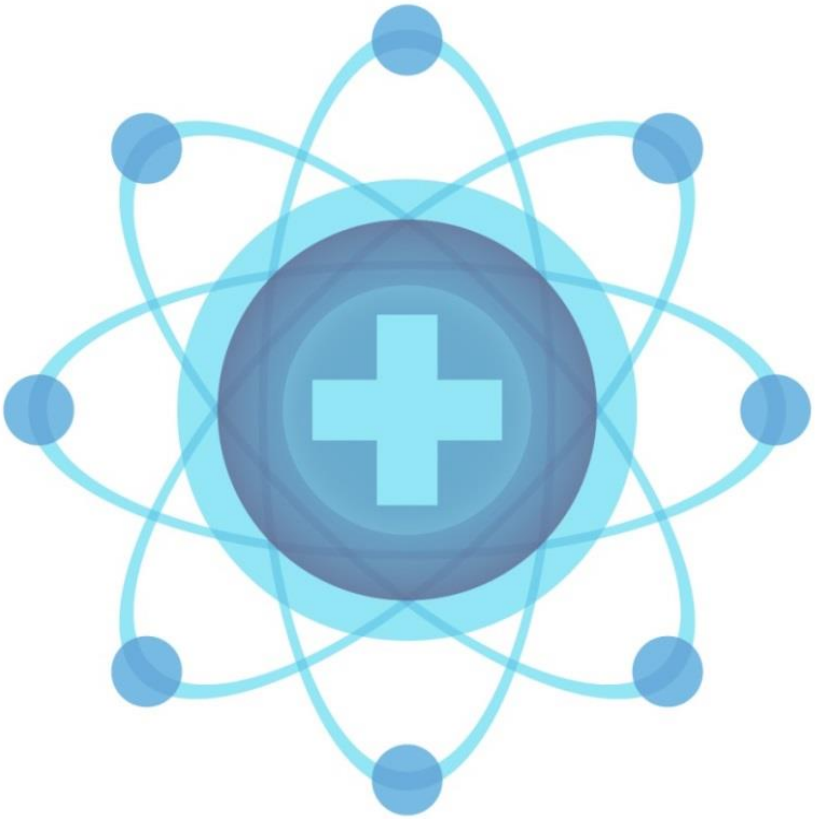

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FEATURES OF THE CLINICAL CURRENT AND DIAGNOSTICS MUSCULO - SKELETAL COMPLICATIONS OF ACROMEGALY

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Abstract: Acromegaly is one of the chronic endocrinopathies, which is based on hypersecretion of growth hormone (GH) and, accordingly, insulin-like growth factor 1 (IGF-1) by a pituitary tumor. Human GH and the main mediator of its stimulation effects, IGF-1, play an important role in the regulation of bone tissue metabolism. It is known that although GH deficiency in adults contributes to the phenomenon of bone loss and the development of osteoporosis, the effect of excess GH on bone health is still unclear.

Keywords: acromegaly, insulin-like growth factor, bone tissue

Issues of diagnostics and treatment of osteoarticular complications in acromegaly, including the frequency of exposure of people to this disease on a global scale, are widely represented in the works of a number of foreign experts. At the same time, an increase in the complex of pathological, irreversible complications in the musculoskeletal system undoubtedly has an unconditional effect on the activity of patients, methods of treatment, and, most importantly, on mortality. Here, the primary task is to identify and study the frequency of osteoarticular complications and the risk factors affecting their development, early diagnosis and development of effective methods of treatment. Nevertheless, it should be especially noted that today there are no fundamental works that could collectively reflect the issues of monitoring and studying osteoarticular complications in relation to gender, age characteristics and quality of life, as well as the duration of hypersomatotropinemia.

