DOI: 10.20514/2226-6704-2024-14-3-173-180
УДК 616.71-007.234-07:616-006.441-053.81
EDN: EEXQLQ

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ОСОБЕННОСТИ ДЕНСИТОМЕТРИЧЕСКОЙ ОЦЕНКИ КОСТНОЙ ТКАНИ У МОЛОДЫХ ПАЦИЕНТОВ С ЛИМФОМОЙ ХОДЖКИНА

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Features of Densitometric Assessment of Bone Tissue in Young Patients with Hodgkin's Lymphoma

Резюме

Лимфома Ходжкина встречается преимущественно у лиц в возрасте от 15 до 45 лет. Применение в качестве патогенетической терапии цитостатических препаратов может вызывать осложнения со стороны опорно-двигательного аппарата, такие как остеопения и остеопороз. На сегодняшний день актуальным остается вопрос применения денситометрического исследования у пациентов молодого возраста. **Цель.** Изучить особенности денситометрической оценки костной ткани у пациентов молодого возраста с лимфомой Ходжкина. **Материалы и методы.** В исследование включены 63 пациента с установленным диагнозом лимфомы Ходжкина после патогенетической терапии и 30 человек, составляющих группу контроля. Всем пациентам проведено исследование минеральной плотности костной ткани посредством двухэнергетической абсорциометрии в трех областях: проксимальном отделе бедра, шейке бедренной кости и поясничном отделе позвоночника. Также для каждого пациента был подсчитан Z-критерий. С целью выявления оптимальных областей денситометрического измерения применен метод однофакторного регрессионного анализа. **Результаты.** Согласно результатам денситометрии снижение минеральной плотности костной ткани более распространено в исследуемой группе по сравнению с группой контроля. При этом у пациентов с лимфомой Ходжкина минеральная плотность снижается одинаково в проксимальном отделе и шейке бедра. Тем не менее, проявления остеопороза более выражены в шейке бедра, тогда как явления остеопении преобладают в проксимальном отделе. Однако, снижение Z-критерия в поясничном отделе позвоночника наблюдается чаще, чем в шейке и проксимальном отделе бедра. **Заключение.** Ранняя диагностика осложнений со стороны опорно-двигательного аппарата у молодых пациентов позволит проводить своевременную профилактику остеопороза.

Ключевые слова: *Лимфома Ходжкина, денситометрия, остеопороз, минеральная плотность костной ткани*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

Источники финансирования

Авторы заявляют об отсутствии финансирования при проведении исследования

Статья получена 01.12.2023 г.
Принята к публикации 04.04.2024 г.

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Для цитирования: Бадыкова К. М., Китаева Ю. С., Праскурничий Е. А. ОСОБЕННОСТИ ДЕНСИТОМЕТРИЧЕСКОЙ ОЦЕНКИ КОСТНОЙ ТКАНИ У МОЛОДЫХ ПАЦИЕНТОВ С ЛИМФОМОЙ ХОДЖКИНА. Архивъ внутренней медицины. 2024; 14(3): 173-180. DOI: 10.20514/2226-6704-2024-14-3-173-180. EDN: EEXQLQ

Abstract

Hodgkin's lymphoma occurs mainly in people aged 15 to 45 years. The use of cytostatic drugs as pathogenetic therapy can cause complications from the musculoskeletal system, such as osteopenia and osteoporosis. To date, the issue of the use of densitometric examination in young patients remains relevant. **The aim of the work.** To study the features of densitometric assessment of bone tissue in young patients with Hodgkin's lymphoma. **Materials and methods.** The study included 63 patients with an established diagnosis of Hodgkin's lymphoma after pathogenetic therapy and 30 people who make up the control group. All patients underwent a study of bone mineral density by means of two-energy absorptiometry in three areas: the proximal femur, femoral neck and lumbar spine. The Z-criterion was also calculated for each patient. In order to identify the optimal areas of densitometric measurement, the method of one-factor regression analysis was applied. **Results.** According to the results of densitometry, a decrease in bone mineral density is more common in the study group compared with the control group. At the same time, in patients with Hodgkin's lymphoma, mineral density decreases equally in the proximal femur and femoral neck. Nevertheless, the manifestations of osteoporosis are more pronounced in the femoral neck, whereas the phenomena of osteopenia prevail in the proximal region. However, a decrease in the Z-criterion in the lumbar spine is observed more often than in the neck and proximal femur. **Conclusion.** Early diagnosis opens up the possibility of early prevention of osteoporosis in young patients.

