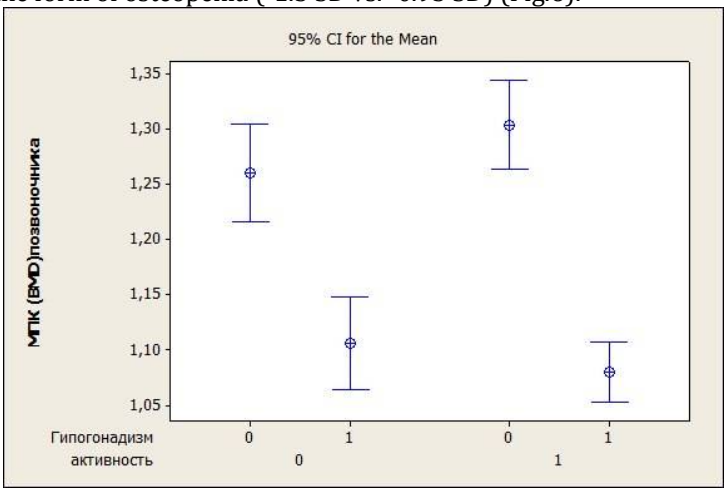

Fig. 6.Changes in the BMD of the femoral neck in patients with acromegaly, depending on the activity of the disease and gonadal status.

Analysis of the femoral densitometric parameters in patients with acromegaly without gonadal dysfunction showed the absence of BMD disorders, both in the active (0.75 SD) and inactive (0.6 SD) stages of the disease. (fig. 7).

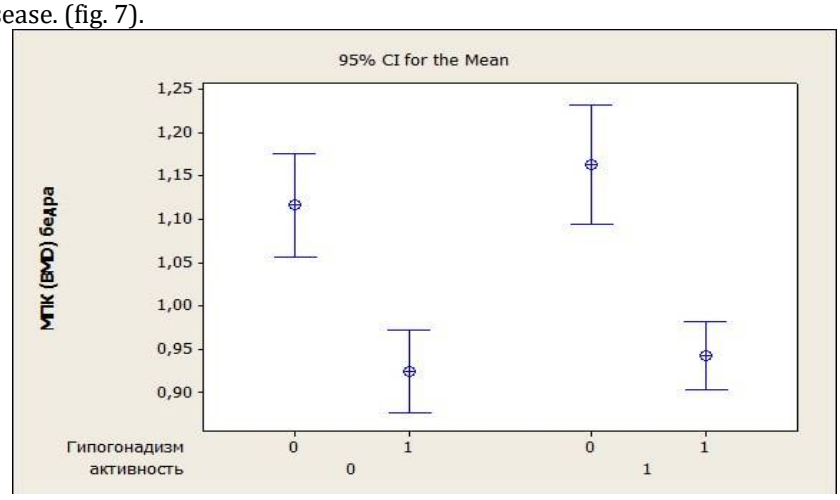

Fig. 7.Changes in hip BMD in patients with acromegaly depending on the activity of the disease and gonadal status.

At the same time, patients with hypogonadism had BMD disorders in the form of osteopenia, regardless of the activity of the disease (active: -1.55 SD, p<0.001; inactive:-1,3 SD, p<0,01). The correlation analysis between the activity of the disease and bone BMD showed the presence of this relationship only in the femoral neck, where a negative correlation was revealed (R= -0.25, p<0.05).

DISCUSSION

Sex hormones play an important role in maintaining bone density and microstructure, especially in trabecular bones, and the detrimental effect of hypogonadism on bone microstructure has been shown in postmenopausal women [22, 23]. In a study conducted by the authors of Madeira Miguel et al. (2013), hypogonadism also turned out to be a factor affecting the microstructure of the trabecular bone in acromegaly. After analysis using multiple linear regression, positive correlations were maintained between the eugonadal status and IPC [24]. By means of bone densitometry, the authors determined a significant prevalence of osteoporosis (24.3%) and below the expected values of BMD, depending on age, in 24.4% of all patients, which suggests the existence of a negative effect on the condition of bones of a general hormonal disorder [24].

Our studies revealed low BMD in both men and women suffering from hypogonadism, while men had osteopenia (-1.8 SD, p<0.01), and women had osteoporosis (-2.5 SD, p<0.001). At the same time, the BMD indicators in patients with eugonadism were within the normal range (0.4 SD in men, -0.25 SD in women). The analysis of the correlation relationship between the studied parameters showed the presence of a negative correlation between the development of hypogonazdism and the BMD of the spine (R=- 0.46, p<0.01), hip neck (R= -0.41, p<0.01), hip (R= -0.37, p<0.01).

All these results taken together suggest a higher bone density and normalized microstructure in patients with eugonadal status, indicating the importance of sex hormones for bone health in acromegaly.

