UDC 616.37-002-036.1:612.015.3

The role of phosphorus-calcium homeostasis and vitamin D in the pathogenesis of acute pancreatitis and assessment of its severity

I.V. Kolosovych, I.V. Hanol

Bogomolets National Medical University, Department of Surgery No.2, Kyiv, Ukraine; e-mail: ganoli@ukr.net

The aim of the study was to determine the role of phosphorus-calcium homeostasis and vitamin D in the pathogenesis of acute pancreatitis and assess the severity of its course. We examined 72 people, who were divided into two groups: the first group (comparison group) - men and women without pathology of the gastrointestinal tract and any other conditions or diseases that could affect the state of calcium-phosphorus metabolism (n = 36) and the second group (main group) - patients with acute pancreatitis (n = 36). Additionally, patients in the main group were divided into two subgroups: the first subgroup included patients with severe disease (n = 18), and the second (n = 18) - with mild and moderate disease. In patients with acute pancreatitis, the incidence of vitamin D deficiency (<20 ng/ml) was significantly higher than in the comparison group and was 72.2 and 5.6%, respectively (χ^2 = 33.1, 95% CI 46.1-79.2). The incidence of severe vitamin D deficiency (<10 ng/ml) in patients with severe acute pancreatitis was significantly higher than in patients with mild to moderate disease and was 55.6 and 5.6% respectively (χ^2 = 10.3, 95% CI 20.2-70.4). Hypocalcemia in terms of total calcium was registered probably more often in patients with severe acute pancreatitis - 61.1% than in patients with mild and moderate - 16.7% (χ^2 = 7.3, 95% CI 12.5-65.9). Patients with the lowest quartile of vitamin D and total calcium had a significantly more severe course of acute pancreatitis than those with the highest quartile. Thus, the content of vitamin D levels ≤13.28 ng/ml for patients with acute pancreatitis can be considered as a threshold at which severe disease is predicted is predicted, at the same time the level of calcium decrease correlates with an increase in the severity of acute pancreatitis, which can be considered a reliable criterion for the severity of the disease, however, significant changes in phosphorus metabolism are not identified.

Key words: acute pancreatitis; vitamin D; calcium; the severity of the disease.

INTRODUCTION

The incidence of acute pancreatitis is constantly growing both in Ukraine (up to 25 cases per 100,000 adults and up to 50 cases in children) and worldwide (from 4.6 to 100 cases per 100,000 population) [1]. The proportion of patients with severe disease is also increasing. Among a number of etiological factors in Ukraine and other Eastern European countries, the leading factor is alimentary (alcohol abuse - 17-65% of cases), the second place is occupied by gallstone disease (21-58% of cases) [2]. Other factors in the development of acute pancreatitis include mechanical damage to the pancreas (including iatrogenic genesis), hypertriglyceridemia, tissue ischemia (atherosclerotic vascular lesions), virsungolithiasis, chemotherapy (drug pancreatitis), hyperparathyroidism, etc. [3]. Focusing on primary and secondary hyperparathyroidism, it should be noted that the basis of this disease is a violation of calcium levels in the blood, but the mechanism of acute pancreatitis in this pathology has not been fully studied [4]. It is known that calcium is a powerful release of peptides that stimulate the secretion of the pancreas, as well as intracellular secondary stimulators of the synthesis and secretion of pancreatic enzymes [5]. However, according to other data, in severe forms of acute pancreatitis, hypocalcemia is observed [6].

Acute pancreatitis with a severe course is accompanied by a high risk of complications (up to 50%), mortality in which reaches 70% [7]. To date, many clinical and laboratory prognostic markers of adverse course of acute pancreatitis have been proposed. Aggravating factors for acute pancreatitis include age, duration of early multiple organ failure syndrome, severe obesity, hematocrit ≥47%, C-reactive protein ≥150 mg/l during the first 48 hours after hospitalization, but sensitivity and specificity indicators vary widely [8].

Thus, the search for new pathogenetic factors of acute pancreatitis, and screening methods for predicting the severity of the disease remains relevant. As mentioned above, the role of disorders of calcium-phosphorus metabolism in this process is still not fully defined and controversial [9]. At the same time, the role of vitamin D in the pathogenesis of acute pancreatitis and as a predictor of its complications, in general, is just beginning to be studied and needs further study, which, in fact, is the subject of this work.

The aim of this study was to determine the role of phosphorus-calcium homeostasis and vitamin D in the pathogenesis of acute pancreatitis and assess the severity of its course.

