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STUDY OF HORMONAL STATUS AND BONE METABOLISM IN UNDERAGE FEMALE ATHLETES WITH PRIMARY AMENORRHEA

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Introduction. Fractures, particularly low-energy ones, are more common in female athletes with oligo/amenorrhea compared to their peers without menstrual disorders. This problem is associated with various hormonal changes and impaired bone remodeling processes.
Objective. Assessment of bone metabolism and serum hormonal parameters in highly qualified under-18 female athletes both with primary amenorrhea and without menstrual cycle disorders.
Materials and methods. A single-center single-stage study involved 111 young female athletes aged 15–18 years (median age 15.9 [14.9; 16.6] years), who were members of Russian national teams in five sports. All the participants underwent comprehensive medical examination at the Federal Scientific and Clinical Center for Children and Adolescents of FMBA of Russia between March 2021 and July 2023. The athletes were divided into two groups based on the presence of primary amenorrhea. The group with primary amenorrhea included 23 athletes (median age 15.8 [15.1; 16.3] years); the comparison group consisted of 88 athletes (median age 15.9 [14.9; 16.6] years) with a regular menstrual cycle. Serum levels of osteocalcin, C-terminal telopeptide (β-CrossLaps), type 1 procollagen (P1NP), parathyroid hormone (PTH), vitamin D (25(OH)D3), and alkaline phosphatase (ALP) activity were measured. To assess hormonal status, levels of luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol, and leptin were evaluated. Sexual maturity was assessed according to the Tanner rating, and body composition was evaluated using bioelectrical impedance analysis. Statistical data processing was performed using the Statistica v. 10.0 software package (StatSoft Inc., USA).
Results. Athletes with primary amenorrhea were characterized by lower body weight ($p < 0.0001$) and body fat percentage ($p < 0.0001$) compared to their peers without menstrual disorders. The analysis of LH ($p = 0.328$) and FSH ($p = 0.069$) levels did not reveal statistically significant differences between the study groups; however, the adolescent athletes with primary amenorrhea had lower levels of estradiol 182.0 [123.0; 227.0] and 244.0 [143.5; 518.5] ($p = 0.002$) and leptin 2.1 [1.2; 4.1] and 9.1 [5.1; 14.9] ($p < 0.0001$) compared those without menstrual cycle disorders. The athletes with primary amenorrhea showed an increase in both bone formation markers (P1NP, osteocalcin) and bone resorption markers (β-CrossLaps and ALP) compared to their peers without menstrual disorders.
Conclusions. Minors with primary amenorrhea are characterized by disharmonious physical development due to underweight, accompanied by reduced body fat content, decreased levels of leptin and estradiol, preserved gonadostat function, and increased markers of bone metabolism. The identified hormonal and metabolic features may represent a significant risk for impaired bone remodeling in this group of athletes.

Keywords: young athletes; sports medicine; primary amenorrhea; leptin; hormones; bone metabolism markers; vitamin D

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ИЗУЧЕНИЕ ГОРМОНАЛЬНОГО СТАТУСА И МЕТАБОЛИЗМА КОСТНОЙ ТКАНИ У НЕСОВЕРШЕННОЛЕТНИХ СПОРТСМЕНОК С ПЕРВИЧНОЙ АМЕНОРЕЕЙ

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Введение. Переломы, в особенности низкоэнергетические, чаще встречаются у спортсменок с олиго/аменореей по сравнению со сверстницами без нарушений менструального цикла, что связано с различными гормональными изменениями и нарушением процессов ремоделирования костной ткани.
Цель. Оценка состояния метаболизма костной ткани и гормональных показателей в сыворотке крови у высококвалифицированных спортсменок, не достигших 18-летнего возраста, с первичной аменореей и без нарушений менструального цикла.

Материалы и методы. Проведено одномоментное одноцентровое исследование с участием 111 юных спортсменок в возрасте 15–18 лет (средний возраст 15,9 [14,9; 16,6] года), входящих в состав сборных команд РФ по 5 видам спорта и проходивших углубленное медицинское обследование в ФГБУ «ФНКЦ детей и подростков ФМБА России» в период с марта 2021 по июль 2023 г. Спортсменки были разделены на 2 группы в зависимости от наличия первичной аменореи. В группу с первичной аменореей включены 23 спортсменки (средний возраст 15,8 [15,1; 16,3] года); в группу сравнения — 88 спортсменок (средний возраст 15,9 [14,9; 16,6] года) с регулярным менструальным циклом. У спортсменок определяли уровень остеокальцина, С-концевого телопептида (β-CrossLaps), проколлагена 1-го типа (P1NP), паратиреоидного гормона (ПТГ), витамина D (25(OH)D3) и активности щелочной фосфатазы (ЩФ) в сыворотке крови. Для оценки гормонального статуса проведена оценка уровней лютеинизирующего гормона (ЛГ), фолликулостимулирующего гормона (ФСГ), эстрадиола и лептина. Оценка полового развития проведена по классификации Tanner, оценка композиционного состава тела — методом биоимпедансного анализа. Статистическая обработка данных произведена с использованием пакета прикладных программ Statistica v. 10.0 (StatSoft Inc., США).
Результаты. Для спортсменок с первичной аменореей характерны более низкие значения массы тела ($p < 0,0001$) и содержания жировой ткани (%) в организме ($p < 0,0001$) по сравнению со сверстницами без нарушений менструального цикла. Анализ уровней ЛГ ($p = 0,328$) и ФСГ ($p = 0,069$) не выявлял статистически значимых различий в исследуемых группах, однако у девочек с первичной аменореей отмечали более низкие уровни эстрадиола 182,0 [123,0; 227,0] и 244,0 [143,5; 518,5] ($p = 0,002$) и лептина 2,1 [1,2; 4,1] и 9,1 [5,1; 14,9] ($p < 0,0001$) по сравнению со спортсменками без нарушений менструального цикла. У спортсменок с первичной аменореей выявлено повышение как маркеров костеобразования (P1NP, остеокальцин), так и костной резорбции (β-CrossLaps и ЩФ) по сравнению со сверстницами без нарушений менструального цикла.
Выводы. Для несовершеннолетних спортсменок с первичной аменореей характерно дисгармоничное физическое развитие за счет дефицита массы тела, сопровождающееся снижением содержания жировой ткани в организме, снижением уровня лептина и эстрадиола и сохранной функцией гонадостата, а также повышением маркеров метаболизма костной ткани. Выявленные гормональные и метаболические особенности могут являться значимым фактором риска развития нарушений ремоделирования костной ткани у данной группы спортсменок.

Ключевые слова: юные спортсменки; спортивная медицина; первичная аменорея; лептин; гормоны; маркеры костного метаболизма; витамин D

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INTRODUCTION

Relative energy deficiency in sport (RED-s) in adolescent females is often associated with the development of functional hypothalamic amenorrhea (FHA) [1, 2]. Prolonged energy deficiency is accompanied by a decrease in the pulsatile secretion of gonadotropin-releasing hormone in the hypothalamus, followed by impaired release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the pituitary gland. In turn, this leads to decreased estradiol levels and the development of menstrual disorders, such as primary and secondary amenorrhea [3]. Underweight and particularly reduced adipose tissue in athletes with long-term energy deficit are also associated with decreased leptin levels — a hormone produced by adipose tissue that is an important regulator of gonadostat functional activity [4].

The FHA development is associated with reduced bone mass accumulation and impaired bone microarchitecture, being a leading risk factor in low-energy fractures in professional female athletes, particularly those under 18 years of age [1, 5, 6].

Studies into bone metabolism markers and their relationship with hormonal parameters in underage highly trained female athletes with primary amenorrhea are limited and show contradictory results [5].

The aim of this study is to assess bone metabolism and serum hormonal parameters in highly qualified under-18 female athletes both with primary amenorrhea and without menstrual cycle disorders.

MATERIALS AND METHODS

A single-center single-stage study involved young athletes from the Russian national teams who underwent comprehensive medical examination at the Federal Scientific and Clinical Center for Children and Adolescents of FMBA between March 2021 and July 2023. A total of 111 young female athletes aged 15–18 years (median age 15.9 [14.9; 16.6] years), representing five sports (rhythmic gymnastics, artistic gymnastics, figure skating,

softball, synchronized swimming), included in the study, were divided into two groups based on the presence of primary amenorrhea. Primary amenorrhea was diagnosed based on the absence of menstruation by age 15[1] (provided that secondary sexual characteristics had developed).

The group with primary amenorrhea included 23 athletes (median age 15.8 [15.1; 16.3] years); the comparison group consisted of 88 athletes (median age 15.9 [14.9; 16.6] years) with a regular menstrual cycle. The study groups were comparable in age (p = 0.794) and sexual maturity stage, although showing statistically significant differences in the key anthropometric parameters (Table 1). Anthropometric measurements of the underage athletes included: height, body weight, and calculation of body mass index (BMI). BMI was assessed for the specific age and sex and presented as the number of standard deviations from the mean (SDS). Body composition assessment was performed using bioelectrical impedance analysis (InBody 570 analyzer, South Korea). Sexual maturity of the underage athletes was assessed according to the Tanner rating.

When assessing sexual maturity, 21 (92%) athletes in the study group and 88 (100%) athletes in the comparison group had completed or nearly completed sexual maturity. Sexual maturity was assessed according to the Tanner rating [7]. Inclusion criteria for study participants were female athletes from Russian national teams aged 15–18 years and the presence of primary amenorrhea. Inclusion criteria for the comparison group were regular menstrual cycle, gynecological age > 1 year.

For clinical and laboratory analysis, blood samples were collected from a peripheral vein in the morning after fasting. All young athletes had their serum levels of osteocalcin (Roche, Switzerland), N-terminal propeptide of human type 1 procollagen (P1NP) (Roche, Switzerland), C-terminal telopeptide (β-CrossLaps) (Roche, Switzerland), vitamin D (25-hydroxycholecalciferol-25(OH)D3) (Roche, Switzerland) measured (ng/mL). Parathyroid hormone (PTH) (Roche, Switzerland) in serum (pmol/L). Leptin (ng/mL), luteinizing hormone (LH) (IU/L), follicle-stimulating hormone (FSH) (IU/L), and estradiol (pmol/L) levels were determined by enzyme immunoassay (manufacturer Bender MedSystems, Austria). β-CrossLaps testing was performed by electrochemiluminescence using a Cobas e411 analyzer (Roche Diagnostics, Germany). Testing of P1NP, osteocalcin, PTH, 25(OH)D3 was carried out by solid-phase enzyme immunoassay. Serum alkaline phosphatase (ALP) activity (U/L) was determined by a kinetic colorimetric method.

Statistical data processing was performed using the Statistica v. 10.0 software package (StatSoft Inc., USA). Since the studied quantitative indicators had a non-normal distribution (according to the Kolmogorov–Smirnov test), all data are presented as median (M_e) and 1st and 3rd quartiles [Q_1; Q_3]. The Mann–Whitney U test was used to assess the statistical significance of differences in quantitative characteristics. Qualitative characteristics are presented as percentages (%) with absolute values. Contingency tables were constructed to assess differences between qualitative characteristics, followed by evaluation using Pearson's chi-square test (χ^2) with Yates' correction. Correlation analysis was performed using Spearman's criterion. A statistical significance level of $p \leq 0.05$ was accepted for differences.

RESULTS

Athletes with primary amenorrhea were characterized by lower parameters of height (p = 0.023), body weight

Table 1. Clinical characteristics of the study groups

Parameter	Group with primary amenorrhea (n = 23)	Group with regular menstrual cycle (n = 88)	Statistical significance level, p
Age, years	15.8 [15.1; 16.3]	15.9 [14.9; 6.6]	0.794
Height, m	1.63 [1.56; 1.67]	1.66 [1.61; 1.71]	0.023
Height SDS	0.15 [–1.17; 0.87]	0.66 [–0.06; 1.5]	0.016
Body weight, kg	46.8 [40.5; 48.8]	60.6 [54.2; 67.7]	< 0.0001
BMI	17.4 [16.6; 18.2]	21.8 [19.7; 24.0]	< 0.0001
BMI SDS	–1.34 [–1.69; –0.88]	0.5 [–0.07; 1.14]	< 0.0001
Sexual maturity: Tanner II–III Tanner IV–V	 2 (8%) 21 (92%)	 – (–) 88 (100%)	0.059

Table compiled by the authors based on their own data

Note: n = number of athletes; "–" — the absence of athletes at Tanner sexual maturity stages II–III in this group.

[1] Clinical guidelines "Amenorrhea and oligomenorrhea"; 2024 (In Russ.). URL: https://cr.minzdrav.gov.ru/preview-cr/644_2?ysclid=mdyjwyzaqy766941934

($p < 0.0001$), BMI ($p < 0.0001$), and BMI SDS ($p < 0.0001$) compared to their peers without menstrual disorders.

An analysis of gonadotropin levels (Table 2) did not reveal statistically significant differences between the study groups ($p = 0.328$ for LH; $p = 0.069$ for FSH). However, adolesent althleters with primary amenorrhea had lower levels of estradiol, 182.0 [123.0; 227.0], and leptin, 2.1 [1.2; 4.1], compared to those without menstrual cycle disorders: 244.0 [143.5; 518.5] ($p = 0.002$) and 9.1 [5.1; 14.9] ($p < 0.0001$), respectively.

A correlation analysis revealed a strong positive correlation between leptin levels and body fat percentage ($r_s = 0.74$; $p < 0.05$), LH levels ($r_s = 0.16$; $p < 0.05$), and estradiol levels ($r_s = 0.24$; $p < 0.05$).

According to the assessed bone metabolism parameters, athletes with primary amenorrhea showed an increase in both bone formation markers (P1NP by 2.5 times and osteocalcin by almost 2 times) and bone resorption markers β-CrossLaps and ALP compared to their peers without menstrual disorders; the corresponding data are presented in Table 2. The study groups did not show statistically significant differences in PTH levels ($p = 0.242$). However, when assessing vitamin D status, athletes with a regular menstrual cycle had lower levels of 25(OH)D3 compared to the primary amenorrhea group ($p = 0.001$).

An evaluation of body composition in underage athletes with primary amenorrhea revealed a statistically significant reduction in body fat percentage (%) compared to the group of athletes with a regular menstrual cycle: 10.8 [9.3; 12.8] vs. 20.5 [16.1; 24.4], ($p < 0.0001$).

The conducted correlation analysis established a moderate negative association between leptin levels and osteocalcin ($r_s = -0.33$), P1NP ($r_s = -0.39$), β-CrossLaps ($r_s = -0.45$), and ALP ($r_s = -0.43$). Meanwhile, bone metabolism markers in underage athletes were not dependent on estradiol and gonadotropin levels.

DISCUSSION

It is known that fractures, particularly low-energy ones, are more common in athletes with oligo/amenorrhea compared to their peers without menstrual disorders and with normal physical activity levels [8]. The presence of primary amenorrhea is currently considered by the International Olympic Committee expert panel as an important risk factor used for stratifying the risks of developing RED-s syndrome, including in underage athletes [1].

Analysis of bone metabolism markers is an effective diagnostic tool for assessing the functional state of the skeletal system in clinical practice [9]. Our work demonstrated that underage athletes with primary amenorrhea demonstrate elevated levels of key bone metabolism markers compared to athletes without menstrual disorders. It is known that estrogens promote the inhibition of bone resorption processes [10], and their deficiency, identified in athletes with primary amenorrhea, leads to an increase in bone resorption markers. However, our results are not consistent with the data by Christo et al., who found reduced levels of N-terminal telopeptide (NTX) and P1NP in athletes with amenorrhea and low bone mineral density (BMD). The authors explained their finding by a “slowdown” in bone metabolism due to chronic energy deficiency in athletes [5].

Some authors have shown that the presence of menstrual disorders in young athletes is accompanied by reduced BMD, as determined by X-ray densitometry

Table 2. Hormonal parameters and bone metabolism markers in underage highly qualified female athletes depending on the presence of primary amenorrhea

Studied parameters	Group with primary amenorrhea ($n = 23$)	Group with regular menstrual cycle ($n = 88$)	Statistical significance level, p
Osteocalcin, ng/mL	92.2 [60.0; 110.0]	49.0 [37.0; 65.0]	< 0.0001
P1NP, ng/mL	505.3 [406.8; 750.8]	200.7 [136.0; 244.9]	< 0.0001
ALP, U/L	200.2 [161.7; 285.1]	92.7 [75.3; 127.3]	< 0.0001
β-CrossLaps, ng/mL	1.78 [1.39; 2.11]	1.27 [0.98; 1.51]	0.0001
PTH, pmol/L	4.6 [2.7; 5.4]	5.0 [3.6; 6.6]	0.242
25(OH)D3, ng/mL	23.5 [13.3; 32.8]	14.3 [11.1; 19.8]	0.001
LH, IU/L	2.8 [2.3; 4.1]	3.4 [2.0; 5.8]	0.328
FSH, IU/L	5.4 [4.6; 6.5]	4.8 [3.5; 6.1]	0.069
Estradiol, pmol/L	182.0 [123.0; 227.0]	244.0 [143.5; 518.5]	0.002
Leptin, ng/mL	2.1 [1.2; 4.1]	9.1 [5.1; 14.9]	< 0.0001

Table compiled by the authors based on their own data

Note: n = number of athletes.

[5]. The reduction in bone tissue mineralization in highly qualified young athletes occurs despite the presence of strength and intensive physical loads, which have a protective effect on bone tissue [11].

Our work demonstrated that athletes with primary amenorrhea had lower BMI SDS values, which, according to the literature, is a predictor of reduced BMD [12]. The group of athletes with primary amenorrhea was predominantly represented by rhythmic gymnastics and figure skating. In these sports, low body weight is a key factor for success; for this reason, athletes often resort to hypocaloric unbalanced diets, which is one of the causes of developing FHA within RED-s explaining the presence of primary amenorrhea [13]. For example, in a study of athletes aged 11–17 years engaged in rhythmic gymnastics, disharmonious physical development due to underweight was revealed, accompanied by a reduction in body fat and a high prevalence of primary amenorrhea (38%) [14].

Therefore, BMI SDS and estrogen deficiency can be considered as the leading independent factors contributing to impaired mineralization and microarchitecture of bone tissue in athletes with FHA. Underweight in athletes is associated with a reduction in adipose tissue and circulating leptin. Normally, leptin, by affecting the secretory activity of gonadotrophs, increases the pulsatile secretion of LH and, to a lesser extent, FSH [15]. Currently, leptin is believed to be a crucial endogenous regulator and modulator of reproductive system functions, the dysfunction of which is a key factor in impaired bone remodeling and reduced BMD in athletes with RED-s syndrome [1, 17].

In addition to weight deficiency, athletes with menstrual disorders have been recorded to have lower height and height SDS indicators, which may be due to reduced secretion of insulin-like growth factor-1 and the development of partial resistance to growth hormone [1, 2].

An important limitation of our study is the presence of vitamin D deficiency or insufficiency in the majority of athletes in both study groups, which could have influenced the levels of the studied bone metabolism markers. We did not assess the impact of sports type on the levels of the investigated bone metabolism markers due to the small sample size of athletes with primary amenorrhea. Furthermore, underage athletes did not undergo assessment of biological (bone) age using hand radiography. It is known that bone age is an independent predictor of bone remodeling marker levels, which physiologically increase during active growth in puberty [17–19]. The greater the bone maturation values, the less growth potential the child has, and the lower the levels of bone remodeling markers he or she demonstrates.

Further studies into the characteristics of hormonal status and bone remodeling markers and their influence on BMD may have important practical significance for developing an individualized approach to diagnosing impaired bone remodeling and stratifying the risks of low-energy fractures in underage athletes with FHA.

CONCLUSION

The development of primary amenorrhea in underage highly trained athletes with FHA is accompanied by decreased estrogen levels, although not being associated with impaired gonadostat function. The state of underweight identified in athletes with primary amenorrhea is caused by a deficit in adipose tissue and is accompanied by reduced blood leptin levels, which may contribute to the progression of reproductive system disorders.

Elevated bone metabolism markers in athletes with FHA may indicate disturbances in bone remodeling processes or may reflect ongoing growth and development in adolescents. Given the known negative impact of estrogen deficiency on BMD, underage athletes with underweight and FHA constitute a high-risk group for developing low-energy fractures.

The influence of elevated bone metabolite levels in athletes with amenorrhea on bone mineral density, bone structure, and the risk of increased trauma requires further research and elucidation.

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