According to various studies, the time from the onset of the first symptoms of acromegaly to the diagnosis varies from 3 to 25 years, averaging 4.5-5 years [11,19,20,21]. In Uzbekistan, this figure is from 3 to 6 years [1, 22]. Age at diagnosis and disease duration are determinants of disease outcome, reflecting exposure to high circulating levels of GH and IGF-1 [3, 17].

The delay in establishing the diagnosis and, as a result, prolonged chronic hypersecretion of GH/IGF-1 leads to the development of severe, often irreversible complications of the disease, contributing to an increase in mortality [2,4,5,6]. The mortality rate in patients with acromegaly is 4-5 times higher than in the control population [12,13]. The most common causes of death in acromegaly are a higher prevalence of hypertension, hyperglycemia or diabetes, cardiomyopathy, and sleep apnea [9,10,14]. Therefore, timely diagnosis and treatment of complications of the disease are crucial to ensure a favorable long-term outcome of this chronic disease [16]. It is known that GR has gender and age characteristics [7,8]. Given these factors, we set a **goal** to study the features of the clinical course and diagnosis of

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musculoskeletal complications (ADO) of acromegaly depending on gender, age of patients, duration and activity of the disease.

Material and methods. The object of the study were 120 patients with acromegaly with confirmed acromegaly, diagnosed according to the recommendations of the International Consensus Agreement for the Diagnosis and Treatment of Acromegaly [15], who applied to the RSSPMCE for the period from 2000 to 2020 and were included in the register of patients with acromegaly in the Republic of Uzbekistan. Of the 120 patients, 90 were hospitalized at the RSSPMCE. Each patient was examined at the time of the first visit and was regularly monitored at 3, 6, 12 months and annually thereafter. So, we examined 120 patients with acromegaly, aged 20 to 75 years (mean age was 47.7±11.5 years). Among them, 43 (35.83%) men and 77 (64.17%) women. The diagnosis of acromegaly was established on the basis of clinical findings and was confirmed by high serum levels of GH, which were not suppressed below 0.4 ng /ml after OGTT, and IPRP-1 levels, which were above the corresponding age norm [18].

All these patients were divided into groups: by sex and age (Table 1) and duration of the disease (Table 2).

To study the incidence by sex and age, patients were divided into groups according to the WHO classification from 2016 (Table 1).

Table 1

Age and sex composition of patients with acromegaly in the Republic of Uzbekistan (according to WHO, 2016)

Age	Men		Women		Total	
	abs	%	abs	%	abs	%
16-29	3	6.98	one	1.3	four	3.34
30-44	17	39.5	thirty	38.97	47	39.17
45-59	17	39.5	37	30.84	54	45
60-74	6	14.02	9	28.89	fifteen	12.49
Total	43	35.84	77	64.16	120	100

Note: The percentage of patients in the third and fifth columns is given in relation to the total number of patients.

Age-sex analysis of the studied patients revealed a high frequency of persons aged 45-59 years (45%) and the lowest in 16-29 years (3.34%). Overall, this trend continued for both men and women.

table 2

Distribution of patients according to the duration of the disease

prescription	Men	Women	Total
1-9 years old	twenty	29	49/40.8%
10-19 years old	fifteen	29	44/36.7%

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20 or more	eight	19	27/22.5%
Total	43	77	120/100%

As can be seen from Table. 2 among the examined patients, the duration of the disease was 1-9 years in 40.8%, in more than a third, the duration of acromegaly was 10-19 years, and 22.5% of patients suffered for more than 20 years.

According to the results of serum levels of GH and IGF-1, we divided the patients into subgroups: with an active form of acromegaly and controlled (inactive). In patients with controlled acromegaly, IGF-1 levels were within reference, age-adjusted limits, and randomly measured GH concentrations were below 1 ng /mL [15] (Table 3).

Table 3

Distribution of patients by disease activity

Stages of the disease	Total
Active	62/51.7
controlled	58/48.3
Total	120 /100%

The survey included patients who received and continue to receive treatment for the underlying disease (Table 4)

Table 4

Distribution of patients by treatment methods

Groups	**Number of patients**	
	abs .	%
medical	32	26.7
radial	32	26.7
surgical	19	15.8
Combination (surgical + medical)	eleven	9.2
Combined(surg+beam .)	19	15.8
Newly identified	7	5.8
Total	120	100

As can be seen from the table, 49 patients (9.2%) were operated on. They underwent transsphenoidal adenomectomy under the conditions of the neurosurgical department of the RSSPMCE named after Y.Kh. Turakulov , the Military Medical Academy of St. Petersburg, the Research Institute named after. Burdenko in Moscow. At the same time, 11 (9.2%) of them took dopamine agonists after the operation; were on combination therapy and 19 (15.8%) additionally received radiation therapy.

32 (26.7%) of the examined patients were on monotherapy - radiation therapy in the Republican Cancer Research Center (RCSC), in oncological dispensaries in Tashkent and regions of the republic. Patients underwent traditional gamma therapy of the hypothalamic-pituitary region by a multifield convergent method at a total dose

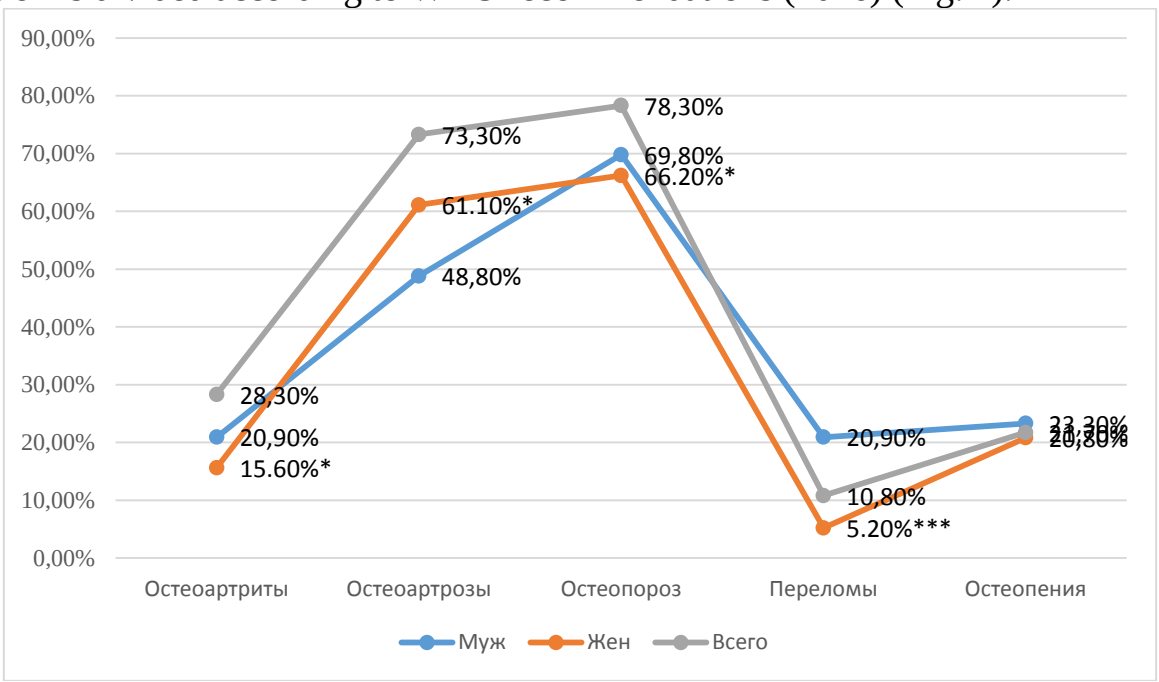
of 5000-6000 rads for 4-6 weeks. After radiation therapy, they were prescribed dopamine agonists at a dose of 5 to 7.5 mg/ day .

Among the patients examined by us, 32 (26.7%) received only medical treatment. These patients were taking dopamine agonists (bromergone , bromocriptine , parlodel). The dose of the drug varied from 2.5 mg to 12.5 mg/ day . Patients in this group were on drug therapy from the moment of diagnosis to the present day.

From Table. Table 4 shows that 7 patients (5.8%) are newly diagnosed, who have only been diagnosed and have not yet begun treatment.

A comprehensive examination of patients included the following: examination by a neuroendocrinologist, a neurosurgeon and an ophthalmologist. Conducted general clinical studies; dual energy absorptiometry (DEXA), 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 visual field). Laboratory biochemical studies were aimed at: determination of insulin-like growth factor-I, luteotropic hormone (LH), follicle-stimulating hormone (FSH), thyroid -stimulating hormone (TSH), determination of somatotropic hormone (GH), estradiol (E), parathyroid hormone (PTH) progesterone, testosterone (T), free thyroxine (fT4). Hormonal studies were carried out by the chemiluminescent (ICLA) method in a biochemical laboratory using HITACHI, COBOS E 411 kits.

Results and discussion. Among all ODS violations, the most common ones were identified, according to our own research and world literature data [1,6,8]. Age gradation is divided according to WHO recommendations (2016) (Fig. 1).



Notes: *- p< 0.05, **- p<0.01, *** p<0.001.

Fig. 1. Gender features of the frequency of ALC acromegaly.

So, our data showed that in the structure of MSC of acromegaly in the patients examined by us, osteoporosis prevailed (78.3%) with the same frequency in men

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(69.8%) and women (66.2%). At the same time, there were gender differences in some complications of CCS. So, if fractures prevailed in men (10.8% versus 5.2%, p< 0.001), then osteoarthritis was more common in women (61.1% versus 48.8%, p<0.05).

Next, we studied the features of the ODO structure depending on age (Table 5).

Table 5

The structure of the ALC of acromegaly in different age groups.

Age	18-44 (n=51)	45-59 (n=54)	60-74 (n=13)
Ostearthritis	25 /49%	6/ 11.1%***	-
Osteoarthritis	15/ 29.4%	39/ 72.2%***	15/ 100%***
osteopenia	18/ 35.3%	7/ 12.9%***	-
Osteoporosis	14/ 27.4%	42/ 77.8%***	15/ 100%***
fractures	5/9.8%	4/ 7.4%	4/ 26.7%**

Notes: the percentage was calculated relative to the total number of patients at this age; *- p < 0.05, ** - p < 0.01, *** p < 0.001.

As can be seen from Table. 5, the structure of the ODO of acromegaly had its own characteristics depending on age. Thus, in young patients, osteopenia (35.3% vs. 12.9%, p< 0.001 in persons aged 45-59 years) and osteoarthritis (49% vs. 11.1%, p<0.001, respectively) were more often observed. With increasing age, more severe, sometimes irreversible complications develop: osteoporosis (at the age of 60-74 years - 100%, against 77.8% - at 45-59 years, p<0.05 and 27.4% - at 18-44 years, p<0.01), osteoarthritis (at the age of 60-74 years - 100%, against 72.2% - at 45-59 years old, p<0.05 and 29.4% - at 18-44 years old. p<0.001) and fractures (at the age of 60-74 years - 26.7%, against 7.4% - at 45-59 years old, p<0.01 and 9.8% - at 18-44 years old, p< 0.05).

Interesting results were obtained when studying the structure of the MSC depending on the duration of the disease (Fig. 2).

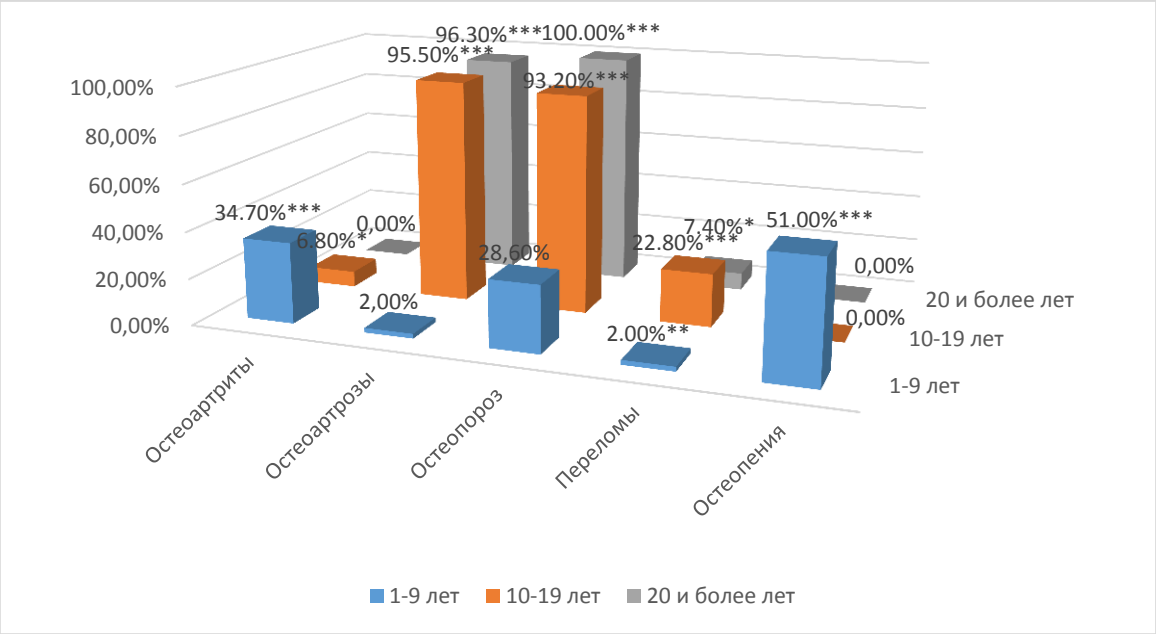

Fig. 2. The structure of the MSC in patients with acromegaly depending on the duration of the disease Notes: *- p< 0.05, **- p<0.01, *** p<0.001.

As the results of the study showed, in the first 10 years of the disease in patients with acromegaly, osteoarthritis and osteopenia prevailed in the structure of MSC. Long-term chronic hypersecretion of GH led to an aggravation of MSC and an increase in the incidence of osteoarthritis (93.2% - with a duration of 10-19 years, p < 0.001 and 100% - with a duration of 20 years or more, p < 0.001) and osteoporosis (95.5% - with a duration of 10-19 years, p<0.001 and 96.3% - with a duration of 20 or more years, p<0.001). At the same time, the highest incidence of fractures occurred in patients with a disease duration of 10–19 years, which is associated with the prevalence of patients with the active stage of the disease in this group (43.5% vs. 29%, p < 0.05), who more often recorded these fractures (14.5% vs. 6.9%, p<0.05) (Fig. 2).

As can be seen from Fig. 3, patients with active acromegaly had a higher frequency of ADO in the form of osteoarthritis (32.3% versus 0.01%, p< 0.001), osteoarthritis (70.9% versus 43.1%, p< 0.001), osteoporosis (85.5% vs 50.0%, p<0.01), and fractures (14.5% vs 6.9%, p<0.05).

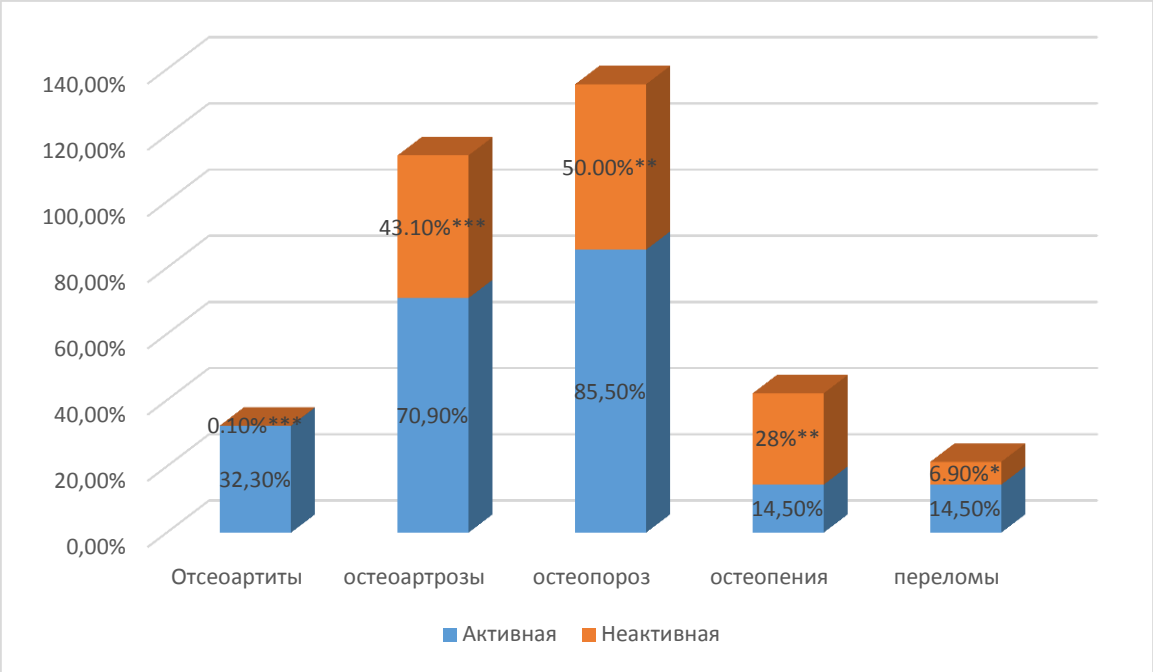

Fig.3. The relationship of the development of MSC acromegaly with the activity of the process.

Notes: *- p< 0.05, ** - p< 0.01, *** p< 0.001

Thus, MSC acromegaly in the patients examined by us was clinically more often manifested by swelling of the joints (93.6%), extensions of the distal phalanges (91.7%), prognathism (81.7%) and diastema (71.7%), enlargement of the hands and feet (100%), limited mobility of the knee joints (70.8%) and polyarthralgia (66.7%). At the same time, the most frequent complaints of patients were changes in appearance (87.5%), enlargement of the nose, lips (91.7%), enlargement of the lower jaw (81.7%), swelling of the face and hands (81.7%). More than half of the patients complained of pain (in the spine and knees - 56.7%, on the inner surface of the thigh - 50%). All this led to general weakness and reduced ability to work (83.3%). In 85% of patients, the BMI was greater than or greater than 25 kg/m², which was associated with an increase in lean tissue mass in patients with the active stage of acromegaly compared with the control group (53256.2 ± 5668.64 gr versus 43615.3 ± 1947.4 gr, p=0.001).

In the structure of MSC acromegaly in the patients examined by us, there were gender differences in the complications of CAS with a prevalence of fractures in men (10.8% vs. 5.2%, p < 0.001), and osteoarthritis in women (61.1% vs. p<0.05).

As can be seen from Table. 5., the structure of the ODO of acromegaly had its own characteristics depending on age. Thus, in young patients, osteopenia (35.3% vs. 12.9%, p< 0.001) and osteoarthritis (49% vs. 11.1%, p<0.001) were more often observed. With increasing age, more severe, sometimes irreversible complications develop: osteoporosis (at the age of 60-74 years - 100%, against 77.8% - at 45-59 years, p<0.05 and 27.4% - at 18-44 years, p<0.01), osteoarthritis (at the age of 60-74 years - 100%, against 72.2% - at 45-59 years old, p<0.05 and 29.4% - at 18-44 years old. p<0.001) and fractures (at the age of 60-74 years - 26.7%, against 7.4% - at 45-59 years old, p<0.01 and 9.8% - at 18-44 years old, p< 0.05).

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Patients in the active stage of the disease have a high frequency of ALC acromegaly in the form of osteoarthritis (32.3% versus 0.01%, p< 0.001), osteoarthritis (70.9% versus 43.1%, p<0.001), osteoporosis (85 .5% vs. 50.0%, p<0.01), and fractures (14.5% vs. 6.9%, p<0.05) and despite the subsidence of activity, almost half of the patients still have osteoporosis (50%) and osteoarthritis (43.1%). At the same time, the severity of MSC also depended on the duration of hypersomatotropinemia, which led to aggravation of ADO and an increase in the incidence of osteoarthritis (93.2% - with a duration of 10-19 years, p<0.001 and 100% - with a duration of 20 years or more, p<0.001) and osteoporosis (95.5% - with a duration of 10-19 years, p<0.001 and 96.3% - with a duration of 20 years or more, p<0.001). At the same time, the highest incidence of fractures occurred in patients with a disease duration of 10–19 years, which is associated with the prevalence in this group of patients with an active stage of the disease in this group (43.5% vs. 29%, p < 0.05), in whom these fractures were more frequently recorded (14.5% versus 6.9%).

So, the musculoskeletal complications of acromegaly were characterized by a high incidence of osteoarthritis (32.3%), osteoarthritis (70.9%), osteoporosis (85.5%) with vertebral compression fractures in 14.5%, osteopenia (28%) with limited mobility of the knee joints (70.8%) and polyarthralgia (66.7%) and their predominance in males, significantly increasing with age and duration of hypersomatotropinemia. In 85% of patients, BMI exceeded or was greater than 25 kg/m², which was associated with an increase in lean tissue mass in patients with the active stage of acromegaly compared with controls (53256.2 ± 5668.64 g versus 43615.3 ± 1947.4 g , p=0.001).

In the structure of the musculoskeletal complications of acromegaly, there were gender and age differences with a significant prevalence of fractures in males (10.8% versus 5.2%, p < 0.001), osteoarthritis in women (61.1% versus 48.8%, p<0.05); young people were more likely to have osteopenia (35.3% versus 12.9%, p<0.001) and osteoarthritis in middle-aged people (49% versus 11.1%, p<0.001). With increasing age, severe complications develop: osteoporosis (at the age of 60-74 years - 100%, against 77.8% - at 45-59 years, p<0.05 and 27.4% - at 18-44 years. p< 0.01), osteoarthritis (at the age of 60-74 years -100%, against 72.2% - at 45-59 years old, p<0.05 and 29.4% - at 18-44 years old. p<0.001) and fractures (at the age of 60-74 years - 26.7%, against 7.4% - at 45-59 years old, p<0.01 and 9.8% - at 18-44 years old, p<0.05) .

The severity of musculoskeletal complications also depended on the duration of hypersomatotropinemia, which led to aggravation of musculoskeletal complications and an increase in the incidence of osteoarthrosis (93.2% - with a duration of 10-19 years, p < 0.001 and 100% - with a duration of more than 20 years, p <0.001) and osteoporosis (95.5%, p<0.001 and 96.3%, p<0.001, respectively). The highest incidence of fractures was found in patients with a disease duration of 10–19 years, which is associated with the prevalence in this group of patients with active acromegaly of the disease in this group (43.5% vs. 29%, p < 0.05), in which these fractures (14.5% vs. 6.9%).

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Based on the above results, we recommend that in order to timely detect musculoskeletal complications of acromegaly and reduce disability in patients with established acromegaly, it is necessary to regularly assess the state of the musculoskeletal system and, if necessary, treat arthropathies.

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