METHODS

The study was conducted by staff of the Department of Surgery No. 2 Bogomolets National Medical University and was approved by the Ethics Committee of the University (protocol No.141, 17.12.2020). All patients were examined during 2021 and signed informed consent to participate in this study and/or treatment at the clinic.

We examined 72 people aged 26-83 years, who were divided into two groups: the first group (comparison group) - men and women without gastrointestinal pathology and any other conditions or diseases that could affect the state of calcium-phosphorus metabolism (n = 36) and the second (main) group - patients with acute pancreatitis (n = 36). Patients of the first group were examined on an outpatient basis. All patients in the second group were hospitalized at the surgical clinic.

The diagnosis of acute pancreatitis in patients of the main group was established by the presence of two of the following three criteria: clinical (upper abdominal pain), laboratory (serum amylase or lipase level 3 times higher than the maximum normal value), imaging (CT, MRI, Ultrasound) criteria. The study used the classification proposed by the Acute Pancreatitis Classification Working Group and the International Association of Pancreatology/American Pancreatic Association in 2012 [14]. The severity of the course was determined using the APACHE II scale (severe course more than 8 points). The diagnosis of mild acute pancreatitis was established in the absence of reliable signs of pancreatic necrosis based on a typical set of clinical and laboratory data, moderate - the presence of transient multiorgan failure or local/systemic complications without organ failure, severe - in the presence of persistent multiorgan failure. According to the etiological factor, acute pancreatitis of alcoholic etiology occurred in 24 (66.7%) patients, and biliary pancreatitis - in 12 (33.3%) patients.

Exclusion criteria for both groups were any chronic disease affecting calcium-phosphorus metabolism, mental illness, recent surgery, glucocorticoids, calcium or vitamin D for 3 months before enrollment. Patients in the two groups did not differ significantly in age (51.8 ± 17.8 and 51.2 ± 18.1 old year; $P > 0.05$, respectively) and sex (men 86.1 and 83.3%, women 13.9 and 16.7%; $P > 0.05$, respectively). In addition, in order to determine the prognostic criteria for the severity of the disease, patients in the main group were divided into two subgroups. The first subgroup included patients with severe disease (n = 18), the second (n = 18) - with mild and moderate disease.

Blood sampling in patients of the comparison group was performed on an empty stomach, and in patients in the main group - during hospitalization before infusion therapy. Deter-

mination of total calcium, albumin, total phosphorus, and alkaline phosphatase in serum was performed on a biochemical automatic analyzer A15 ("BioSystems", Italy). The level of albumin-adjusted calcium was determined by the formula: Adjusted calcium (mmol/l) = total Ca (mmol/l) + 0.02 (40 - serum albumin [g/l]). Determination of vitamin D (25(OH)D) and parathyroid hormone was performed using the electrochemiluminescent method on the Cobas analyzer ("Roche Diagnostics", Germany).

Statistical analysis. The normality of data distribution was determined by the Shapiro-Wilk test. The difference between the groups was established using Student's t-test for independent samples. Differences in sample distribution were assessed using the χ^2 test criterion. Correlation analysis was performed using Pearson correlation for parametric and Spearman correlation for nonparametric data distribution. The relationship between the indicators was determined using ROC analysis and odds ratio. The results are presented as means and their standard deviation (M ± SD). Differences between indicators were considered significant at $P < 0.05$.

Statistical analysis was performed using Statistica 10, IBM SSPS Advanced Statistics 22.0, and MEDCALC® (open-source Internet resource, https://www.medcalc.org/calc/).

RESULTS

Changes in phosphorus-calcium homeostasis and levels of vitamin D in individuals of both groups are shown in Table 1. The incidence of vitamin D deficiency (<20 ng/ml) in patients with acute pancreatitis was significantly higher than in the comparison group and was 72.2 and 5.6%, respectively ($\chi^2 = 33.1$, 95% CI 46.1–79.2, $P < 0.0001$). Optimal vitamin D content (>30 ng/ml) was reported in only two (5.6%) patients with acute pancreatitis. Albumin, total, and albumin-corrected calcium levels were significantly lower, parathyroid hormone levels did not differ significantly and alkaline phosphatase levels were significantly higher than in the patients of the comparison group.

The division of patients with acute pancreatitis according to the severity of the course showed that the incidence of severe vitamin D deficiency (<10 ng/ml) in patients with severe acute pancreatitis was probably higher than in patients with mild to moderate disease, and was 55.6 and 5.6%, respectively ($\chi^2 = 10.3$, 95% CI 20.2-70.4, $P = 0.001$). Significant changes were also found in total calcium and albumin, and the content of albumin-adjusted calcium and other indicators of calcium-phosphorus metabolism (alkaline phosphatase, phosphorus, parathyroid hormone) probably did not differ (Table 2).

Hypocalcemia in terms of total calcium was registered probably more often in patients with severe acute pancreatitis - 61.1% than in patients with mild and moderate - 16.7% ($\chi^2 = 7.3$, 95% CI 12.5-65, 9, $P < 0.05$), but the groups probably did not differ in terms of albumin-corrected calcium (16.7 and 11.1%).

Thus, a decrease in total calcium can be considered as a criterion for the severity of acute pancreatitis, but a significant decrease

Table 1. Indicators of phosphorus-calcium homeostasis and levels of vitamin D in both groups

Indexes	Rate	Comparison group (n = 36)	Main group (n = 36)	P
Total calcium, mmol/l	2.15-2.58	2.36 ± 0.09	2.17 ± 0.23	0.0001
Albumin, g/l	35-50	43.14 ± 3.25	31.87 ± 6.29	0.0001
Albumin-adjusted calcium, mmol/l	2.15-2.58	2.36 ± 0.09	2.32 ± 6.29	0.16
Vitamin D, ng/ml	30-50	29.44 ± 8.44	15.41 ± 8.09	0.001
Parathormone, pg/ml	15.0-65.0	49.22 ± 13.26	40.69 ± 23.62	0.06
Phosphorus, mmol/l	0.81-1.45	1.14 ± 0.023	1.08 ± 0.38	0.46
Magnesium, mmol/l	0.70-0.98	0.80 ± 0.04	0.82 ± 0.09	0.07

Table 2. Indicators of phosphorus-calcium homeostasis and levels of vitamin D levels in patients with acute pancreatitis with different degrees of severity

Indexes	Severe course (n = 18)	Mild and moderate course (n = 18)	P
Total calcium, mmol/l	2.08 ± 0.18	2.25 ± 0.24	0.03
Albumin, g/l	29.46 ± 6.42	34.29 ± 5.27	0.02
Albumin-adjusted calcium, mmol/l	2.28 ± 0.14	2.35 ± 0.17	0.09
Vitamin D, ng/ml	10.02 ± 4.69	20.81 ± 7.15	0.0001
Parathormone, pg/ml	39.95 ± 16.78	41.43 ± 29.44	0.85
Phosphorus, mmol/l	1.12 ± 0.28	1.05 ± 0.24	0.64
Magnesium, mmol/l	0.81 ± 0.10	0.83 ± 0.07	0.07

in albumin content leads to the retention of albumin-corrected calcium within the normative values, so patients do not develop hypocalcemia. This should be taken into account when deciding on additional calcium intake in such patients.

At the next stage, the dependence of the severity of acute pancreatitis (according to the APACHE II scale) on the content of total calcium (Fig. 1) and vitamin D (Fig. 2) was determined using quartile analysis.

Patients with the lowest total quartile of calcium were found to have a more severe course of acute pancreatitis than patients with the highest quartile. A similar situation is observed with the content of vitamin D. At the same time, the relationship between the content of calcium and vitamin D was not found, which indicates the independence of these predictors.

The next step in the study was to set a threshold value for serum vitamin D that can be used as a criterion for predicting the severity of acute pancreatitis. For this purpose, ROC analysis was used.

According to the results of the analysis, the area under the ROC curve (AUROC) is 0.907 (95% CI 0.807-0.99; P = 0.001), the cut-off point corresponds to 13.28 ng/ml, Yoden index 0.667, that is for patients with acute pancreatitis serum vitamin D level ≤13.28 ng/ml can be considered as a probable predictor of severe course (sensitivity 83.3%, specificity 94.4%).

DISCUSSION

According to a number of clinical studies, hypercalcemia is considered one of the leading

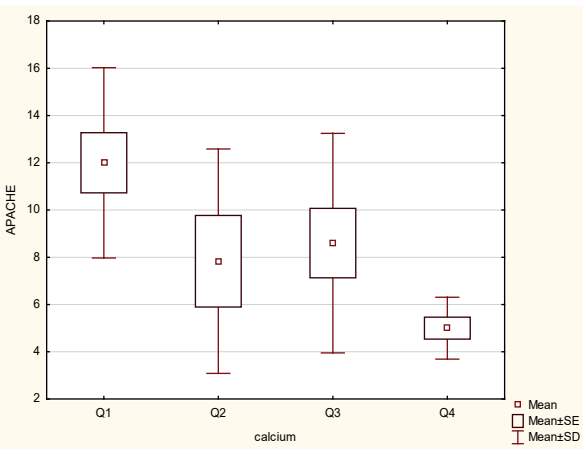

Fig. 1. The severity of acute pancreatitis in patients with different levels of total calcium (quartile distribution). Note: F = 4.8; P = 0.007

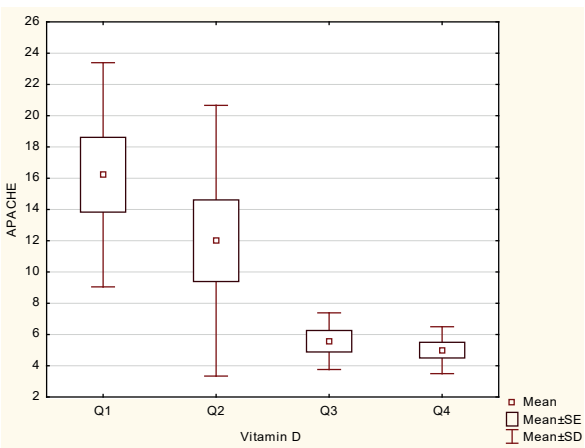

Fig. 2. The severity of acute pancreatitis in patients with different levels of vitamin D (quartile distribution). Note: F = 6.7; P = 0.001

factors in the development of acute pancreatitis, leading to exocytosis of proteins and enzymes [11, 12]. This trend is observed in most cases of the disease caused by a number of different causes (hypoxia, hyperlipidemia, pharmacological drugs with established dependence on the development of pancreatitis (tetracyclines, thiazides, etc.), alcohol) [13]. At the same time, serum calcium below 1.97 mmol/l is included as a criterion in most international scales for assessing the severity and prediction of acute pancreatitis with fairly high sensitivity (89.7%) [14].

We confirmed the development of hypocalcemia in severe disease, and also observed a direct correlation of this indicator with the APACHE II scoring system, as an important indicator of severe acute pancreatitis.

As for the relationship between the severity of acute pancreatitis and vitamin D content, the data accumulated today are quite controversial and even questionable [15]. At the same time, we found a direct link between vitamin D deficiency and acute pancreatitis. This trend was particularly pronounced in patients with severe disease, in whom the incidence of significant vitamin D deficiency (<10 ng/ml) was likely to be higher (55.6%) compared to patients with mild and moderate disease (5.6%) (χ^2 = 10.3, 95% CI 20.2-70.4, P = 0.001).

Modern approaches to the treatment of acute pancreatitis vary widely, but the main trend is the predominance of methods of complex conservative therapy over early surgery. It is clear that the choice of treatment for acute pancreatitis depends on a number of reasons: the clinical picture of the disease, methods of diagnosis and prediction of complications of acute pancreatitis, and the chosen tactics of the patient. Correct, objective and most importantly timely assessment of the severity of acute pancreatitis based on known assessment prognostic scales significantly affects the final results of comprehensive treatment of patients. The effectiveness of different methods varies widely. Thus, the sensitivity and specificity of the Ranson scale are 88.6 and 91.4%, and the most common scale and the popular APACHE II scale are 70.4 and 92.6%, respectively [16].

The results of reducing the level of vitamin D in the serum of patients with acute pancreatitis indicate that this indicator can be used as a criterion for assessing the severity of the disease. Reducing the level of vitamin D in the serum of patients below 13.28 ng/ml can predict the severe course of acute pancreatitis (sensitivity of the method is 83.3% and specificity - 94.4%), timely start the comprehensive treatment of patients, which will prevent fatal complications of acute pancreatitis.

CONCLUSIONS

It was found that the incidence of vitamin D deficiency (<20 ng/ml) in patients with acute pancreatitis was significantly higher than in virtually healthy individuals (72.2 and 5.6%, respectively) (χ^2 = 33.1, 95% CI 46.1-79.2, P < 0.0001).

In patients with severe acute pancreatitis, the incidence of severe vitamin D deficiency (<10 ng/ml) was significantly higher than in patients with moderate to mild disease (55.6 and 5.6%, respectively) (χ^2 = 10.3, 95% CI 20.2-70.4, P = 0.001).

Hypocalcemia is more common in individuals with severe acute pancreatitis (χ^2 = 7.3, 95% CI 12.5-65.9, P < 0.05), the level of calcium decrease correlates with an increase in the severity of acute pancreatitis, which can be considered a reliable criterion for the severity of the disease, however, significant changes in phosphorus metabolism are not identifiad.

Serum vitamin D levels ≤13.28 ng/ml for patients with acute pancreatitis can be considered as a threshold at which a severe course of the disease is predicted (sensitivity 83.3%, specificity 94.4%).

The work was performed in accordance with the plan of research work of the Department of Surgery No. 2 of Bogomolets National Medical University: "Development and implementation of methods for

diagnosis and treatment of surgical pathology of the abdominal cavity and blood circulation". The authors did not receive additional financial support.

The authors of this study confirm that the research and publication of the results were not associated with any conflicts regarding commercial or financial relations, relations with organizations and/or individuals who may have been related to the study, and interrelations of co-authors of the article.

І.В. Колосович, І.В. Ганоль

РОЛЬ ФОСФОРНО-КАЛЬЦІЄВОГО ОБМІНУ ТА ВІТАМІНУ D У ПАТОГЕНЕЗІ ГОСТРОГО ПАНКРЕАТИТУ

Національний медичний університет імені О.О. Богомольця, Київ; e-mail: ganoli@ukr.net

Вивчали роль показників фосфорно-кальцієвого обміну та вітаміну D у патогенезі гострого панкреатиту та оцінці тяжкості його перебігу. Було обстежено 72 особи, яких розділили на дві групи: перша група (група порівняння) – чоловіки та жінки без патології шлунково-кишкового тракту (n = 36) та друга (основна) група – хворі на гострий панкреатит (n = 36). Додатково пацієнти основної групи були розділені на дві підгрупи. До першої підгрупи ввійшли пацієнти з тяжким перебігом захворювання (n = 18), до другої (n = 18) – з легким та середньої тяжкості перебігом. У пацієнтів з гострим панкреатитом частота дефіциту вітаміну D (<20 нг/мл) була вірогідно вищою, ніж у осіб групи порівняння, і становила 72,2 та 5,6% відповідно (χ^2 = 33,1, 95% ДІ 46,1–79,2). Частота вираженого дефіциту вітаміну D (<10 нг/мл) у пацієнтів з тяжким ступенем гострого панкреатиту була вірогідно вищою, ніж у пацієнтів з легким та середнім перебігом захворювання, і сягала 55,6 та 5,6% відповідно (χ^2 = 10,3, 95% ДІ 20,2–70,4). Гіпокальціємія за вмістом загального кальцію реєструвалася вірогідно частіше у пацієнтів з тяжким перебігом гострого панкреатиту – 61,1%, ніж у пацієнтів з легким та середнім – 16,7% (χ^2 = 7,3, 95% ДІ 12,5–65,9). У пацієнтів з найнижчим квартилем вітаміну D та кальцію загального вірогідно більш тяжкий перебіг гострого панкреатиту, ніж у пацієнтів з найвищим квартилем. Таким чином вміст вітаміну D у сироватці крові ≤13,28 нг/мл для пацієнтів на гострий панкреатит можна розглядати, як пороговий показник, при якому прогнозується тяжкий перебіг захворювання, при цьому зниження вмісту кальцію корелює зі зростанням тяжкості гострого панкреатиту. Це може вважатися достовірним критерієм тяжкості перебігу захворювання, проте суттєвих змін з боку фосфорного обміну не визначається..

Ключові слова: гострий панкреатит; вітамін D; кальцій; тяжкість перебігу.

REFERENCES

1. Petrov MS, Yadav D. Global epidemiology and holistic prevention of pancreatitis. Nat Rev Gastroenterol Hepatol. 2019 Mar;16(3):175-84.
2. Roberts SE, Morrison-Rees S, John A, Williams JG, Brown TH, Samuel DG. The incidence and aetiology of acute pancreatitis across Europe. Pancreatology. 2017 Mar-Apr;17(2):155-65.
3. Rawla P, Bandaru SS, Vellipuram AR. Review of infectious etiology of acute pancreatitis. Gastroenterol Res. 2017;10(3):153-8.
4. Misgar RA, Bhat MH, Rather TA, Masoodi SR, Wani AI, Bashir MI, Wani MA, Malik AA. Primary hyperparathyroidism and pancreatitis. J Endocrinol Invest. 2020 Oct;43(10):1493-8.
5. Thareja S, Manrai M, Shukla R, Kumar Sood A, Jha A, Tyagi AK, Upreti V, Gahlot GPS, Maggo S. Pancreatitis and hyperparathyroidism: Still a rare association! Med J Armed Forces Ind. 2019 Oct;75(4):444-9.
6. Ahmed A, Azim A, Gurjar M, Baronia AK. Hypocalcemia in acute pancreatitis revisited. Ind J Crit Care Med. 2016 Mar;20(3):173-7.
7. Kolosovych IV, Hanol IV. Hemocoagulation factors of hemorrhagic complications in acute pancreatitis. Fiziol Zh. 2022;68(1):56-61. [Ukrainian].
8. