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CHARACTERISTICS OF CALCIUM-PHOSPHORUS METABOLISM AND BONE TURNOVER INDICATORS IN PATIENTS WITH LIVER CIRRHOSIS AND THEIR DIAGNOSTIC VALUE FOR ASSESSING BONE STRUCTURES DISORDER

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Abstract.

Introduction: Information about calcium-phosphorus metabolism (CPM) and bone turnover in patients with liver cirrhosis (LC), as well as clarifying their diagnostic value for assessing bone structure disorder, will help doctors to detect their lesions in timely manner and, based on the information received, to choose well-founded comprehensive treatment strategy.

Aim: To characterize the indicators of calcium-phosphorus metabolism and bone turnover in patients with liver cirrhosis, and to find out their diagnostic value for detecting bone structure disorder.

Materials and methods: In randomized manner 90 patients with LC (27 women and 63 men of age from 18 to 66), who were treated at the Lviv Regional Hepatological Center (Communal Non-Commercial Enterprise of Lviv Regional Council "Lviv Regional Clinical Hospital") between 2016 and 2020, were included in the research. The research was carried out in two stages. The purpose of the first stage was to obtain information that would allow characterizing indicators of CPM (total calcium, ionized calcium, phosphorus, total vitamin D (25-hydroxyvitamin D), and parathyroid hormone) and bone turnover (osteocalcin, P1NP, alkaline phosphatase (bone formation markers), and β-Cross Laps (bone resorption marker)) in patients with LC, and the purpose of the second stage was to find out their diagnostic value for assessing bone structure disorder of them. To perform research, an experimental group (EG) (72 patients with impaired bone mineral density (BMD)), which was divided into EG A (46 patients with osteopenia) and EG B (26 patients with osteoporosis), and a comparison group (18 patients with normal BMD) were formed. The control group consisted of 20 relatively healthy people.

Results: At the first stage, it was established that the frequency of cases of increased alkaline phosphatase content was statistically significantly different in LC patients with osteopenia and osteoporosis ($p = 0.002$), as well as with osteoporosis and normal BMD ($p = 0.049$). Impaired BMD in general had significant direct stochastic relationship with vitamin D deficiency, decrease in osteocalcin content and increase in P1NP content in serum (Yule's Coefficient of Association (YCA)) >0.50); osteopenia – with decrease in phosphorus content, vitamin D deficiency and increase in P1NP content (YCA >0.50); and osteoporosis – with vitamin D deficiency, decrease in osteocalcin content, increase in P1NP content, and increase in alkaline phosphatase content in serum (YCA >0.50). Significant inverse stochastic relationship was recorded between vitamin D insufficiency and each of the impaired BMD manifestations (YCA <-0.50), which most likely indicates that it is characteristic of normal BMD. At the second stage, it was found that among indicators of CPM and bone turnover, only increase in alkaline phosphatase content in serum can be diagnostically valuable marker of osteoporosis in patients with LC ($p <0.050$; YCA >0.50; coefficient contingency = 0.32), which has medium sensitive (80.77 %) and positive predictive value (70.00 %) for it. Although other indicators of CPM and bone turover did not confirm their diagnostic value in our research, they may be useful for monitoring pathogenetic changes in bone structure disorder and evaluating the effectiveness of their treatment in patients with LC.

Conclusion: Indicators of calcium-phosphorus metabolism and bone turnover, which are characteristic of bone structure disorder and its absence in patients with liver cirrhosis, were revealed. Among them, an increase in alkaline phosphatase content in serum, which is a moderately sensitive marker of osteoporosis, is diagnostically valuable.

Key words. Liver cirrhosis, osteoporosis, osteopenia, bone mineral density, calcium-phosphorus metabolism, bone turnover, vitamin D, parathyroid hormone, osteocalcin, P1NP, alkaline phosphatase, β-Cross Laps.

Introduction.

Bones structure disorder, which is the main cause of spontaneous fractures, complicate the course of liver cirrhosis (LC) and can lead to deterioration of life quality and life expectancy shortening [1-4].

Regulation of the processes responsible for state of bone tissue occurs with the help of calcium-phosphorus metabolism (CPM), namely maintenance of the electrolyte balance, the main indicators of which are general and, especially, ionized calcium and phosphorus. The exchange of these electrolytes is controlled by calcium-regulating hormones – 25-hydroxyvitamin D and parathyroid hormone (PTH). Dynamic bone reconstruction is ensured by constant remodeling of the bone tissue. Osteocalcin, which is vitamin K-dependent bone non-collagen protein, amino-terminal propeptide of type I procollagen, specific for the formation of type I collagen (P1NP), and alkaline phosphatase, especially its bone-specific fraction are responsible for osteoblastic bone function (formation). The osteoclastic function (resorption) of bone is indicated by the isomerized C-terminal telopeptide, specific for type I collagen degradation in bone tissue (β-Cross Laps) [5-8]. Listed indicators are recommended for diagnosing bone structure disorders, choosing the appropriate treatment, and monitoring its effectiveness in the patient [7,9-11].