Key words: *Hodgkin's lymphoma, densitometry, osteoporosis, bone mineral density*

Conflict of interests

The authors declare no conflict of interests

Sources of funding

The authors declare no funding for this study

Article received on 01.12.2023

Accepted for publication on 04.04.2024

For citation: Badykova K. M., Kitaeva Ju. S., Praskurnichij E. A. Features of Densitometric Assessment of Bone Tissue in Young Patients with Hodgkin's Lymphoma. The Russian Archives of Internal Medicine. 2024; 14(3): 173-180. DOI: 10.20514/2226-6704-2024-14-3-173-180. EDN: EEXQLQ

Introduction

Hodgkin lymphoma (HL) is a lymphoid tissue malignancy, the main morphological substrate of which is malignized B-lymphocytes. HL develops mainly at the age of 15 to 45 years old [1, 2]. As of today, this disease responds to therapy relatively well: long-lasting remission is observed in over 90 % of patients [3].

However, of note, HL therapy comprises a wide array of cytostatic drugs and glucocorticosteroids, which negatively impact some organs and systems [4]. One of the late complications of the antitumour therapy is impaired bone remodelling [5]. Pathogenetic therapy, including autologous haematopoietic stem cell transplantation (autoHSCT), causes abnormalities in the bone mineral composition and changes in its microarchitectonics, thus resulting in reduced bone mineral density (BMD), up to osteoporosis development, even in young patients [6].

Osteoporosis is known to be a disease, associated with impaired metabolic processes in bone tissue, leading to reduced physical durability of bones and fractures even in minimal traumas [7]. This complication impairs the quality of life and incapacitates young patients with HL.

Osteoporotic processes in this patient category are caused by impaired metabolic processes in bone tissue, resulting in changes in bone content and microarchitectonics, making bones more brittle. Impaired osteoblast and osteoclast activity underlies the complex process of BMD reduction and facilitates a shift towards osteoresorption. The key factor affecting the bone tissue condition in young patients with HL is the use of cytostatics and glucocorticosteroids, which regulate the activity of hormones and cytokines participating in bone remodelling. Osteoblast and osteoclast differentiation are affected by mediators: osteoprotegerin (OPG) and receptor activator of nuclear factor kappa (RANK) ligand [8]. Interaction of RANK ligands on osteoblast and osteoclast surface affects the function and differentiation of these cells. OPG impacts by inhibiting this interaction and inducing reduced activity of osteoclasts. The RANK/OPG imbalance underlies the development of osteoporotic process in bone tissue [8]. However, a number of mechanisms of reduced BMD in young patients with HL are still unclear and are likely to be associated with diminished formation of bone tissue and more active resorption processes in bones [6].

In recent years, young people have been having more and more traumatic injuries; however, there are few studies of the incidence of low-energy fractures in young patients. A study by Levine J. et al. (2023) demonstrated a high rate of low-energy fractures in people of 25 to 40 years of age [9].

Early diagnosis of osteoporotic changes in bone tissue has vital medical, social and economic significance due to high costs of management and post-fracture rehabilitation of patients [10]. As for HL, it is socially significant, since this disease manifests mainly in young and employable population.

To date, the great majority of works on osteoporosis have been focused on the study of its diagnosis, prevention and treatment in old patients, whereas reduced BMD in younger population remains understudied.

Osteoporosis does not have any clear typical clinical presentation, except for an actual fracture caused by a minimal trauma [11]. Taking into account risk factors of osteoporosis, including an indication of the use of pathogenetic therapy in young patients with HL, early diagnostics of the bone tissue status and timely measures to prevent BMD reduction are crucial. However, the diagnostic features of osteoporotic changes in this category of young patients are still unclear.

Thus, further studies of BMD pathogenesis, as well as identification of risk factors of osteoporosis in young people, are still a burning issue.

Study objective: To study specific features of bone tissue densitometry in young patients with Hodgkin lymphoma.