Our next task was to conduct a comparative analysis of the state of BMD in patients with acromegaly, depending on the activity of the disease. Most studies suggest the effect of acromegaly activity and/or hyogonadism on bone density. et al. [19] examined 121 patients and analyzed the data in terms of disease activity and gonads: patients with eugonadism had higher BMD in the spine and hip, and patients with hypogonadism had higher BMD in the spine. Bolanovsky et al. [18] studied 62 patients and demonstrated higher BMD only in the femur in active men with eugonadism. Ueland et al. [20] analyzed 73 patients and reported an increase in BMD in the whole body, regardless of the state of the gonads. Battista et al. [25], computed tomography was used in 46 patients and showed higher BMD in the lumbar spine only in the active and eugonadic groups. A multicenter study by Scillitani et al. [21] examined 152 patients and showed an increase in BMD in the lumbar spine only in patients with eugonadism, regardless of the activity of the disease, and in the femur only in patients with active disease, regardless of the condition of the gonads.

Our studies have established the presence of a negative correlation between the development of hypogonadism and the BMD of the spine (R=- 0.46, p<0.01), hip neck (R= -0.41, p<0.01), hip (R= -0.37, p<0.01). At the same time, both men (-2.6 SD vs. 0.2 SD, p<0.05) and women with hypogonadism (-2.5 SD vs. 1.15 SD, p<0.001) had osteoporosis of the spine and osteopenia of the femur (men: -1.2 SD; women:-1.6 SD,p<0.05). Osteopenia (-1.8 SD, p<0.01) was detected in the femoral neck area in men, and osteoporosis (-2.5 SD, p<0.001) in women. The presence of a negative correlation between the development of hypogonadism and the BMD of the spine (R=- 0.46, p<0.01), hip neck (R= -0.41, p<0.01), hip (R= -0.37, p<0.01) was established. The study of the spine BMD at the L1-L4 level revealed the development of osteoporosis in patients with hypogonadism in the active stage of the disease compared with patients with inactive acromegaly (-2.55 SD vs. -1.6 SD, p<0.05). At the same time, patients with inactive acromegaly with aneugonadic status have the development of osteopenia (-0.2 SD vs. - 0.1 SD), which more often developed in patients who had a longer active stage before the onset of disease control. Assessment of hip neck BMD in the active stage of the process showed the development of osteoporosis in patients with hypogonadism, compared with patients with normal gonadal function (-2.6 SD vs. 0.75 SD, p<0.001). A negative correlation was found between hip neck BMD and disease activity (R= -0.25, p<0.05).

Lesse et al. The data were analyzed from the point of view of disease activity and gonadal condition, higher BMD in the spine and femur was found in patients with eugonadism, and a decrease in BMD in the spine was found in patients with hypogonadism [27]. Kaji et al. (2001) examined 26 patients with active disease and found a higher BMD in the spine, hip and forearm compared to the control [26].

The authors of Scillitani A et al (2003) retrospectively evaluated BMD in both the spine and the femoral neck in more than 150 patients with acromegaly who were included in nine specialized Italian centers that participated in the Italian acromegaly research group under the auspices of the Italian Society of Endocrinology [21] and concluded that BMD in the spine correlates with the "duration of acromegaly"

and "duration of hypogonadism" and confirms, in the spine, BMD was higher in persons with eugonadism and lower in patients with hypogonadism compared to the control group. This discovery demonstrates that in the spine, the anabolic effect of GR is manifested only in the presence of normal gonadal status, whereas it is overlapped by the catabolic effect of hypogonadism. This effect did not depend on the activity of the disease and gender [21].

Thus, the presence of a negative correlation between the development of hypogonadism and the BMD of the spine (R=- 0.46, p<0.01), hip neck (R= -0.41, p<0.01), hip (R= -0.37, p<0.01) was established. At the same time, both men (-2.6 SD vs. 0.2 SD, p<0.05) and women with hypogonadism (-2.5 SD vs. 1.15 SD, p<0.001) had osteoporosis of the spine and osteopenia of the femur (men: -1.2 SD; women:-1.6 SD,p<0.05). Osteopenia (-1.8 SD, p<0.01) was detected in the femoral neck area in men, and osteoporosis (-2.5 SD, p<0.001) in women. The presence of a negative correlation between the development of hypogonadism and the BMD of the spine (R=- 0.46, p<0.01), hip neck (R= -0.41, p<0.01), hip (R= -0.37, p<0.01) was established.

The study of the spine BMD at the L1-L4 level revealed the development of osteoporosis in patients with hypogonadism in the active stage of the disease compared with patients with inactive acromegaly. At the same time, patients with inactive acromegaly with a eugonadic status have the development of osteopenia, which more often developed in patients who had a longer active stage before the onset of disease control. Assessment of hip neck BMD in the active stage of the process showed the development of osteoporosis in patients with hypogonadism, compared with patients with normal gonadal function. Based on these data, in order to prevent the development of severe acromegaly, it is recommended to start hormone replacement therapy in hypogonadism in a timely manner.

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CITATION OF THIS ARTICLE

Kholikova A O, Safarova S M, Alieva D A, Savchuk D V. Changes in BMD in Patients with Acromegaly Depending on The Gonadal Status and Activity of The Disease. Bull. Env.Pharmacol. Life Sci., Vol 12 [8] July 2023: 49-55