Information about CPM and bone turnover in patients with LC, as well as clarifying their diagnostic value for assessing bone structure disorder, will help doctors to detect their lesions in timely manner and, based on the information received, to choose well-founded comprehensive treatment strategy.

This study aimed to characterize the indicators of calcium-phosphorus metabolism and bone turnover in patients with liver

cirrhosis, and to find out their diagnostic value for detecting bone structure disorder.

Materials and methods.

After obtaining voluntary consent to participate in the prospective study, which was carried out in compliance with the Helsinki Declaration of Human Rights and the Council of Europe Convention on Human Rights and Biomedicine, 90 patients (27 women and 63 men of age from 18 to 66), who were treated at the Lviv Regional Hepatological Center (Communal Non-Commercial Enterprise of Lviv Regional Council "Lviv Regional Clinical Hospital") between 2016 and 2020, were included in the study in randomized manner with preliminary stratification according to the presence of LC [12]. Exclusion criteria were the refusal to sign a voluntary consent to participate in the study, the use of drugs that can have a direct effect on the state of bone tissue (containing calcium, vitamin D, vitamin K, bisphosphonates, etc.) and the presence of oncological diseases with possible bone metastases.

The research was carried out in two stages. At the first stage of the study, the purpose of which was to obtain information that would allow to characterize CPM and bone turnover in patients with LC, the content of the following indicators in blood serum was examined: mineral metabolism indicators – total calcium (colorimetric analysis (18–60 years old: 2.15–2, 5 mmol/l; 60–90 years old: 2.2–2.55 mmol/l)), ionized calcium (ion selective analysis (1.15–1.27 mmol/l)), phosphorus (spectrophotometry (0.81– 1.45 mmol/l); calcium-dependent indicators – total vitamin D (25-hydroxyvitamin D) (enzyme immunoassay (normal – ≥30.0 ng/ml; insufficiency – 20.0–30.0 ng/ml; deficiency – <20.0 ng/ml)) and PTH (enzyme immunoassay (15.0–65.0 pg/ml)); indicators of bone remodeling rate, as well as bone formation markers – osteocalcin (electrochemiluminescence immunoassay (ECLIA) (2.0–22.0 ng/ml)), P1NP (ECLIA (women: premenopause – 15.13–58.59 ng/ml, postmenopause – 16.27–73.87 ng/ml; men – 15.00–80.00 ng/ml)) and alkaline phosphatase (colorimetric analysis (women – <98.0 units/l; men – <128.0 units/l)), and bone resorption marker – β-Cross Laps (ECLIA (women: premenopause – <0.573 ng/ml, postmenopause – <1.008 ng/ml; men: 30–50 years – <0.584 ng/ml, 50–70 years – <0.704 ng/ml, over 70 years – <0.854 ng/ml)).

To assess bones state, we used calcaneal quantative ultrasound [13] (Sonost–2000 device) to determine the T-score, which was the ground for detecting impared bone mineral density (BMD) (T–score < –1.0 standard deviation (SD), namely osteopenia (T–score –1.0—2.5 SD) and osteoporosis (T–score ≤–2.5 SD)), or establishing normal BMD (T–score ≥–1.0 SD) [14].

Based on this information, an experimental group (EG) (72 patients with impaired BMD), which was divided into EG A (46 patients with osteopenia) and EG B (26 patients with osteoporosis), and a comparison group (CG) (18 patients with normal BMD) were formed. The control group consisted of 20 relatively healthy people.

With the help of R. Fisher's exact test, which makes it possible to evaluate studied characteristics even in small samples [15], statistically significant differences were found between the frequency of changes in CPM and bone turnover indicators in the studied groups ($p < 0.050$). R. Fisher's exact test is complicated for calculations but gives the most accurate p-value and can be applied when expected frequency in cells of contingency tables less than 5 [16].

The use of J. Yule's coefficient of association (YCA), or coefficient contingency (CC), if YCA was equal to 1.00, made it possible to identify significant stochastic relationships between changes of these indicators and certain manifestations of bone structure disorder (YCA ≥ 0.50, or ≤–0.50; CC≥0.30, or ≤–0.30) [17-19].

At the second stage, in order to find out the diagnostic value of CPM and bone turnover indicators for assessing bone structure disorder, their sensitivity, specificity, positive and negative predictive values were studied, positive and negative likelihood ratios were evaluated [15]. For the assessment of listed diagnostic characteristics, changes in CPM and bone turnover indicators, detected at the first stage, were chosen, which were significantly different, or had significant stochastic relationship with the manifestations of BMD disorder. An indicator was considered to be diagnostically valuable if its statistical significance was simultaneously confirmed by the p-value (< 0.050) and the presence of significant direct stochastic relationship with certain violation of bone structure (YCA ≥0.50; CC ≥0.30).

Statistical processing of the obtained results was carried out in Microsoft Excel program using Real Statistic Resource Pack add-on [16].

Results and discussion.

The results of the first stage of the study are shown in table 1.

The decrease in serum total calcium was detected to be present in 21.74 % of cases and the increase was not recorded in any patient with LC. At the same time, patients with reduced indicators of total calcium were more often recorded to have BMD disorder (80.00 %) (osteopenia – 40.00 %; osteoporosis – 40.00 %) than normal BMD (20.00 % of cases), but statistically significant difference between groups, or the existence of significant stochastic relationship of indicator changes with certain bone disorder, were not recorded ($p > 0.050$; YCA <0.50 and >-0.50).

51.06 % of patients with LC had decrease in ionized calcium content in serum, 70.83 % had impaired BMD (45.83 % – osteopenia and 25.00 % – osteoporosis) and 29.17 % – normal BMD. On the contrary, increase in ionized calcium content in serum was observed in 12.77 % of cases among patients with LC, 66.67 % of whom had impaired BMD (50.00 % – osteopenia and 16.67 % – osteoporosis) and 33.33 % – normal BMD. The indicator changes did not have significant stochastic relationship with violation of bone structure (YCA <0.50 and >–0.50) and were not statistically significantly different in the studied groups ($p > 0.050$).

6.25 % of patients with LC had both decrease in phosphorus content in serum and increase in it. But decrease in phosphorus content was typical for patients with osteopenia (100.00 %) and increase in phosphorus content was characteristic for patients with normal BMD (100.00 %). No statistically significant difference between groups was found ($p > 0.050$). There is significant direct stochastic relationship only between decrease in phosphorus content in serum and osteopenia (CC = 0.33).

Table 1. *Characteristics of calcium-phosphorus metabolism and bone turnover indicators in patients with liver cirrhosis with and without bone structure disorder (n, %, p, YCA, CC).*

Indicators (Reference ranges)			**Total number of cases (n, %) N=90**		**Frequency of cases in the studied groups (n, %)**							
					EG (With bone structure disorder)						CG (Without bone structure disorder) N=18	
					Total N=72		EG A (osteo-penia) N=46		EG B (osteopo-rosis) N=26			
			n	%	n	%	n	%	n	%	n	%
Mineral metabolism indicators	Total calcium (18–60 years old: 2.15–2, 5 mmol/l; 60–90 years old: 2.2–2.55 mmol/l)		n=23		n=18		n=10		n=8		n=5	
		↓	5	21,74	4	80,00	2	40,00	2	40,00	1	20,00
		↑	0	0,00	0	0,00	0	0,00	0	0,00	0	0,00
	Ionized calcium (1.15–1.27 mmol/l)		n=47		n=34		n=22		n=12		n=13	
		↓	24	51,06	17	70,83	11	45,83	6	25,00	7	29,17
		↑	6	12,77	4	66,67	3	50,00	1	16,67	2	33,33
	Phosphorus (0.81– 1.45 mmol/l)		n=16		n=11		n=5		n=6		n=5	
		↓	1	6,25	1	100,00	1	100,00^	0	0,00	0	0,00
		↑	1	6,25	1	100,00	0	0,00	1	100,00	0	0,00
Calcium-dependent indicators	Total vitamin D (Normal – ≥30.0 ng/ml; insufficiency – 20.0–30.0 ng/ml; deficiency – <20.0 ng/ml)		n=16		n=11		n=5		n=6		n=5	
		Insuffi-ciency	3	18,75	1	33,33∨	0	0,00∨	1	33,33∨	2	66,67
		Defi-ciency	13	81,25	10	76,92^	5	38,46^	5	38,46^	3	23,08
	PTH (15.0–65.0 pg/ml)		n=16		n=11		n=5		n=6		n=5	
		↓	1	6,25	1	100,00	0	0,00	1	100,00	0	0,00
		↑	6	37,50	4	66,67	2	33,33	2	33,33	2	33,33
Bone formation markers	Osteocalcin (2.0–22.0 ng/ml)		n=16		n=11		n=5		n=6		n=5	
		↓	11	68,75	9	81,82^	3	27,27	6	54,55^	2	18,18
		↑	0	0,00	0	0,00	0	0,00	0	0,00	0	0,00
	P1NP (Women: premenopause – 15.13–58.59 ng/ml, postmenopause – 16.27–73.87 ng/ml; men – 15.00–80.00 ng/ml)		n=15		n=10		n=5		n=5		n=5	
		↓	0	0,00	0	0,00	0	0,00	0	0,00	0	0,00
		↑	9	60,00	8	88,89^	4	44,44^	4	44,44^	1	11,11
	Alkaline phosphatase (Women – <98.0 units/l; men – <128.0 units/l)		n=90		n=72		n=46		n=26		n=18	
		↑	50	55,56	41	82,00	20	40,00	21	42,00*#^	9	18,00
Bone resorption marker	β-Cross Laps (Women: premenopause – <0.573 ng/ml, postmenopause – <1.008 ng/ml; men: 30–50 years – <0.584 ng/ml, 50–70 years – <0.704 ng/ml, over 70 years – <0.854 ng/ml)		n=15		n=10		n=5		n=5		n=5	
		↑	4	26,67	3	75,00	2	50,00	1	25,00	1	25,00