Materials and Methods

We conducted a cross-sectional study of 63 patients with confirmed HL (30 males and 33 females, median age: 30 years old), who were treated with a standard multiagent chemotherapy with autoHSCT (Table 1). A control group included 30 healthy volunteers (12 males, 18 females, median age: 30 years old). The study protocol was approved by the Local Ethics Committee at Sverdlovsk Regional Clinical Hospital No. 1. All subjects signed an informed consent form to participate in the study.

The inclusion criteria for the study were: 1) confirmed HL (histological and immunohistochemical confirmation); 2) indications for a standard pathogenetic chemotherapy and autoHSCT. The exclusion criteria for the study were: 1) rheumatoid and endocrine diseases (hyperparathyroidism, thyrotoxicosis, rheumatoid arthritis, systemic lupus erythematosus); 2) GI diseases (malabsorption syndrome, hepatic insufficiency); 5) a history of cancer.

Table 1 shows that the study groups were similar in sex, age and body mass index. HL was diagnosed with the held of histological and immunohistochemical examination of a lymph node biopsy sample.

In the group of patients with HL, stage II disease prevailed; and there were fewer stage III and IV cases. As for the clinical status of HL patients, symptoms of tumour intoxication prevailed. In terms of histological HL variant, the distribution in the group was as follows: the majority of patients had nodular sclerosis; a small amount of patients had mix-cellular variant and depleted lymphocyte variant.

When pathogenetic therapy is selected, patients with HL require a personalised approach and thorough review of the underlying and concomitant diseases, as well as comprehensive diagnostics. Our study shows that the comorbidity structure in this category of young patients undergoing antitumour therapy for HL is dominated by cardiovascular and GIT diseases. At the same time, over a half of all patients did not have any concomitant pathology when the underlying disease manifested.

All patients in the study group were treated with a standard pathogenetic therapy, depending on the tumour spread and response to the pathogenetic

Table 1. *Characteristics of the studied groups.*

Characteristics	A group of patients with Hodgkin's Lymphoma	Control Group	p
Number of patients	n=63	n=30	-
Gender:			
Мужской/Male	30 (48.0 %)	12 (40.0 %)	0.490
Женский/Female	33 (52.0 %)	18 (60.0 %)	
Median age, years	30 [17;45]	30 [25;38]	1.000
Body Mass Index, kg/m²	25 [18;38]	24 [18;33]	0.328
Stage of Hodgkin's lymphoma:			
II	22 (35.0 %)	-	<0.001
III	20 (32.0 %)	-	
IV	21 (33.0 %)	-	
Symptoms of tumor intoxication:			
A	22 (35.0 %)	-	<0.001
B	41 (65.0 %)	-	
Morphological variant of Hodgkin's lymphoma:			
Nodular sclerosis	59 (94.0 %)	-	<0.001
Mixed cellularity	3 (5.0 %)	-	
Lymphocyte depletion	1 (2.0 %)	-	
Chronic diseases:			
Diabetes mellitus	2 (3.0 %)	-	
Chronic diseases of the gastrointestinal tract	3 (5.0 %)	2 (7.0 %)	p=0.453
Hypertension	6 (10.0 %)	3 (10.0 %)	
Chronic gastritis	10 (16.0 %)	4 (13.0 %)	

therapy. First-line therapy was multiagent chemotherapy regimens: ABVD[1], BEACOPP-14[2], escBEACOPP[3], COPDAC[4]. Second- and third-line therapy was escBEACOPP, DHAP[5], Gemzar-containing regimens[6], bendamustine, immune therapy, etc. [1]. According to clinical guidelines, currently patients with refractory or recurrent HL are recommended to undergo autoHSCT [6, 12]. BEAM regimen was used for conditioning before autoHSCT[7]. This therapy was used for all patients in the study group during the conditioning stage. Mean multiagent chemotherapy duration was 10.5 [4; 53] months. HL patients did not undergo radiation therapy of their residual tumours.

In order to assess the bone tissue condition, all patients underwent BMD measurement by dual-energy bone absorptiometry using HOLOGIC device (Hologic Inc, Bedford, United States) in three regions: proximal femur, neck of the femur and lumbar spine. Presence or absence of osteopenia/osteoporosis was assessed depending on the level of mineral bone density reduction, observed during the measurement; also, Z-criterion (an age-dependant variable) was calculated.

