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Hyperparathyroidism in Patients with End-Stage Chronic Liver Disease (Clinical Observations)

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Aim: to present disorders of mineral and bone metabolism in patients with chronic liver diseases through clinical observations.
Key points. The liver plays an important role in mineral metabolism: metabolic activation of vitamin D, synthesis of vitamin D-binding protein and albumin, metabolism of parathyroid hormone, etc. However, data on the development of mineral metabolism disorders, particularly hyperparathyroidism, in this population are very limited. Bone diseases such as osteoporosis and osteomalacia are quite common in chronic liver disease, especially in cirrhosis and cholestatic diseases; however, the pathogenesis of these disorders and their relationship with mineral metabolism remain poorly understood. The article presents cases of severe primary hyperparathyroidism (PHPT) in patients with chronic liver disease. In one patient with a long history of viral hepatitis C and cirrhosis, PHPT manifested with severe bone complications, including multiple vertebral compression fractures and a subsequent femoral neck fracture. Imaging studies revealed lesions of all four parathyroid glands, and the removal of the largest lesion did not result in disease remission. In the second case described, PHPT was diagnosed in a patient with bone pain and osteoporosis following orthotopic liver transplantation for Budd — Chiari syndrome with cirrhosis. One year after the initial surgical treatment for PHPT, the patient experienced a recurrence of the disease, with confirmed multiglandular lesion.
Conclusion. In patients with chronic liver diseases, disorders of mineral and bone metabolism remain a significant yet not fully understood problem. Further studies are needed to develop therapeutic approaches for this group of patients to prevent the onset of late, disabling complications.
Keywords: hyperparathyroidism, chronic liver diseases, liver cirrhosis, osteoporosis
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Гиперпаратиреоз у пациентов с терминальной стадией хронических заболеваний печени (клинические наблюдения)

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Цель: представить нарушения минерального и костного обмена у пациентов с хроническими заболеваниями печени на примере клинических наблюдений.
Основные положения. Печень является важным звеном минерального обмена: она участвует в активации витамина D, синтезе витамин D-связывающего белка и альбумина, метаболизме паратиреоидного гормона и других процессах. В то же время данные о развитии нарушений минерального обмена, в частности гиперпаратиреоза, в этой группе пациентов весьма ограничены. При хронических заболеваниях печени достаточно часто наблюдается поражение костной ткани в виде остеопороза и остеомаляции, особенно при циррозе и холестатических заболеваниях, однако патогенез этих нарушений и их связь с минеральным обменом мало изучены. В статье представлены случаи тяжелого течения первичного гиперпаратиреоза (ПГПТ) у пациентов с хроническими заболеваниями печени. У пациентки с длительным анамнезом вирусного гепатита С

и циррозом печени ПГПТ дебютировал с тяжелых костных осложнений — множественных компрессионных переломов позвонков, а впоследствии и перелома шейки бедренной кости. При топической диагностике были выявлены образования четырех околощитовидных желез, а удаление наиболее крупного образования не привело к ремиссии заболевания. Во втором описанном случае ПГПТ был диагностирован у пациентки с болями в костях и остеопорозом после ортотопической пересадки печени по поводу синдрома Бадда — Киари с формированием цирроза печени. Спустя год после первичного хирургического лечения ПГПТ отмечен рецидив заболевания, что подтвердило мультигландулярное поражение.

Заключение. У пациентов с хроническими заболеваниями печени нарушения минерального и костного обмена остаются серьезной и не до конца изученной проблемой. Для разработки терапевтических подходов к этой группе больных и методов профилактики развития поздних инвалидизирующих осложнений требуются дальнейшие исследования.

Ключевые слова: гиперпаратиреоз, хронические заболевания печени, цирроз печени, остеопороз

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Liver cirrhosis is a socially significant disease associated with severe complications, a high risk of disability, and elevated patient mortality. In the structure of all causes of death, liver cirrhosis ranks 11th, and in the structure of morbidity — 15th. Until recently, the leading causes of liver cirrhosis were viral hepatitis and alcohol consumption. However, an increasing proportion of liver cirrhosis cases are now attributed to metabolic dysfunction-associated steatotic liver disease (MASLD), affecting 20–25 % of the population (up to 37 % in some countries). This trend is likely related to the increasing prevalence of obesity [1]. According to the results of the Global Burden of Disease Study 2017, mortality from liver cirrhosis in Russia increased from 9.6 to 24.3 per 100,000 population from 1990 to 2017 [2].

The liver is one of the key organs involved in maintaining mineral homeostasis. Studies on parathyroid gland disease associated with chronic liver disease are limited, primarily focusing on vitamin D deficiency or insufficiency and hypocalcemia, yielding highly variable results [3]. Data on the course of primary hyperparathyroidism (PHPT) in patients with chronic liver disease are limited, primarily restricted to descriptions of a few clinical cases. It is possible that both diseases exacerbate one another. On one hand, osteoporosis prevalence in patients with liver cirrhosis ranges from 12 to 55 %, which is significantly higher than in the general population [4], and is more common in cholestatic liver diseases, where vitamin D absorption is impaired. In addition, up to 40 % of patients with chronic liver disease suffer from fractures [5, 6]. On the other hand, bone disorders are among the most common complications of PHPT and can manifest as a progressive decrease in bone mineral density (BMD), along with pathological fractures and cystic fibrous osteitis. According to a Russian Registry, the total incidence of bone complications in patients with PHPT reaches 62.5 % (primarily in combination with visceral complications — 45.7 %), of which low-energy fractures at various sites were diagnosed in 41.1 % of cases [7].

Most endocrine society guidelines primarily identify chronic liver disease as a secondary cause of osteoporosis, which does not fully capture the condition's pathogenesis [8, 9]. In patients with coexisting liver disease and parathyroid gland disorders, there may be additional "points of intersection". These may include vitamin D metabolism at various stages, protein metabolism, and more subtle mechanisms regulating bone remodeling. However, data on this topic are lacking, indicating a need for further scientific research.

This article presents several patients with severe hyperparathyroidism and significant bone disorders associated with various underlying liver diseases.

Clinical Case 1

Patient L., a 63-year-old female with a long history of viral hepatitis C and liver cirrhosis, had not been regularly monitored by doctors and had not received antiviral therapy.

Elevated blood calcium level was first noted in 2014, at the same time as scintigraphy data revealed right inferior parathyroid gland. She was diagnosed with severe osteoporosis (confirmed by

DEXA and X-ray), a compression fracture of L_I, and compression of L_V. Despite these findings, she did not seek medical care between 2014 and 2020. During this time, she sustained low-energy fractures of both the humerus and right radius. The medical documentation regarding the patient's previous fractures was not provided.

In July 2020, primary hyperparathyroidism (PHPT) was diagnosed, characterized by hypercalcemia, 25-OH vitamin D deficiency, and an estimated glomerular filtration rate (eGFR) of 57–80 mL/min/1.73 m² (CKD-EPI formula), along with an increase in parathyroid hormone (PTH) levels. The results of laboratory studies during the observation period are presented in Table 1. DEXA showed a negative trend in bone mineral density (BMD, Table 2), while X-ray revealed new compression fractures of L_{III} (29 % bone mass loss), L_{II} (24 %), and compression of L_{IV} (18 %) vertebrae. Despite the absolute indication for surgical treatment, it was postponed due to identified esophageal varices.

In 2021, the patient was repeatedly admitted to a gastroenterology clinic, where endoscopic ligation of esophageal varices was performed. She was diagnosed with hepatitis C-related liver cirrhosis, classified as Child — Pugh Class A (5 points) with portal hypertension. No antiviral therapy was prescribed according to the discharge summary. During her treatment in the gastroenterology clinic, denosumab was prescribed to prevent further progression of bone complications related to PHPT and to correct hypercalcemia. However, only one injection was administered (in April 2021).

In September 2021, the patient was admitted to the Department of Parathyroid Glands Pathology and Disorders of mineral metabolism at the National Medical Research Center for Endocrinology. The results of the laboratory tests are presented in Table 1. Given the marked hypercalcemia, cinacalcet 30 mg/day was initiated, resulting in a reduction of the albumin-adjusted calcium level to 2.74 mmol/L. A progressive decrease in BMD was observed (Table 2). Computed tomography revealed bilateral kidney stones up to 4 mm in size. Imaging methods identified four parathyroid glands: right superior (2.1 × 1.1 × 0.9 cm), right inferior (0.8 × 0.6 × 0.4 cm), left superior (2.1 × 0.9 × 0.6 cm), and left inferior (1.2 × 0.7 × 0.8 cm). The patient did not have any clinical signs of multiple endocrine neoplasia syndrome type 1 (MEN1); therefore, considering her age, genetic screening was not recommended.

The liver examination revealed no clinically significant abnormalities: AST — 48.1 U/L (norm: 5–34), ALT — 31.8 U/L (norm: 0–55), total bilirubin — 13.8 μmol/L (norm: 3.4–20.5), total protein — 79.4 g/L (norm: 64–83), albumin — 37 g/L (norm: 34–48), prothrombin time 10.1 sec (norm: 9.4–12.5), prothrombin — 151 %

Table 1. Laboratory parameters of Patient L. during the observation period
Таблица 1. Лабораторные показатели пациентки Л. за период наблюдения

Parameter / *Параметр*	Before parathyroidectomy *До паратиреоидэктомии*			After parathyroidectomy *После паратиреоидэктомии*	
	07.2020	03.2021	09.2021	10.2021	08.2022
PTH, pg/mL / *ПТГ, пг/мл* (norm / *норма:* 15–65)	132.02	119.9	147.6	57.99	84.37
Ca total, mmol/L / *Ca общ., ммоль/л* (norm / *норма:* 2,15–2,55)	2.72	2.84	2.88	2.49	2.72
Ca adj., mmol/L / *Альбумин-скорр. Ca, ммоль/л* (norm / *норма:* 2,15–2,55)	–	2.82	2.88	–	2.74
P, mmol/L / *P, ммоль/л* (norm / *норма:* 0,74–1,52)	0.67	0.71	0.69	–	0.81
Vitamin D, ng/mL / *Витамин D, нг/мл* (norm / *норма:* > 30)	12.79	–	26	–	–
ALP, U/L / *ЩФ, Ед./л* (norm / *норма:* 40–150)	363	971.6	277	–	236
GFR CKD-EPI, mL/min/1,73 m² *рСКФ по CKD-EPI, мл/мин/1,73 м²*	80	57	69	–	73
Daily urine Ca, mmol/day / *Ca сут. мочи, ммоль/сут* (norm / *норма:* 2,5–8)	–	–	6.3	–	1.7

Note: PTH — parathyroid hormone; Ca total — total calcium; Ca adj. — albumin-adjusted serum calcium; P — phosphorus; ALP — alkaline phosphatase; Daily urine Ca — daily urine calcium.
Примечание: ПТГ — паратгормон; Ca общ. — кальций общий; альбумин-скорр. Ca — альбумин-скорректированный кальций; P — фосфор; ЩФ — щелочная фосфатаза; Ca сут. мочи — кальций суточной мочи.

Table 2. Results of DEXA of the lumbar spine, femur and radius of Patient L. during the observation period
Таблица 2. Результаты DEXA поясничного отдела позвоночника, бедренной и лучевой костей пациентки Л. за период наблюдения

Region / *Отдел*	BMD, SD *T*-score / *МПК, SD по Т-критерию*		
L_I	–	–	–5.2
L_{II}	–	–	–6.1
L_{III}	–	–	–5.5
L_{IV}	–	–	–5.6
L_I–L_{IV}	–4.5	–5.5	–5.6
Femur neck / *Шейка бедра*	–3.6	–3.8	–4.0
Femur total / *Бедро в целом*	–3.7	–4.0	–4.1
Radius 33 % / *Лучевая кость 33 %*	–	–5.3	–5.4
Radius total / *Лучевая кость в целом*	–	–6.5	–6.4

(norm: 70–140), INR – 0.87 (norm: 0.9–1.2), fibrinogen – 3.15 g/L (norm: 2–4).

Surgery was performed in September 2021. During the isolation of the right superior parathyroid gland, the absence of signal from the right recurrent laryngeal nerve was noted, while visual confirmation of its integrity was maintained; thus, selective parathyroidectomy was performed. Postoperatively, serum PTH concentration decreased from 115.5 to 57.9 pg/mL resulting in normocalcemia. Histological examination reported an atypical tumor of the right superior parathyroid gland (pTis, WHO 2017). Postoperatively, colecalciferol was initiated at a dosage of 1000 IU/day.

Due to the non-radical surgical treatment, the patient had persistence of PHPT (Table 1). A dynamic evaluation of the disease complications severity confirmed the progressive decrease in BMD (Table 2) and an increase in both number and size of renal stones. Imaging studies indicated that the right inferior and left superior and inferior parathyroid glands persisted.

The clinical diagnosis at the discharge:

• *Primary disease:* Primary hyperparathyroidism, symptomatic form, the relapse after removal of an atypical adenoma of the right superior parathyroid gland. Right inferior, left superior and inferior parathyroid lesions.

• *Background disease:* Liver cirrhosis of HCV etiology, Child – Pugh Class A (5 points). Portal hypertension: portosystemic shunts, esophageal varices 1. Endoscopic ligation in 2021. Portal vein thrombosis.

• *Complications of underlying disease:* Bilateral nephrolithiasis. Severe osteoporosis of mixed etiology with compression fractures of the LI–III vertebrae, with a maximum decrease in BMD in the radius up to –7.1 SD (T score).

• *Associated diseases:* Left-sided multinodular euthyroid goiter (total thyroid volume – 9.5 cm^3). Mild iron deficiency anemia. Vitamin D insufficiency. Multiple renal cysts. Chronic kidney disease C2.

Repeated surgical treatment was recommended. However, the patient developed acute obstructive pyelonephritis during her next hospitalization due to right ureter obstruction. After undergoing urethrocystoscopy in the urology department, the patient suffered a low-energy fracture of the left femur. She was then transferred to the trauma department. Following orthopedic treatment and considering the necessary rehabilitation time, it was recommended that she resume antiresorptive therapy. Unfortunately, after her discharge from the hospital, communication with the patient was lost, and her relatives later reported her death (the cause could not be clarified).

Clinical Case 2

Patient O., 47-years-old female, underwent orthotopic liver transplantation in 2007 due to Budd – Chiari syndrome, which resulted in the development of cirrhosis. Since the transplant, she has been on immunosuppressive therapy (cyclosporine 200 mg/day), and graft function has remained satisfactory. Data on her BMD were unavailable prior to the liver transplantation and continued until 2019.

In November 2019, an examination for bone pain revealed elevated serum PTH concentration, hypercalcemia, and vitamin D deficiency (Table 3).

In March 2020, the patient was first admitted to the Department of Parathyroid Glands Pathology and Disorders of mineral metabolism at the National Medical Research Center for Endocrinology. An increase in serum PTH concentration with normal calcium levels and hypocalciuria was found, against a background of preserved renal function (Table 3). Secondary hyperparathyroidism was suspected. To assist with differential diagnosis, alfacalcidol 1 μg/day was initiated. On the fifth day of administration,

Table 3. Laboratory parameters of Patient O. during the observation period
Таблица 3. Лабораторные показатели пациентки О. за период наблюдения

Parameter / *Параметр*	Before parathyroidectomy *До паратиреоидэктомии*			After parathyroidectomy *После паратиреоидэктомии*		
	11.2019	**03.2020**	**03.2021**	**10.2021**	**12.2021**	**09.2023**
PTH, pg/mL / *ПТГ, пг/мл* (norm / *норма:* 15–65)	187.9	490.2	225.3	110.8	185	190.2
Ca total, mmol/L / *Ca общ., ммоль/л* (norm / *норма:* 2,15–2,55)	2.76	2.55	2.58	2.41	2.46	2.73
Ca adj., mmol/L / *Альбумин-скорр. Ca, ммоль/л* (norm / *норма:* 2,15–2,55)	–	2.51	2.58	–	–	2.64
P, mmol/L / *P, ммоль/л* (norm / *норма:* 0,74–1,52)	–	1.15	1.05	–	–	1.09
Vitamin D, ng/mL / *Витамин D, нг/мл* (norm / *норма:* > 30)	18.9	–	–	–	30	43.4
ALP, U/L / *ЩФ, Ед./л* (norm / *норма:* 40–150)	–	225	105	–	–	–
GFR CKD-EPI, mL/min/1,73 m^2 *рСКФ по CKD-EPI, мл/мин/1,73 м^2*	–	105	97	–	–	88
Daily urine Ca, mmol/day / *Ca сут. мочи, ммоль/сут* (norm / *норма:* 2,5–8)	–	1.37	4.4	–	–	3.8

Note: PTH — parathyroid hormone; Ca total — total calcium; Ca adj. — albumin-adjusted serum calcium; P — phosphorus; ALP — alkaline phosphatase; Daily urine Ca — daily urine calcium.
Примечание: ПТГ — паратгормон; Ca общ. — кальций общий; альбумин-скорр. Ca — альбумин-скорректированный кальций; P — фосфор; ЩФ — щелочная фосфатаза; Ca сут. мочи — кальций суточной мочи.

a decrease in PTH concentration to 316.1 pg/mL was noted, while maintaining normocalcemia (albumin-corrected calcium — 2.54 mmol/L). It was recommended that the test be continued for up to one month; however, after discharge, the patient took the medication irregularly. In March 2021, elevated PTH levels, moderate hypercalcemia, and hypocalciuria were observed (Table 3). The calculated calcium/creatinine clearance ratio was 0.01. Taking into account persistent hypocalciuria with preserved eGFR, *CASR* gene sequencing was performed to exclude familial hypocalciuric hypercalcemia — no pathogenic, likely pathogenic, or variants of unknown clinical significance were identified, thus the condition was diagnosed as PHPT.

DEXA scan revealed osteoporosis in the lumbar spine, femoral neck, and distal radius (Table 4). X-ray of the thoracic and lumbar spine showed no signs of vertebral compression fractures, and renal ultrasound indicated bilateral micronephrolithiasis.

Imaging studies (ultrasound and contrast-enhanced computed tomography) revealed a left superior parathyroid neoplasm (1.8 × 1.0 × 0.6 cm).

Liver function tests showed no clinically significant abnormalities: AST — 33 U/L (norm: 5–34), ALT — 25 U/L (norm: 0–55), total bilirubin — 6.9 μmol/L (norm: 3.4–20.5), total protein — 70 g/L (norm: 64–83), albumin — 42 g/L (norm: 35–50).

In September 2021, the left superior parathyroid gland was surgically removed. On the first postoperative day, PTH levels decreased from 157.7 to 110.8 pg/mL, and normocalcemia was observed. Histological examination confirmed the presence of the parathyroid adenoma. However, complete normalization of PTH levels was not achieved in the postoperative period.

In December 2022, alfacalcidol 1 μg/day was resumed, followed by dose titration, against which the increase in PTH concentration with normocalcemia persisted. The subsequent increase in alfacalcidol dose to 2 μg/day was associated with hypercalcemia with preserved hyperparathyroidism (Table 3), confirming the relapse of PHPT. DEXA data (Table 4) showed negative BMD dynamics in the lumbar spine and in the proximal part of the left femur. Imaging methods (ultrasound and contrast-enhanced computed tomography) confirmed the presence of a left inferior parathyroid mass (1.2 × 1.0 × 0.5 cm). In addition, according to the computed tomography data, another mass 1.0 × 0.6 × 0.5 cm was visualised paratracheally along the inferior contour of the left thyroid lobe.

Given the confirmed recurrence of PHPT, multiple parathyroid glands neoplasms, and the relatively young age of the patient at the time of disease manifestation, a hereditary origin of PHPT was suspected. No clinical data characteristic of MEN1

Table 4. Results of DEXA of the lumbar spine, femur and radius of Patient O. during the observation period

Таблица 4. Результаты DEXA поясничного отдела позвоночника, бедренной и лучевой костей пациентки О. за период наблюдения

Region / *Отдел*	BMD, SD *T*-score / *МПК, SD по Т-критерию*		
L_I	–3.4	–2.3	–3.1
L_{II}	–4.0	–2.7	–3.3
L_{III}	–3.5	–2.2	–3.4
L_{IV}	–3.9	–3.0	–4.0
L_I–L_{IV}	–3.7	–2.5 (+18.2 %)	–3.4 (–12.3 %)
Femur neck / *Шейка бедра*	–2.5	–2.0	–2.3 (–6.2 %)
Femur total / *Бедро в целом*	–2.3	–1.9 (+9.8 %)	–2.3
Radius 33 % / *Лучевая кость 33 %*	–4.3	–4.2	–3.9
Radius total / *Лучевая кость в целом*	–4.8	–4.6 (+2.2 %)	–4.6 (+3.7 %)

syndrome were found. In addition, sequencing of the *MEN1* gene and examination of blood relatives were recommended — these recommendations were not followed.

In February 2024, a left inferior parathyroid neoplasm was surgically removed; histological examination showed diffuse hyperplasia. Postoperatively, PTH decreased from 454 to 175.7 pg/mL and normocalcemia was observed.

The clinical diagnosis at the discharge:

• *Primary disease:* Primary hyperparathyroidism, symptomatic form, remission following the removal of left superior and inferior parathyroid gland adenomas.

• *Background disease:* Orthotopic liver transplantation for cirrhosis secondary to Budd — Chiari syndrome in 2007.

• *Complications of primary disease:* Osteoporosis of mixed etiology with maximal decrease in BMD in radius up to -4.6 SD (T score).

• *Associated diseases:* Primary hypothyroidism resulting from autoimmune thyroiditis, medically compensated. Combined thrombophilia (hereditary and acquired: antiphospholipid syndrome with circulating lupus anticoagulant). Mild iron deficiency anemia. Premature ovarian failure. Secondary amenorrhoea. Mild climacteric syndrome. Cysts of both kidneys. Chronic kidney disease C2.

Discussion

We analysed two cases of severe PHPT: one patient with liver cirrhosis and another who underwent liver transplantation. A notable feature of these cases is the significant decrease in BMD across all examined sites, as well as the presence of multiple low-energy fractures in the first patient.

Bone disease in PHPT is characterised by a decrease in BMD, predominantly affecting cortical bone [10]. Consequently, the most pronounced changes observed on DEXA scans are usually in the distal radius. However, in the cases presented, we observed a pronounced and relatively uniform decrease in BMD in all examined sites, including the spine, which primarily comprises trabecular bone. We believe this may be due to the combined effects of PHPT and liver disease.

Patients with liver cirrhosis have lower BMD values in the lumbar spine compared to those in the femoral neck [11, 12], suggesting a differential impact on cortical and trabecular bone lesions. Most studies investigating osteoporosis in patients with chronic liver disease, including liver cirrhosis, focused on BMD in the lumbar spine and proximal femur, while data regarding BMD in the distal radius remain limited. Available data suggest no significant decrease in BMD in the radius among patients with chronic liver disease and liver cirrhosis [13].

The mechanisms underlying the development of osteoporosis in patients with chronic liver disease are complex and not fully understood. Proposed factors include reduced levels of insulin-like growth factor-1, fibronectin, sex hormones and sex hormone-binding globulin, all of which arise from impaired synthetic liver function. Under the influence of hormones involved in bone metabolism, the liver normally produces various cytokines (e.g., IL6 in response to the action of PTH). The spectrum and concentrations of these cytokines are altered in chronic liver disease, particularly in cases of chronic viral hepatitis [5]. Furthermore, patients with metabolic syndrome and conditions like MASLD are more likely to have impaired bone metabolism, where insulin resistance and systemic inflammation play significant pathogenetic roles [14]. An imbalance in the RANKL-RANK-OPG system, a critical regulator of bone homeostasis, has also been implicated

in the development of osteoporosis in patients with chronic liver disease [15].

A significant concern is the progressive decrease in BMD due to high bone turnover observed soon after liver transplantation [16], especially in the context of immunosuppressive therapy, including glucocorticoids. Given the high incidence of osteoporosis in chronic liver disease patients, it is possible that maintaining optimal bone metabolism in these individuals requires different blood concentrations of PTH, calcium, phosphorus, and various vitamin D metabolites compared to the general population. This hypothesis necessitates further investigation. In the second case described, the patient did not undergo evaluation for bone pathology before or after liver transplantation until 2019, which hinders our ability to assess the age of these changes or the influence of specific factors.

The multiple lesions of the parathyroid glands observed in our patients are noteworthy. The first clinical case is remarkable for the development of lesions of all four parathyroid glands in a woman with a long history of chronic viral hepatitis C. Notably, hyperparathyroidism persisted even after the selective removal of the largest lesion, which was identified as an atypical adenoma. In the second patient, the recurrence of hyperparathyroidism one year after the surgery also suggested the presence of multiple lesions of the parathyroid glands. Such polyglandular lesions may indicate a hereditary basis for the condition. Although the patients were clinically assessed for multiple endocrine neoplasia type 1 (MEN1) syndrome, the recommendation for *MEN1* gene sequencing in the second case — due to the relatively young age of onset and the multiple lesions — was not followed for various reasons. However, the absence of clinical and laboratory signs indicative of other components of MEN1 syndrome, along with a lack of family history, supports the notion of a sporadic nature of the disease.

Multiple lesions in the parathyroid glands are also frequently observed in patients with secondary hyperparathyroidism who have a long history of chronic kidney disease (CKD); in such cases, the development of hyperparathyroidism is largely attributed to the disruption of the final step of vitamin D activation. The liver plays a significant role in vitamin D metabolism, facilitating hydroxylation to form 25-hydroxyvitamin D (the primary circulating form) and synthesizing carrier proteins like albumin and vitamin D-binding protein. Therefore, a combination of primary and secondary hyperparathyroidism can be expected in patients with chronic liver disease.

The role of vitamin D in the regulation of the "PTH — calcium" axis in patients with chronic liver disease remains poorly understood, and studies thus far have yielded conflicting results. Many studies indicate a high prevalence of vitamin D deficiency among patients with chronic liver disease, particularly liver cirrhosis, where an inverse relationship between vitamin D levels and disease severity, as measured by the Child — Pugh scale, has been reported [17]. Potential mechanisms for reduced 25-OH vitamin D concentrations in this population include decreased exposure to exogenous vitamin D sources (sunlight, diet), intestinal malabsorption of dietary vitamin D, decreased endogenous production of vitamin D-binding protein and albumin, and impaired hydroxylation of colecalciferol in the liver [3].

Given these observations, hypocalcemia and secondary hyperparathyroidism would be expected in patients with chronic liver disease. However, a study by K. Narayanasamy et al. involving 236 patients found that the median 25-OH vitamin D concentration was 23 ng/mL (norm: 15–35), albumin-adjusted calcium was 1.9 mmol/L (norm: 1.5–2.1), and PTH was 21 pg/mL (norm: 13–31), findings which are inconsistent with the classical understanding of secondary hyperparathyroidism pathogenesis [18]. Similarly, A. Miroliaee et al. reported a low prevalence of secondary hyperparathyroidism (6.7 %) among patients with 25-OH vitamin D deficiency in chronic liver disease [19]. Other studies have echoed these findings [17, 20]. Due to the low incidence of secondary hyperparathyroidism, structural changes of the parathyroid glands were not evaluated in the presented studies.

The relatively low incidence of hyperparathyroidism (including hypocalcemia) reported in these studies may stem from methodological limitations, such as small sample sizes and the use of means (rather than medians) in group comparisons. Analytical errors could also play a role, alongside disturbances in the synthesis of PTH, albumin, and vitamin D-binding protein due to impaired liver function. Furthermore, alterations in the half-life of the PTH molecule in the bloodstream during chronic liver disease may contribute to these outcomes [20]. It is also plausible that changes akin to secondary hyperparathyroidism seen in CKD may not manifest until the later stages of chronic liver disease, resulting in many patients undergoing liver transplantation before these changes develop. Nevertheless, these hypotheses warrant further investigation.

Conclusion

Abnormalities of mineral and bone metabolism present a significant yet poorly understood challenge in patients with chronic liver disease. Further studies are essential to develop targeted therapeutic approaches for this patients' population and to prevent the onset of late, disabling complications.

Литература / References

1. *Cheemerla S., Balakrishnan M.* Global epidemiology of chronic liver disease. *Clin Liver Dis (Hoboken)*. 2021;17(5):365–70. DOI: 10.1002/cld.1061
2. *GBD 2017 Cirrhosis Collaborators.* The global, regional, and national burden of cirrhosis by cause in 195 countries and territories, 1990–2017: A systematic analysis for the Global Burden of Disease Study 2017. *Lancet Gastroenterol Hepatol*. 2020;5(3):245–66. DOI: 10.1016/S2468-1253(19)30349-8
3. *Stokes C.S., Volmer D.A., Grünhage F., Lammert F.* Vitamin D in chronic liver disease. *Liver Int*. 2013;33(3):338–52. DOI: 10.1111/liv.12106
4. *Patel N., Muñoz S.J.* Bone disease in cirrhosis. *Clin Liver Dis*. 2015;6(4):96–9. DOI: 10.1002/cld.498
5. *Nakchbandi I.A.* Osteoporosis and fractures in liver disease: Relevance, pathogenesis and therapeutic implications. *World J Gastroenterol*. 2014;20(28):9427–38. DOI: 10.3748/wjg.v20.i28.9427
6. *Compston J.E., Mcclung M.R., Leslie W.D.* Osteoporosis. *Lancet*. 2019;393(10169):364–76. DOI: 10.1016/S0140-6736(18)32112-3
7. *Mokrysheva N.G., Eremkina A.K., Elfimova A.R., Kovaleva E.V., Miliutina A.P., Bibik E.E., et al.* The Russian registry of primary hyperparathyroidism, latest update. *Front Endocrinol (Lausanne)*. 2023;14:1203437. DOI: 10.3389/fendo.2023.1203437
8. *Eastell R., Rosen C.J., Black D.M., Cheung A.M., Murad M.H., Shoback D.* Pharmacological management of osteoporosis in postmenopausal women: An Endocrine Society* clinical practice guideline. *J Clin Endocrinol Metab*. 2019;104(5):1595–622. DOI: 10.1210/jc.2019-00221
9. *Arceo-Mendoza R.M., Camacho P.M.* Postmenopausal osteoporosis: Latest guidelines. *Endocrinol Metab Clin North Am*. 2021;50(2):167–78. DOI: 10.1016/j.ecl.2021.03.009
10. *Marcocci C., Cianferotti L., Cetani F.* Bone disease in primary hyperparathyrodism. *Ther Adv Musculoskelet Dis*. 2012;4(5):357–68. DOI: 10.1177/1759720X12441869
11. *Muhsen I.N., AlFreihi O., Abaalkhail F., Alkhenizan A., Khan M., Eldali A., et al.* Bone mineral density loss in patients with cirrhosis. *Saudi J Gastroenterol*. 2018;24(6):342–7. DOI: 10.4103/sjg.SJG_74_18
12. *Turkeli M., Dursun H., Albayrak F., Okçu N., Uyanik M.H., Uyanik A., et al.* Effects of cirrhosis on bone mineral density and bone metabolism. *Eurasian J Med*. 2008;40(1):18–24.
13. *Yurci A., Kalkan A.O., Ozbakir O., Karaman A., Torun E., Kula M., et al.* Efficacy of different therapeutic regimens on hepatic osteodystrophy in chronic viral liver disease. *Eur J Gastroenterol Hepatol*. 2011;23(12):1206–12. DOI: 10.1097/MEG.0b013e32834cd6f6
14. *Musio A., Perazza F., Leoni L., Stefanini B., Dajti E., Menozzi R., et al.* Osteosarcopenia in NAFLD/MAFLD: An underappreciated clinical problem in chronic liver disease. *Int J Mol Sci*. 2023;24(8):7517. DOI: 10.3390/ijms24087517
15. *Jeong H.M., Kim D.J.* Bone diseases in patients with chronic liver disease. *Int J Mol Sci*. 2019;20(17):4270. DOI: 10.3390/ijms20174270
16. *Li X.Y., Lew C.CH, Kek P.C.* Bone mineral density following liver transplantation: A 10-year trend analysis. *Arch Osteoporos*. 2021;16(1):169. DOI: 10.1007/s11657-021-01037-x
17. *Fisher L., Fisher A.* Vitamin D and parathyroid hormone in outpatients with noncholestatic chronic liver disease. *Clin Gastroenterol Hepatol*. 2007;5(4):513–20. DOI: 10.1016/j.cgh.2006.10.015
18. *Narayanasamy K., Karthick R., Koodal Raj A.* High prevalent hypovitaminosis D is associated with dysregulation of calcium-parathyroid hormone-vitamin D axis in patients with chronic liver diseases. *J Clin Transl Hepatol*. 2019;7(1):15–20. DOI: 10.14218/JCTH.2018.00018
19. *Miroliaee A., Nasiri-Toosi M., Khalilzadeh O., Esteghamati A., Abdollahi A., Mazloumi M.* Disturbances of parathyroid hormone-vitamin D axis in non-cholestatic chronic liver disease: A cross-sectional study. *Hepatol Int*. 2010;4(3):634–40. DOI: 10.1007/s12072-010-9194-2
20. *Corey R.L., Whitaker M.D., Crowell M.D., Keddis M.T., Aqel B., Balan V., et al.* Vitamin D deficiency, parathyroid hormone levels, and bone disease among patients with end-stage liver disease and normal serum creatinine awaiting liver transplantation. *Clin Transplant*. 2014;28(5):579–84. DOI: 10.1111/ctr.12351

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