*Notes: ↓ – decrease in indicator; ↑ – increase in indicator; * – significant difference between EG B and CG (p < 0.050); # – significant difference between EG A and EG B (p < 0.050); ^ – significant direct stochastic relationship between indicator and certain bone structure disorder (YCA >0.50 or CC >0.30); ∨ – significant inverse relationship between indicator and certain bone structure disorder (YCA <-0.50 or CC <-0.30).*

The analysis of calcium-dependent parameters revealed that vitamin D content was reduced in all patients with LC, 18.75 % of which had its insufficiency (33.33 % in EG: 0.00 % in EG A, 33.3 % in EG B 33.33 %; in CG – 66.67 % of cases), and 81.25 % – deficiency (in EG – 76.92 %: in EG A – 38.46 %, in EG B – 38.46%; in CG – 23.08 % of cases). All manifestations of bone disorder had significant inverse stochastic relationship with vitamin D insufficiency (YCA <-0.50) and significant direct stochastic relationship with vitamin D deficiency (YCA >0.50), although the frequency of signs in the groups was not statistically significantly different (p > 0.050).

Decrease in PTH indicator was observed in 6.25 % (only in patients with osteoporosis (100.00 %)), and its increase – in 37.50 % of cases in patients with LC (in EG – 66.67 %: in EG A – 33.33 %, in EG B – 33.33 %, in CG – 33.33 %). Neither the frequency of cases of decreased PTH content nor the frequency of cases of increased PTH content in serum was statistically significantly different between groups (p > 0.050). Significant

stochastic relationships of PTH content changes with bone structure disorders were also not observed (YCA <0.50 and >-0.50).

Based on the assessment of bone turnover indicators in serum of patients with LC, it was found that among the markers of bone formation, osteocalcin content was reduced in 68.75 % of cases (in EG – 81.82 %: in EG A – 27.27 %, in EG B – 54.55 %; in CG – 18.18 %), and its increase was not recorded in any case (0.00 %). P1NP content, on the contrary, was never reduced (0.00 %), although increase in P1NP content was detected in 60.00 % of serum samples of patients with LC (in EG – 88.89 %: in EG A – 44.44 %, in EG B – 44.44 %; in CG – 11.11 %). Increase in alkaline phosphatase content in serum was recorded in 55.56 % of cases. 82.00 % of them were detected in patients with impaired BMD (40.00 % of patients with osteopenia and 42.00 % – with osteoporosis) and 18.00 % – in patients with normal BMD. Significant direct stochastic relationship was recorded between decrease in osteocalcin content and impaired BMD in general and osteoporosis in particular (YCA >0.50), between increase in P1NP content in serum and each of the manifestations of bone structure disorder (YCA >0.50), and between increase in alkaline phosphatase content and osteoporosis (YCA >0.50). The frequency of cases of increased alkaline phosphatase content in serum of LC patients with osteoporosis and normal BMD (p = 0.049) and in patients with osteopenia and osteoporosis (p = 0.002) differed statistically significantly.

β-Cross Laps content in serum (marker of bone resorption) was increased in 26.67 % of cases, 75.00 % of which – in patients of EG (50.00 % – in EG A and 25.00 % – in EG B) and 25.00 % – in CG. We did not find any significant differences between groups, or significant stochastic relationships of indicator changers with manifestations of bone structure disorder (p > 0.050; YCA <0.50 and >-0.50).

So, the frequency of cases of increased alkaline phosphatase content only was statistically significantly different in patients with LC with osteopenia and osteoporosis, as well as in patients with osteoporosis and normal BMD. Vitamin D deficiency, decrease in osteocalcin content and increase in P1NP content in blood serum had significant direct stochastic relationship with impaired BMD in general; decrease in phosphorus content, vitamin D deficiency and increase in P1NP content – with osteopenia; and vitamin D deficiency, decrease in osteocalcin content, increase in P1NP content, and increase in alkaline phosphatase content in serum – with osteoporosis. Significant inverse stochastic relationship was recorded between vitamin D insufficiency and each of the impared BMD manifestations, which most likely indicates that it is characteristic of normal BMD.

The information obtained at the second stage, the aim of which was the study of diagnostic value of CPM and bone turnover indicators for detecting bone structure disorders, is shown in table 2.

It was established that the decrease in phosphorus content in serum, although it had significant direct stochastic relationship with osteopenia (YCA = 1.00; CC = 0.33) and high diagnostic characteristics of positive result (specificity and positive predictive value of 100.00 %), there was no statistically significant difference between osteopenia and normal BMD (p > 0.050).

Table 2. *Diagnostic characteristics of indicators of calcium-phosphorus metabolism and bone turnover in liver cirrhosis patients with bone structure disorder (n; %; p; YCA; CC).*

Indicators	Studied groups	TP	FN	FP	TN	Se, %	Sp, %	PPV, %	NPV, %	LR+	LR-	DE, %	p_1	p_2	YCA	CC
↓ Phosphorus	EG	1	10	0	5	9,09	100,00	100,00	33,33	INF	0,91	37,50	1,000	0,455	1,00	0,17
	EG A	1	4			20,00		100,00	55,56	INF	0,80	60,00	1,000		1,00	0,33^
	EG B	0	6			0,00			45,45	INF	1,00	45,45	1,000		0,00	0,00
Vitamin D insufficiency	EG	1	10	2	3	9,09	60,00	33,33	23,08	0,23	1,52	25,00	0,214	1,000	-0,74	-0,37
	EG A	0	5			0,00		0,00	37,50	0,00	1,67	30,00	0,444		-1,00	-0,50
	EG B	1	5			16,67		33,33	37,50	0,42	1,39	36,36	0,545		-0,54	-0,26
Vitamin D deficiency	EG	10	1	3	2	90,91	40,00	76,92	66,67	1,52	0,23	75,00	0,214	1,000	0,74^	0,37^
	EG A	5	0			100,00		62,50	100,00	1,67	0,00	70,00	0,444		1,00	0,50^
	EG B	5	1			83,33		62,50	66,67	1,39	0,42	63,64	0,545		0,54^	0,26
↓ Osteocalcin	EG	9	2	2	3	81,82	60,00	81,82	60,00	2,05	0,30	75,00	0,245	0,182	0,74^	0,42^
	EG A	3	2			60,00		60,00	60,00	1,50	0,67	60,00	1,000		0,38	0,20
	EG B	6	0			100,00		75,00	100,00	2,50	0,00	81,82	0,061		1,00	0,67^
↑ P1NP	EG	8	2	1	4	80,00	80,00	88,89	66,67	4,00	0,25	80,00	0,089	1,000	0,88^	0,58^
	EG A	4	1			80,00		80,00	80,00	4,00	0,25	80,00	0,206		0,88^	0,60^
	EG B	4	1			80,00		80,00	80,00	4,00	0,25	80,00	0,206		0,88^	0,60^
↑ Alkaline phosphatase	EG	41	31	9	9	56,94	50,00	82,00	22,50	1,14	0,86	55,56	0,606	0,002*	0,14	0,06
	EG A	20	26			43,48		68,97	25,71	0,87	1,13	45,31	0,780		-0,13	-0,06
	EG B	21	5			80,77		70,00	64,29	1,62	0,38	68,18	0,049*		0,62^	0,32^

*Notes: ↓ – decrease in indicator's content; ↑ – increase in indicator's content; TP – true positive results; FN – false negative results; FP – false positive results; TN – true negative results; Se – sensitivity; Sp – specificity; PPV – positive predictive value; NPV – negative predictive value; LR+ – positive likelihood ratio; LR- – negative likelihood ratio; DE – diagnostic efficiency (accuracy); p1 – comparison of the studied groups with the comparison group; p2 – comparison of osteopenia with osteoporosis; * – statistically significant difference (p < 0.050); ^ – significant direct stochastic relationship between the indicator and certain bone structure disorder (YCA ≥0.50 or/and CC ≥0.30).*

Vitamin D insufficiency in serum is not valuable for detecting or ruling out bone disorder, as it has significant inverse stochastic relationship with all manifestations of impared BMD (YCA >-0.50), indicating that the feature is most likely characteristic of normal BMD, although it is not diagnostically valuable in this case ($p > 0.050$).

Vitamin D deficiency in serum, which has significant direct stochastic relationship with all manifestations of bone structure disorders (YCA >0.50), has sensitivity for impaired BMD in general – 90.91 %, for osteopenia – 100.00 %, for osteoporosis – 83.33 %, specificity – 40.00 % for each manifestation of the bone disorder, positive predictive value – 76.92 % for impaired BMD in general and 62.00 % each for osteopenia and osteoporosis, negative predictive value – 66.67 %, 100.00 % and 66.67 %, respectively, positive likelihood ratio is 1.52, 1.37 and 1.39, respectively, and negative likelihood ratio is 0.23, 0.00 and 0.42, respectively, however statistically significantly does not differ between the studied groups and the comparison group ($p > 0.050$).

Decrease in serum osteocalcin content has significant direct stochastic relationship with impaired BMD in general (YCA = 0.74; CC = 0.42) and osteoporosis in particular (YCA = 1.00; CC = 0.67); has sensitivity for impaired BMD in general – 81.82 % and for osteoporosis – 100.00 %; specificity – 60.00 % for each of the manifestations; positive predictive value – 81.82 % for impaired BMD in general and 75.00 % – for osteoporosis; negative predictive value is 60.00 % and 100.00 %, respectively, positive likelihood ratio is 2.05 and 2.50, respectively, and negative likelihood ratio is 0.30 and 0.00, respectively, but not statistically significantly different between groups ($p > 0.050$).

Increase in P1NP content in serum has significant direct stochastic relationship with each bone structure disorder (YCA >0.50; CC >0.30). Sensitivity and specificity for each of bone lesions are 80.00 %. Positive predictive value for impaired BMD in general is 88.89 %, negative predictive value is 66.67 %, while for osteopenia and osteoporosis these values are 80.00 % each. Increase in P1NP content for each of the bone disorder has positive likelihood ratio of 4.00 and negative likelihood ratio of 0.25, respectively, but difference between manifestations of impaired BMD and normal BMD is not significant in any of cases ($p > 0.050$).

Increase in alkaline phosphatase content in serum has significant direct stochastic relationship only with osteoporosis (EG B and CG: YCA = 0.62; CC = 0.32) and is statistically significantly different in patients with osteoporosis and normal BMD ($p = 0.049$) and in patients with osteoporosis and osteopenia ($p = 0.002$), so it can be diagnostically valuable marker for osteoporosis. Increase in alkaline phosphatase content is characterized by average sensitivity (80.77 %) to osteoporosis. Specificity for osteoporosis is 50.00 %. Positive and negative predictive values of the test are 70.00 % and 64.29 %, respectively. Probability of detecting an increase in alkaline phosphatase content in serum of LC patient with osteoporosis is 1.26 times higher than in LC patient with normal BMD (positive likelihood ratio is 1.26), and probability that increase in serum alkaline phosphatase will be absent in LC patient with osteoporosis is 2.63 times lower, compared with LC patient with normal BMD (negative likelihood ratio is 0.38).

According to the recommendations for the management of patients with bone structure disorders, bone-specific alkaline phosphatase has a diagnostic value for assessing the state of bones (osteoblastic function). However, in our study we determined the content of total alkaline phosphatase in serum. This is due to the fact that the determination of bone-specific alkaline phosphatase is not always available. In contrast, total alkaline phosphatase is an available indicator and is routinely determined in patients with LC.

The source of approximately 50.00 % of alkaline phosphatase in blood are bones. The obtained result of the studied indicator may also depend on the choice of research methodology. The possibility of cross-reactivity between the liver and bone fractions of alkaline phosphatase does not exclude errors in the research results [3]. An increase in alkaline phosphatase content in the liver may be accompanied by false-positive results during the study of bone-specific alkaline phosphatase.

A study of young people revealed a negative correlation between total alkaline phosphatase and lumbar BMD [14].

In addition, it was found that an increase in alkaline phosphatase content in postmenopausal women serum is associated with an increase in bone metabolism. The content of this indicator was correlated with the bone-specific fraction before and after treatment with bisphosphonates [11].

The degree of liver fibrosis can affect the total alkaline phosphatase content. But this indicator can be useful in evaluating the prescribed treatment of bone disorders in patients with liver disease [7,20].

Therefore, the results obtained by us during the study indicate that only increase in alkaline phosphatase content in serum can be diagnostically valuable medium-sensitive marker of osteoporosis in patients with LC. Although other indicators of CPM and bone turover did not confirm their diagnostic value in our study, they may be useful for monitoring pathogenetic changes in bone structure disorder and evaluating the effectiveness of their treatment in patients with LC.

Conclusion.

Characterization of calcium-phosphorus metabolism and bone turnover indicators in patients with liver cirrhosis and clarification of their diagnostic value for assessing bone structure disorders allow us to state that:

1. Bone structure disorder in general is characterized by vitamin D deficiency, decrease in osteocalcin content, and increase in P1NP content in blood serum, but none of these indicators are diagnostically valuable for assessing violation of bone mineral density in general.
2. Osteopenia is characterized by decrease in phosphorus content, vitamin D deficiency and increase in P1NP content in serum, although they are not diagnostically valuable for it.
3. Osteoporosis is characterized by vitamin D deficiency, decrease in osteocalcin content, increase in P1NP content, and increase in alkaline phosphatase content in serum. Diagnostically valuable marker of osteoporosis in patients with

liver cirrhosis is an increase in alkaline phosphatase content, which has medium sensitivity (80.77 %) and positive predictive value (70.00 %) for it.

4. The absence of bone structure disorder is most likely characterized by vitamin D insufficiency, although it is not diagnostically valuable for normal bone mineral density.

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კალციუმისა და ფოსფორის ცვლისა და ძვლის მეტაბოლიზმის მაჩვენებლების დახასიათება ღვიძლის ციროზის მქონე პაციენტებში და მათი დიაგნოსტიკური მნიშვნელობა ძვლების სტრუქტურის დარღვევის შესაფასებლად

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Abstract.

Introduction: კალციუმისა და ფოსფორის ცვლისა (კფც) და ძვლის მეტაბოლიზმის მდგომარეობის შესახებ ღვიძლის ციროზის (ღც) მქონე პაციენტებში, აგრეთვე მათი დიაგნოსტიკური მნიშვნელობის გარკვევა ძვლის სტრუქტურის დარღვევის შესაფასებლად, ეხმარება ექიმს დროულად აღმოაჩინოს მათი დაზიანება და, მიღებული ინფორმაციის საფუძველზე, საშუალებას აძლევს აირჩიოს გონივრული კომპლექსური მკურნალობის ტაქტიკა.

Aim: ღვიძლის ციროზის მქონე პაციენტებში კალციუმისა და ფოსფორის ცვლისა და ძვლის მეტაბოლიზმის მაჩვენებელთა დახასიათება და მათი დიაგნოსტიკური მნიშვნელობის გამოკვლევა ძვლის სტრუქტურის დარღვევის გამოსავლენად.

Materials and methods: რანდომიზებული წესით, ღვიძლის ციროზის არსებობის მიხედვით წინასწარი სტრატიფიკაციით, კვლევაში იყო ჩართული 90 პაციენტი (27 ქალი და 63 მამაკაცი 18-დან 66 წლამდე ასაკისა), რომლებიც მკურნალობას გადიოდნენ ლვივის საოლქო ჰეპატოლოგიის ცენტრში (ლვივის საოლქო საბჭოს კომუნალური არაკომერციული საწარმო "ლვივის საოლქო კლინიკური საავადმყოფო") 2016-2020 წლებში.კვლევა ორ ეტაპად ჩატარდა. პირველი ეტაპის მიზანი იყო იმ ინფორმაციის მოპოვება, რომელიც მოგვცემდა კალციუმისა და ფოსფორის ცვლის (ზოგადი კალციუმის, იონიზებული კალციუმის, ფოსფორის, ზოგადი ვიტამინი D (25-ჰიდროქსივიტამინი D) და პთგ (პარათირეოიდული ჰორმონის)) მაჩვენებლების დახასიათების საშუალებასა და ძვლის მეტაბოლიზმის (ოსტეოკალცინის, I ტიპის პროკოლაგენის ამინოტერმინალური პროპეპტიდის, სპეციფიკური I ტიპის კოლაგენის (P1NP) ფორმირებისთვის, ტუტე

ფოსფატაზას (ძვლის ფორმირების მარკერები), იზომერიზებული C-ტერმინალური ტელოპეპტიდის, სპეციფიკური I ტიპის კოლაგენის ძვლის ქსოვილში (β-Cross Laps) (ძვლის რეზორბციის მარკერი) დეგრადაციისთვის) მაჩვენებლების დახასიათების საშუალებას ღვიძლის ციროზის მქონე პაციენტებში, ხოლო მეორე ეტაპის მიზანი – გაირკვეს მიღებული ინფორმაციის დიაგნოსტიკური მნიშვნელობა მათში ძვლის სტრუქტურის დარღვევების შესაფასებლად. კვლევის ჩასატარებლად ჩამოყალიბდა საცდელი ჯგუფი (სჯ) (72 პაციენტი ძვლის ქსოვილის მინერალური სიმკვრივის დარღვევით (ძქმს), რომელიც დაყოფილ იქნა A საცდელ ჯგუფად (46 პაციენტი ოსტეოპენიით) და B საცდელ ჯგუფად (26 პაციენტი ოსტეოპოროზით) და შედარების ჯგუფად (ნორმალური ძვლის ქსოვილის მინერალური სიმკვრივის მქონე 18 პაციენტი). საკონტროლო ჯგუფი შედგებოდა 20 პრაქტიკულად ჯანმრთელი ადამიანისგან.

Results: გაირკვა, რომ სტატისტიკურად უტყუარად განსხვავდებოდა მხოლოდ სისხლის შრატში ტუტე ფოსფატაზას შემცველობის მომატების შემთხვევების სიხშირე ღვიძლის ციროზის მქონე პაციენტებში, თანდართული ოსტეოპენიითა და ოსტეოპოროზით ($p = 0.002$), აგრეთვე ოსტეოპოროზისა და ნორმალური ძვლის ქსოვილის მინერალური სიმკვრივის ($p = 0.049$) მქონე პაციენტებში. არსებითი პირდაპირი სტოქასტური კავშირი ძვლის ქსოვილის მინერალური სიმკვრივის დარღვევის მქონეებს ზოგადად აღმოუჩნდა D ვიტამინის დეფიციტი, ოსტეოკალცინის შემცველობის დაქვეითება და სისხლის შრატში P1NP-ის მომატებული შემცველობა (ჯ. იულის ასოციაციის (Yule's Coefficient of Association (YCA)) >0.50); ოსტეოპენიის მქონეებს - ფოსფორის შემცველობის დაქვეითება, D ვიტამინის დეფიციტი და P1NP-ის შემცველობის მომატება (YCA >0.50), ხოლო ოსტეოპოროზის მქონეებს - D ვიტამინის დეფიციტი, ოსტეოკალცინის შემცველობის დაქვეითება, P1NP-ის შემცველობის მომატება და სისხლის შრატში ტუტე ფოსფატაზას შემცველობის მომატება (YCA >0.50). არსებითი სტოქასტური უკუკავშირი დაფიქსირდა D ვიტამინის უკმარისობასა და ძვლის სტრუქტურის დარღვევის თითოეულ გამოვლინებას შორის (YCA <-0.50), რაც, უფრო სავარაუდოა, მიუთითებს იმაზე, რომ ეს თვისება დამახასიათებელია ძვლის ქსოვილის მინერალური სიმკვრივის დარღვევის არარსებობისთვის.

მეორე ეტაპზე გამოვლინდა, რომ კალციუმისა და ფოსფორის ცვლისა და ძვლის მეტაბოლიზმის მაჩვენებლებს შორის, მხოლოდ სისხლის შრატში ტუტე ფოსფატაზას შემცველობის მომატება შეიძლება იყოს ოსტეოპოროზის დიაგნოსტიკურად ღირებული მარკერი ღვიძლის ციროზის მქონე პაციენტებში ($p <0.050$; YCA >0.50; კონტინგენციის კოეფიციენტი = 0.32), რომელსაც გააჩნია საშუალო მგრძნობიაროობა (80.77%) და მისთვის დადებითად სავარაუდო მნიშვნელობა (70.00%). კალციუმისა და ფოსფორის ცვლისა და ძვლის მეტაბოლიზმის სხვა მაჩვენებლებმა, მიუხედავად იმისა, რომ არ დაადასტურეს თავისი დიაგნოსტიკური მნიშვნელობა ჩვენს კვლევაში, შეიძლება სასარგებლო იყოს ძვლის სტრუქტურის დარღვევის პათოგენეტიკური ცვლილებების კონტროლისთვისა და მათი მკურნალობის ეფექტურობის შესაფასებლად ღვიძლის ციროზის მქონე პაციენტებში.

Conclusion: გამოვლინდა კალციუმისა და ფოსფორის ცვლისა და ძვლის მეტაბოლიზმის მაჩვენებლები, რომლებიც დამახასიათებელია ძვლის სტრუქტურის დარღვევისთვის და მისი არარსებობისთვის ღვიძლის ციროზის მქონე პაციენტებში. მათ შორის დიაგნოსტიკურად ღირებულია სისხლის შრატში ტუტე ფოსფატაზას რაოდენობის მომატება, რომელიც არის ოსტეოპოროზის ზომიერად მგრძნობიარე მარკერი.

Key words. ღვიძლის ციროზი, ოსტეოპოროზი, ოსტეოპენია, ძვლის ქსოვილის მინერალური სიმკვრივე, კალციუმისა და ფოსფორის ცვლა, ძვლის მეტაბოლიზმი, ვიტამინი D, პარათირეოიდული ჰორმონი, ოსტეოკალცინი, P1NP, ტუტე ფოსფატაზა, β-Cross Laps.