Collection, systematisation and visual representation of material were performed using Microsoft Excel tables, while statistical analysis was conducted using Python and its tools (Statsmodels.api, Sklearn, Imblearn and Scipy). The Shapiro — Wilk test was used to assess correspondence of quantitative parameters to normal distribution. Further calculations were performed using non-parametric statistic methods, because the analysis had showed that the analysed data did not have normal distribution. The median was used as a distribution centre, while quartiles (Me [Q1; Q3]) were used as markers of variation. The Mann — Whitney U-test was applied to compare unrelated samples. The results are presented as absolute values, and percentage is stated. Within-group data were compared using Pearson's chi-squared test; and where the number of expected observations was under 10, the Fisher test was used. Data were analysed under the one-factor logistic regression method. This method was chosen because the dependent variable is dichotomic, and independent variables characterise both categorial and qualitative attributes. Differences were statistically significant at $p < 0.05$.

Results

We have assessed the bone tissue condition by dual-energy bone absorptiometry in all HL patients who underwent autoHSCT in addition to their standard multiagent chemotherapy, as well in healthy volunteers. The assessment results are presented in Table 2.

Table 2 shows that BMD values in patients with HL are significantly lower in all areas than in controls ($p \le 0.05$). In HL patents, Z-criterion values are often very low and reach osteopenia/osteoporosis levels in lumbar spine ($p \le 0.05$). In controls, this parameter was normal.

The incidence of osteopenia/osteoporosis in HL patients who underwent autoHSCT in addition to their standard multiagent chemotherapy, was assessed on the basis of BMD and Z-criterion in the three areas of measurement and is presented in Figure 1.

Figure 1 shows that reduced BMD is observed in 31 patients (49 %) in their lumbar spine, including 6 patients (9 %) with osteoporosis and 25 patients (40 %) with osteopenia. Reduction in this value in the neck of the femur was recorded in 51 patients (81 %), including 32 patients (51 %) with osteoporosis and 19 patients (30 %) with osteopenia. In the proximal femur area, BMD values reduced to osteopenia were recorded in 34 patients (54 %), to osteoporosis — in 20 patients (32 %). In other words, HL patients have BMD reduced in two areas of measurement: in proximal femur and neck of the femur. Nevertheless, signs of osteoporosis are more marked in the neck of the femur, whereas signs of osteopenia prevail in the proximal femur area.

We have assessed prevalence of osteopenia/osteoporosis based on the Z-criterion values in the three areas of measurement in HL patients who underwent autoHSCT in addition to their standard multiagent chemotherapy (Figure 2).

Figure 2 shows that, in patients with HL, reduced Z-criterion in the neck of the femur area is recorded in 6 patients (10 %), in the proximal femur — in 10 patients (16 %), and in the lumbar spine — 12 patients (19 %). Therefore, Z-criterion reduction to osteopenia/osteoporosis in lumbar spine is observed by 3 % more often than in the proximal femur, and by 9 % more often than in the neck of the femur.

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[1] ABVD (doxorubicine 25 mg/m^2 on days 1 and 15, bleomycin 10 mg/m^2 on days 2 and 15, vinblastine 6 mg/m^2 (max. 10 mg in total) on days 1 and 15, dacarbazine 375 mg/m^2 on days 1 and 15)

[2] BEACOPP–14 (cyclophosphan 650 mg/m^2 on day 1, adriblastin 25 mg/m^2 on day 1, vepesid 100 mg/m^2 on days 1–3, procarbazine 100 mg/m^2 on days 1–7 or dacarbazine 375 mg/m^2 on day 1, prednisolone 40 mg/m^2 on days 1–7, bleomycin 10 mg/m^2 on day 8, vincristine 1.4 mg/m^2 (max. 2 mg in total) on day 8)

[3] escBEACOPP (cyclophosphan 1,250 mg/m^2 on day 1, adriblastin 35 mg/m^2 on day 1, vepesid 200 mg/m^2 on days 1–3, procarbazine 100 mg/m^2 on days 1–7 or dacarbazine 375 mg/m^2 on day 1, prednisolone 40 mg/m^2 on days 1–14, bleomycin 10 mg/m^2 on day 8, vincristine 1.4 mg/m^2 (max. 2 mg in total) on day 8)

