Spectrum Journal of Innovation, Reforms and Development
Volume 29, July - 2024 | ISSN (E): 2751-1731
Website: www.sjird.journalspark.org

BONE MINERAL DENSITY DISORDER IN PATIENTS WITH DIGESTIVE DISEASES

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Abstract
The article is devoted to the study of the clinical features of the course of diseases of the gastrointestinal tract and liver in the formation of osteopenia and osteoporosis. The data on the frequency of occurrence of bone mineral density disorders in patients with chronic pancreatitis, cirrhosis of the liver, cholelithiasis, inflammatory bowel diseases, as well as diseases accompanied by malabsorption syndrome (gluten enteropathy, short small intestine syndrome) are presented. The population (age, gender) has been established, decrease in body mass index, menopause), clinical and laboratory factors indicating a high risk of a decrease in bone mineral density in this category of patients.

Keywords: violation of bone mineral density; densitometry; biliary insufficiency; gallstone disease; chronic pancreatitis; malabsorption syndrome; cirrhosis of the liver.

Introduction

The spectrum of pathology of the gastrointestinal tract, fraught with the development of disorders of bone mineral density (osteoporosis, osteopenia), is very wide: diseases of the liver, intestines, pancreas, biliary tract. All these diseases can provoke a decrease in calcium absorption, often combined with impaired vitamin D metabolism and protein deficiency. Hypocalcemia leads to activation of the parathyroid glands and secondary hyperparathyroidism. An absolute or relative deficiency of vitamin D, moreover, causes a violation of the mineralization of organic the matrix. The result of these complex disorders is in most cases osteopenia. One of the pathogenetic links in the development of osteoporosis is a violation of the oxidation of vitamin D in the liver. According to the literature, it is known that 90% of vitamin D synthesis takes place in the liver, where the first hydroxylation reaction of cholecalciferol and calciferol is carried out with the participation of the microsomal enzyme 25-hydroxylase. Particular importance is attached to bile acids, the main physiological significance of which
lies in the emulsification of fats, the formation of lipoid-bile complexes. In addition, bile acids activate pancreatic lipase, and therefore facilitate the absorption of fat-soluble vitamins, in particular vitamin D. The nature of pathological processes in the digestive organs, their severity and durationdetermine the predominance of one or another type of metabolic osteopathy and its severity. Mechanisms of pathogenetic disorders of bone remodeling processes in gastroenterological patients according to the literatureThey are represented by a violation of the absorption processes of vitamin D, calcium, proteins, fats, which in turn is accompanied by a violation of vitamin D metabolism. The high activity of inflammatory cytokines and the disconnection of bone remodeling processes

lead to a change in the synthesis of parathyroid hormone and thyroid hormones. Accompanying changes in the form of a decrease in estrogen and testosterone levels, as well as ongoing glucocorticoid therapy, cause violations of bone mineralization. Due to the objectification of the diagnosis of metabolic pathology of the bone system (that is, methods that allow assessing bone mineral density, such as densitometry, biochemical markers of bone resorption and osteogenesis), it is now possible to more accurately determine the prevalence of osteopenia in gastroenterological diseases and assess this problem from the point of view of evidence-based medicine. All of the above served as the basis for the purpose of the study — to develop criteria for the prognosis of metabolic disorders of bone tissue and improve the effectiveness of prevention and treatment of osteopenia in gastroenterological patients based on the pathogenetic features of its development.

MATERIALS AND METHODS OF RESEARCH

100 patients with chronic pancreatitis were examined: 47 (47%) men and 53 (53%) women, the average age was 51.0 ± 10.2 years. In 52% of patients, CP was associated with alcohol intake, and 48% were diagnosed with biliary pancreatitis. Of the 53 women surveyed, there were significantly more menopausal women — 40 (75.5%), and 13 (24.5%) women had preserved menstrual function ($\chi 2 = 21.7$, $p < 0.001$). The duration of menopause ranged from 1 year to 15 years. The study included 56 (56%) people with uncomplicated CP. 44 (44%) patients had complications of CP (postnecrotic cysts, calcification, pseudotumor pancreatitis, pancreatic resection). 75 patients suffering from cirrhosis of the liver of various etiologies and duration of the disease were examined. There are 54 women among them (72 ± 6,1%), 39 (72 ± 7,2%) of them were menopausal, and 21 male (28 ± 9.8%). The average age was 56.4 ± 12.3 years for women and 51.2 ± 7.9 years for men. The etiology of liver cirrhosis among the examined patients was distributed as follows: primary biliary cirrhosis was detected in 27 patients (36 ± 9.2%), alcoholic cirrhosis — in 34 (45.3 ± 8.5%), cirrhosis of the liver of other etiology (viral, mixed (alcoholic and viral), Wilson's disease — Konovalov, of unspecified etiology) — in 14 (18.7 ± 10,4%). The duration of the disease in 28 (37.3 ± 9.1%) patients was more than 5 years, in 47 (62.7 ± 7.1%) — less than 5 years. In the analysis of hepatic cell insufficiency on the Child-Pugh scale, class A was established in 44 (58.7% ± 7.4) patients, class B in 16 (21.3 ± 10.2%), class C in 15 (20 ± 10.3%). 60 people with diseases accompanied by impaired absorption syndrome were examined (gluten enteropathy, short thin syndrome intestinal diseases) and inflammatory bowel diseases (Crohn's disease, ulcerative colitis) at the age of 20 to 70 years with a disease duration of one to 20 years. The average age of the patients was 47.4 ± 7.3 years, among them there were 50 (83%) women and 10 (17%) men. About half of all the examined patients were female patients with gluten enteropathy, half of whom were menopausal. The group of patients with postresection syndromes numbered 18.3%, with inflammatory bowel diseases — 26.7%. 68 patients with pathology of the biliary system were examined, including 31 (45.6%) with GI and 37 (54.4%) who underwent cholecystectomy. Among the surveyed, 63 (92.6 ± 3.1%) were women and 5 (7.4 ± 3.1%) of men. The average age was 61.2 ± 10.5 years for women and 54.2 ± 24.4 years for men.

Menopause was observed in 52 (82.5 ± 4.7%) women. The group of patients with GI was dominated by women, there were significantly fewer men ($p < 0.001$) and they were younger ($p = 0.003$). In the group of patients with PCES Also, the majority of those surveyed were women ($p < 0.001$), but the age difference between men and there were no women. The same age and gender characteristics are noted among the general population of patients with GI and those who have undergone

cholecystectomy. Menopause was observed in 18 (62.1 ± 9%) women with GI and in all women with PCES. All patients underwent clinical, instrumental and laboratory examinations, which included anamnesis collection, examination, abdominal ultrasound, esophagastroduodenoscopy, biochemical blood analysis (amylase, creatinine, total protein, albumin, creatinine, alkaline phosphatase, glucose), general clinical blood analysis, general clinical stool analysis, general clinical stool analysis. Have been studied indicators of phosphorous-calcium metabolism (calcium, phosphorus in blood and urine), the level of parathyroid hormone, calcitonin, testosterone, a marker of bone resorption — CrossLaps, TNF
-2, the level of vitamin D metabolites (25OHD3 and 1,25 (OH) 2 D3). Bone mineral density was determined by dual-energy X-ray absorptiometry on the Lunar DPX 21200 apparatus. The state of the BMD was assessed according to the criteria of the Ti Z-scale and in g / cm^2. Statistical processing of the results was performed using Statistica statistical programs 6.0 and Biostat. The significance level of the error (probability of error of the first kind) was considered reliable at $\alpha \leq 0.05$ with sensitivity (probability of error Type II) $\beta = 0.8$.

THE RESULTS AND THEIR DISCUSSION

The results of the study demonstrated a high prevalence of BMD disorders among patients with chronic pancreatitis (CP). Osteopenia occurred in 57% of patients (47.2 – 66.8; 95% CI), and in 32% (19.9 – 44.1; DI 95%) of them showed a decrease in BMD to the values of criterion T, which are classified like osteoporosis. During densitometry, a decrease in BMD to the level of osteopenia was most often noted — in 39% of cases. Of these, in 18% of cases, there was a combined lesion of the spine both the hips and 14% of patients have an isolated lesion of the spine. In 17% of cases, there were changes in BMD before osteoporosis in the spine, and in 6% — osteoporosis in the hip area.Thus, there was no characteristic localization of osteoporosis and osteopenia in patients with CP.

The incidence of osteopenia among the examined women with preserved menstrual function was 61.5% (35-88; CI 95%), among menopausal women — 65% (50.3 – 79.7; CI 95%), and among men — 48.9% (34.6 – 63.2; CI 95%) of patients. The confidence intervals of the frequency of osteopenia overlap each other This indicates that there is no significant difference between men and women in the prevalence of osteopenia in patients with CP. The prevalence of osteopenia and osteoporosis depending on menopause was considered separately. Of the 40 menopausal women, 13 (32.5%) had osteopenia and the same number of women had osteoporosis. Thus, violations BMD was observed in 65% of menopausal women. Among women with preserved menstrual function, a decrease in BMD was observed in 61.5%, and despite the fact that osteoporosis was common in menopausal women More often, 32.5% vs 7.7%, the difference was statistically unreliable (Fisher's criterion p = 0.145). Thus, menopause did not significantly affect the frequency of decrease in BMD. The etiology of CP, age of patients, and BMI had no effect on the incidence of osteopenia. According to the tasks set, the patients were divided into two groups depending on the severity of external secretory pancreatic insufficiency. The criterion for assessing the degree of exocrine insufficiency was the level of pancreatic elastase E1 in the stool. The first group consisted of 59 patients with CP with reduced elastase levels (below 200 mcg / g), and 41 patients in the second group HP with normal levels of fecal elastase (from 200 mcg / g and above). The average level of fecal elastase E1 in the 1st group of patients was 65 ± 41.2 mcg / g and was significantly lower than in the second group: 361 ± 142 mcg / g (p = 0.002). The average age of patients in groups 1 and 2 did not

significantly differ (p = 0.916). Men prevailed in group 1 (-2 = 10, p =0.002), and women in group 2. Significantly, the complicated course of CP was more common among patients with CP with exocrine pancreatic insufficiency ($\chi 2$ = 14.6, p < 0.001) and the alcoholic etiology of CP ($\chi 2$= 9.3, p =0.002). There was no significant difference between the groups in terms of the duration of CP and BMI. The level of calcium and phosphorus in the blood of the patients included in the study was within the normal range, but its level differed depending on the state of the external secretory function of the pancreas. Patients with BPH had significantly lower levels of calcium and significantly higher levels of phosphorus in the blood. Also, urinary calcium excretion was significantly lower. All this indicated a physiological calcium deficiency, which was compensated in this group

an increase in PTH levels, which was significantly higher, and the number of patients with elevated PTH levels was higher. The level of calciotonin was significantly lower in case of BPH. One of the reasons for physiological calcium deficiency is a decrease in vitamin D levels. The results of our study show that patients with BPH had significantly lower levels of 25(OH)D3, and the number of patients with vitamin D deficiency in this group was higher. The level of 1.25(OH)2 D3 — calcitriol was also significantly lower in extracretory pancreatic insufficiency, but the number of patients There was no significant difference with calcitriol deficiency. The level of CrossLaps protein was significantly higher in the group of patients with preserved function Pancreas, its average values exceeded

the norm in 76% of patients, which was significantly more common than in patients with BPH. The average values of TNFa in the blood did not differ significantly. TNFa was elevated in 15% of patients with BPH and in 12% of patients with preserved pancreatic exocrine function, which had no significant differences. Thus, developing exocrine pancreatic insufficiency leads to an increase in the frequency of BMD disorders and leads to to aggravate bone loss. The study of the peculiarities of bone metabolism showed that in this group of patients with BPH there are features of impaired regulation of bone metabolism, the main of which are vitamin D deficiency and secondary hyperparathyroidism.

Among women with CP with osteopenia and preserved menstrual function, the

following factors were noted that contribute to a decrease in BMD and the development of secondary hyperparathyroidism, is vitamin D deficiency in 6 (75%) patients, and in 2 (25%) patients it was most likely It is associated with a deficiency of calcium due to the formation of its compounds with fatty acids (soaps). The level of estradiol and testosterone in women did not significantly affect BMD and the incidence of osteopenia. There was no correlation between BMD and TNF content. Thus, in the patients we examined, there was no effect of sex hormones and the proinflammatory cytokine TNF on the risk of osteopenia.

In men, one of the risk factors is a decrease in BMD is a decrease in testosterone levels. Among the men we examined, only 3 (6.3%) there was a decrease in testosterone levels below normal. Two of them had osteopenia, and one had a normal BMD. The data we obtained do not allow us to establish a relationship between osteopenia and a decrease in testosterone in men, there was no correlation between BMD and testosterone levels. In the examined men, BPH was observed

in 76% of patients, and osteopenia — in 48.9%. Secondary hyperparathyroidism was observed in 17 (74%) patients with osteopenia, of which 15 (88%) developed against the background of vitamin D deficiency, in 3 (12%) secondary hyperparathyroidism was not associated with vitamin D deficiency, but increased excretion of fatty acid salts (soaps) with feces was noted. Thus, out of 23

men with osteopenia, the main cause in 17 (74%) patients was secondary hyperparathyroidism, and in 2 (9%) patients the most likely factor that led to a decrease in MPCT was hypogonadism, which was confirmed by a decrease in testosterone levels. In 4 (17%) patients in our study, it was not possible to find the causes of a decrease in BMD, they can be considered as patients with idiopathic osteoporosis. Among the patients we examined, the main risk factors for osteopenia were calculated. To analyze the statistical significance of demographic
and clinical risk factors, the relative risk of osteopenia was calculated. The relative risk associated with the development of extrasecretory (exocrine) pancreatic insufficiency had the greatest weight. The formation of this risk is due, according to our data, to those significant changes bone metabolism, which were obtained in our study: a change in phosphorus-calcium metabolism, a higher frequency of secondary hyperparathyroidism and vitamin D deficiency. According to the results of the study, secondary osteoporosis can occur in 19-35% of patients with CP, regardless of gender. Among menopausal women with CP, 24-54% have postmenopausal osteoporosis, which is not associated with pancreatic disease, and 46-76% of menopausal women may have a combined variant of osteoporosis – postmenopausal, burdened with secondary osteoporosis. In the process of analyzing the obtained MPCT data in patients with cirrhosis of the liver, all the examined patients were divided into three groups. The first group included patients with osteoporosis in at least one of the studied departments, the second group included patients with osteopenia, respectively, and the third group included patients without BMD disorders.

During the examination, osteopenia was detected in 35 (46.7 ± 8.4%) patients, osteoporosis in 19 (25.3 ± 10%), and no changes in bone mineral density were found in 21 (28 ± 9.8%) patients. Thus, in patients with cirrhosis of the liver, a decrease in BMD was found in 72% (62.2 – 81.8; CI 95%). Osteopenia and osteoporosis in women were found in 77.8% of the surveyed, which was significantly more common than among men — 42.8%, $p = 0.01$. Among women, a decrease in BMD was most often observed in the group of menopausal women — 82%, but the difference between the group of women with preserved menstrual function, in whom a decrease in BMD was found in 66.7%, was not significant. The average age of women and men with osteopenia and osteoporosis did not significantly differ from the group of examined with the saved MPCT. However, there was a significant inverse correlation between age and criterion T: $r = -49$; $p < 0.01$ (lumbar spine) and $r = -0.34$, $p < 0.003$ (hip neck). At the same time, there was no correlation between the decrease in the Z criterion and age: the correlation coefficient between age and the criterion The Z in the hip area was $r = 0.11$ at $p = 0.23$ and the Z criterion of the spine area was $r = 0.19$ at $p = 0.19$. The etiology of liver cirrhosis significantly influenced the prevalence of osteoporosis and osteopenia. Among patients with PBC, a decrease in bone mineral density was found in 96.2% of the examined patients, while among patients with alcoholic cirrhosis of the liver, osteoporosis and osteopenia were found in 47% ($p = 0.0008$). It was not possible to find a relationship between the degree of Child-Pugh liver failure and a decrease in bone mineral density. But there was a significant relationship between the duration of the disease and the frequency of osteoporosis and osteopenia. Thus, among patients with cirrhosis lasting less than 5 years, a decrease in BMD was found in 63.8% of cases, and with a duration of more than 5 years — already in 85.7% of patients ($\chi 2 = 5.3$; $p = 0.021$). An increase in the prevalence of osteoporosis and osteopenia in patients with cirrhosis of the liver, depending on BMI, was not detected, perhaps this It is caused by an increase in the weight of patients due to the presence of edematous ascitic syndrome, which leads to incorrect calculation of BMI. In patients with cirrhosis of the liver, loss of bone density in the

lumbar vertebrae was observed in 85.2% of patients with reduced BMD, isolated osteopenia of the lumbar spine was diagnosed in 18 (33.3%) patients with cirrhosis of the liver, the average T criterion was -1.4 ± 0.3; in combination with hip osteopenia in 9 (16.7%) patients, the average criterion T of the spine was -1.8 ± 0.4; the average criterion of T of the femoral neck was -1.7 ± 0.5. In 31.5% of patients with CP, BMD decreased to the level of osteoporosis. 5 (9.3%) of them had a combination of spinal osteoporosis with hip osteoporosis,

the average criterion of T vertebrae was -4.1 ± 0.2, the average criterion of T of the femoral neck was -3.1 ± 0.3; in 8 (14.8%) osteoporosis of the spine developed simultaneously with osteopenia of the femoral neck, the average criterion of T vertebrae was -3.0 ± 0.4, the average criterion of T of the femoral neck was -1.6 ± 0.3; and 4 (7.4%) patients suffered from osteoporosis of the spine without a decrease in BMD in the hip area, the average criterion of T vertebrae is -3.1 ± 0.2.

Loss of BMD in the femoral neck was significantly less common than in the spine, a decrease in the T criterion in this area was noted in 59.3% ($p = 0.005$). Isolated osteopenia of the femoral neck — in 8 (14.8%) patients (the average criterion of T was -1.2 ± 0.1); osteoporosis of the femoral neck in combination with osteopenia of the spine — in 2 (3.7%), the average criterion of T of the femoral neck -2.6 ± 0.2, the average criterion of T of the vertebrae -1.6. Cases of isolated osteoporosis of the femoral neck among There were no examined patients. When analyzing the localization of osteoporosis and/or osteopenia in patients with different etiologies

of the disease, the following feature was revealed. In patients with PBC, 24 out of 26 patients with reduced BMD indicated spinal damage and only 2 patients had hip neck damage, the significance of the difference according to the Fisher criterion was $p < 0.001$. In patients with alcoholic cirrhosis of the liver and in the group of patients with cirrhosis of the liver of another etiology, there was no significant difference in the localization of osteoporosis and osteopenia. Thus, in the group of patients with cirrhosis of the liver, such population risk factors for osteopenia as age, decreased BMI, and the postmenopausal period in women are relevant. Osteopenia prevails in this pathology of the liver and osteoporosis in the spine compared to changes in bone mineral density in the femoral neck. In women suffering from cirrhosis of the liver, a decrease in bone mineral density is significantly more common than unchanged indicators. Metabolic pathology of bone tissue prevails in patients with primary biliary cirrhosis of the liver compared with cirrhosis of a different etiology. The degree of bone loss increases as the underlying disease progresses. About half of all examined patients with diseases accompanied by malabsorption syndrome were female patients with gluten enteropathy (55 ± 0.087%). During densitometry in this group, BMD was not changed in 27.2 ± 0.148% of patients. Changing the MPCT It was detected in 72.8 ± 0.091% of cases. The second largest group consisted of patients with inflammatory bowel diseases (IBD), among them 56 ± 0.165% of BMD was normal, and 44 ± 0.188% — reduced. And finally, the group of patients with postresection turned out to be the smallest syndromes, among which 82 ± 0.128% of all examined patients had signs of osteopenia / osteoporosis and only 18 ± 0.272% did not. When studying the localization of a violation of the BMD patients with celiac disease have a predominant lesion of the spine. A decrease in BMD by type of osteopenia and/or osteoporosis of the spine was significantly more common ($p = 0.045$) in 72.8% of patients with celiac disease, while hip neck osteopenia was observed in 45.5% of patients. In patients with postresection syndromes, combined spinal and hip lesions of the type of osteopenia were most common and/or osteoporosis — in 7 patients. Isolated hip osteopenia was found in only one person, as well as isolated spinal osteopenia. The decrease in BMD is most rarely found in patients with inflammatory bowel diseases (IBD).

Spinal damage also prevailed in this group of patients. In three of them, spinal osteoporosis was combined with hip osteopenia, spinal osteopenia was also recorded in three patients, one of them had its combination with hip osteopenia; isolated hip neck osteopenia was found in only one patient. These changes are unreliable compared to other groups (gluten enteropathy and postresection syndromes). Thus, spinal damage was most often detected in patients — out of 40 patients with reduced BMD, 38 had both isolated spinal damage (12 people) and in combination with osteopenia / hip porosis (26). And only 28 people out of all the examined had osteopenia / hip porosis (both isolated and in combination with spinal damage). Among patients with GI, normal BMD was observed in 29 (42.6%) patients. Osteopenia and/or osteoporosis were detected in 39 (57.4%) patients. Thus, the prevalence of osteopenia in the group patients with GI, including those who have undergone cholecystectomy, may range from 55.3 – 61.7% (95% CI). A decrease in BMD was observed in 51.7% of women. Among men, a decrease in this indicator was noted in 60% of cases, there was no significant difference in the prevalence of osteoporosis and/or osteopenia between men and women in the examined group, but it should be taken into account that there were only 7% of men in the examined group. Among women with osteoporosis and/or osteopenia, 33 were menopausal, and the prevalence of BMD disorders in them was 63.5%. In women with preserved menstrual function, BMD deviation was less common in 27.3%, but the reliability of the difference in proportions and the criterion of $\chi 2$ It did not reach the required significance ($p = 0.062$), perhaps this is explained by a small sample of patients. The duration of menopause in women with normal BMD was significantly lower ($p = 0.015$). The prevalence of osteoporosis and/or osteopenia in patients with PCES was higher than in patients GI with preserved gallbladder, but the values were not statistically significant ($p = 0.266$). The number of patients with a history of fractures there were more in the group of patients with reduced BMD. The number of fractures per patient in both groups did not differ. When analyzing the correlation relationships, a significant correlation was found between BMI and the T criterion in the lumbar vertebrae and the T criterion in the hip region ($r = 0.32$; $p = 0.009$).

CONCLUSIONS

According to the data obtained, chronic pancreatitis, cirrhosis of the liver, cholelithiasis, inflammatory bowel diseases, as well as diseases accompanied by malabsorption syndrome (gluten enteropathy, short small intestine syndrome), exacerbate the risk of osteopenia / osteoporosis in patients with population risk factors. A decrease in BMD in patients with certain diseases of the digestive system occurs equally in both cortical and trabecular bone tissue, which indicates
the polyethologicity of osteopenia in this group of patients. The main population risk factors for certain diseases of the digestive system are female gender, menopause, and the clinical risk factor is the duration of the disease for more than 10 years. In some women, osteopenia is caused by menopause (primary postmenopausal osteoporosis); at the same time, osteoporosis occurs against the background of physiological menopause, as well as against the background of early or premature menopause due to diseases of the gastrointestinal tract. Some women have a combination of postmenopausal and secondary osteoporosis. For men in the vast majority, secondaryosteopenia is detected (against the background of a decrease in testosterone levels due to diseases of the gastrointestinal tract) or idiopathic.

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