[4] DHAP (dexamethasone 40 mg on days 1–4, cytarabine 2,000 mg/m^2 twice daily on day 2, cisplatin 100 mg/m^2 24-hour infusion on day 1)

[5] Gemzar–containing protocol IGEV (gemzar 800 mg/m^2 on days 1 and 5, iphosphamide 2,000 mg/m^2 on days 1–4, vinorelbine 20 mg/m^2 on day 1, prednisolone 100 mg/m^2 or dexamethasone 40 mg on days 1–5)

[6] COPDAC (prednisolone 40 mg/m^2 on days 1–15, vincristine 1.5 mg/m^2 (max. 2 mg) on days 1 and 8, dacarbazine 250 mg/m^2 on days 1–3, cyclophosphamide 500 mg/m^2 on days 1 and 8)

[7] BEAM (carmustine 60 mg/m^2 or lomustine 100 mg/m^2 on day 1, cytarabine 100 mg/m^2 on days 2–5, etoposide 100 mg/m^2 on days 2–5, melphalan 30 mg/m^2 on day 6)

Table 2. *Parameters of bone mineral density in patients of the studied groups*

Measuring area		A group of patients with Hodgkin's Lymphoma	Control Group	p
Number of patients		63	30	-
Bone mineral density, g/cm^2	Femoral neck	0.92 [0.54;1.22]	0.99 [0.98;1.14]	0.003
	Proximal femur	0.87 [0.62;1.07]	1.00 [0.95;1.22]	0.001
	Lumbar spine (L1-L4)	1.01 [0.66;1.18]	1.04 [0.96;1.16]	0.027
Z -criterion	Femoral neck	-0,66 [-2.7;2.5]	-0,42 [-1.8;2.6]	0.351
	Proximal femur	-0,82 [-2.7;1.9]	-0,36 [-2.3;1.4]	0.333
	Lumbar spine (L1-L4)	-0.77 [-3.3;1.7]	-0.33 [-2;1.4]	0.030

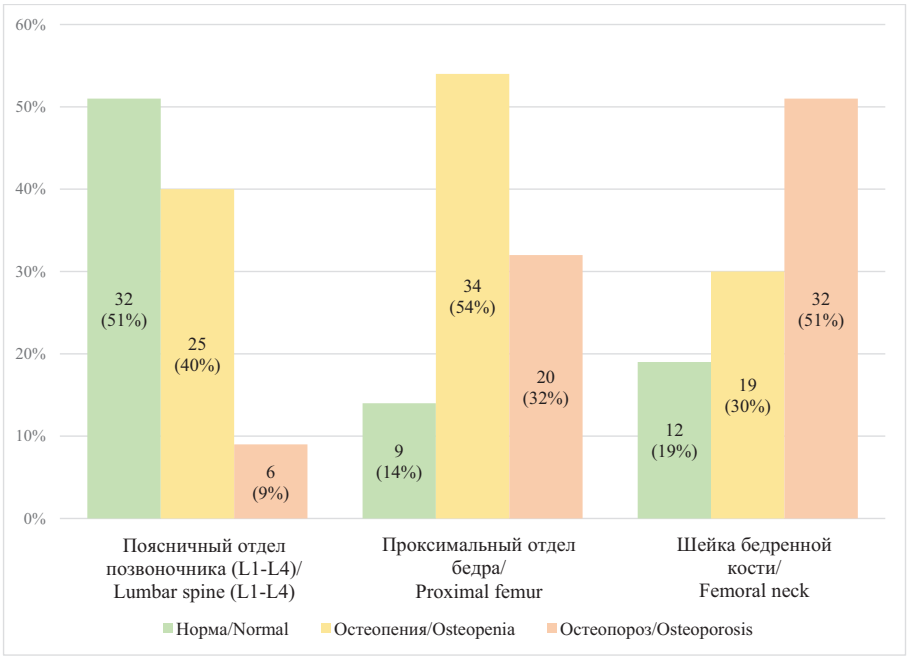

Figure 1. *The prevalence of decreased bone mineral density in the group of patients with Hodgkin's lymphoma who received autologous hematopoietic stem cell transplantation in addition to standard polychemotherapy in different measurement areas*

Note: all differences in the incidence of osteopenia/osteoporosis based on bone mineral density indicators in patients with Hodgkin's lymphoma who received autologous hematopoietic stem cell transplantation in addition to standard polychemotherapy are significant at p <0.05

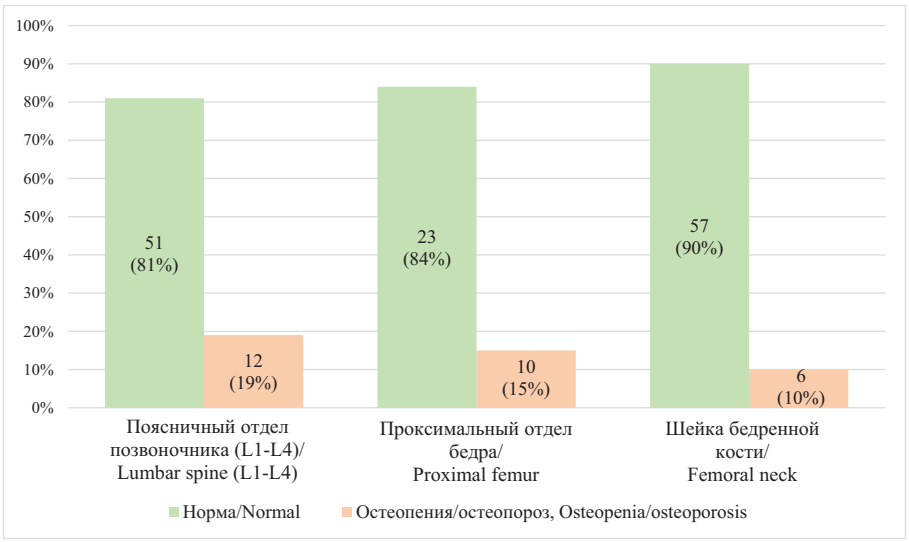

Figure 2. *The prevalence of a decrease in the Z-criterion in a group of patients with Hodgkin's lymphoma who received autologous hematopoietic stem cell transplantation in addition to standard polychemotherapy in different measurement areas*

Note: all differences in the incidence of osteopenia/osteoporosis based on the Z-criterion in patients with Hodgkin's lymphoma who received autologous hematopoietic stem cell transplantation in addition to standard polychemotherapy are significant at p <0.05

Table 3. Determination of the significance of the area of densitometric examination in patients with Hodgkin's lymphoma

Measuring area	A group of patients with Hodgkin's lymphoma	Control Group	p
Number of patients	n=63	n=30	-
Femoral neck	0.8 [0.69; 0.95]	0.8 [0.75; 0.92]	0.687
Proximal femur	0.87 [0.76; 0.92]	0.91 [0.85; 0.99]	0.014
Lumbar spine (L1-L4)	1.01 [0.89; 1.14]	1.03 [0.96; 1.07]	0.475

Table 4. Results of one-factor logistic regression

Measuring area	B	Exp (B) [95 % CI]	p	Pseudo R-squ
Femoral neck	0.184	1.202 [0.074, 19.6]	0.897	0.000
Proximal femur	5.020	151.411 [3.164, 245.634]	0.011	0.062
Lumbar spine (L1-L4)	0.215	1.24 [0.083, 18.545]	0.876	0.000

It is well known that a preferred area to diagnose BMD reduction in young patients with HL is the lumbar spine and the proximal femur [13]. Bone tissue remodelling is the most intense in trabecular tissue, which is the main component of vertebrae and long bones [13].

In order to identify the most optimal areas for densitometric measurements for reduced BMD diagnostics, the one-factor logistic regression method was used (see Table 3).

Table 3 demonstrates that BMD measurements in the proximal femur are associated with statistically significant differences in HL patients and controls (p = 0.014). Therefore, in HL patients, the risk of reduced BMD values is statistically higher in the proximal femur. Simply put, BMD measurements in the proximal femur can be a reason to suspect an osteoporotic process.

The one-factor logistic regression method (Table 4) demonstrated that reduced BMD levels in the proximal femur significantly (p = 0.011) increased the probability of osteopenia/osteoporosis.

Table 4 demonstrates that the dependence of the BMD value on the area of measurement by dual-energy bone absorptiometry is sufficiently valid in the proximal femur (coefficient of determination is 0.062). Thus, HL patients are at a significantly higher risk of reduced BMD in the proximal femur.

Therefore, a reduction in BMD and Z-criterion was most prominent when measured in the proximal femur area.

Discussion

Very often osteoporosis is seen as a disease affecting elderly patients only; however, this idea is incorrect, because this condition is observed in young people as well and depends on a number of factors, including genetic, hormonal and alimentary causes. An epidemiological study demonstrated that reduced BMD values are diagnosed in 10–30 % of healthy children and adolescents [11]. The number of confirmed cases of osteoporosis is growing not only among the elderly population, but also among younger people, including children.

Another problem is the absence of any tailored scales or questionnaires to assess the risk of osteoporosis and low-energy fractures in patients; and protocols for diagnostics and prevention are unavailable as well. Our study demonstrated that reduced BMD values are recorded in the young population at a rate of 50 % and more in various measurement areas. Currently, the issue of osteoporosis in young patients undergoing specialised therapy is very relevant, because it can result in premature disability in this patient group.

The significance of osteoporosis can also be seen in assessing the outcomes for HL patients. The association between densitometric values and areas of measurement in HL patients has been identified. It is known that, in young patients, reliable assessment of the rate of osteopenia/osteoporosis is based on the BMD value measured in lumbar vertebrae. The reason for this is that remodelling is primarily observed in the spongeous bone (vertebrae are 95 % spongeous bone), while the cortex is not prominent [7,13]. At the same time, bone tissue does not demonstrate any adult changes yet, which are a result of long-lasting physical loads and various chronic conditions affecting bone blood supply and microarchitectonics [14].

In this study, over 54 % of young patients with HL undergoing pathogenetic therapy are diagnosed with BMD reduction to osteopenia/osteoporosis in the proximal femur area. The femur (especially its proximal section) is known to bear the highest axial load. Therefore, the cortex of the proximal femur is more pronounced; the cortex is a dense, strong compact substance, while the spongeous section contains wide anastomosing trabeculae of bone, located along the lines towards the highest mechanical stress, and contains the highest amount of bone tissue [15]. These peculiarities result in a higher strength of the femur and explain slow bone

tissue remodelling in this area [13]. Gradual depression of bone tissue and more pronounced changes in microarchitectonics of the proximal femur area are typical for elderly people [14, 15].

Currently, the matter of selection of areas for densitometry in order to assess the bone tissue condition in young patients with HL is understudied. According to sparse literature sources on the study of predictors of reduced bone mineral density and the factors affecting bone remodelling in young HL patients, this problem requires further elaboration [6].

This study demonstrated that BMD reduction to osteopenia/osteoporosis is widely observed in HL patients undergoing antitumour therapy. Despite the fact that osteoporotic changes in the proximal femur are more typical for elderly people, similar results were observed in young patients with HL. It is likely to be associated with pathomorphological features of bone tissue affected by a wide array of specific and non-specific factors, which impact bone remodelling in patients undergoing antitumour therapy [13, 15]. Thus, young people are advised to have their BMD measured in lumbar spine and proximal femur, similar to the elderly population.

Overall, shaping a unified approach to the diagnostic examination of HL patients undergoing pathogenetic therapy, and timely osteopenia/osteoporosis prevention, is essential for reduction of the risk of low-energy fractures and high quality of life of young patients with HL.

Conclusion

Young HL patients more often have lower densitometric values in their proximal femur area, which significantly increases the risk of low-energy fractures in this group of patients. At the same time, early diagnosis of osteoporotic changes ensures timely prevention of these complications and preservation of an acceptable quality of life of young patients.

Вклад авторов:

Все авторы внесли существенный вклад в подготовку работы, прочли и одобрили финальную версию статьи перед публикацией

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Contribution of the authors:

All the authors made a significant contribution to the preparation of the work, read and approved the final version of the article before publication

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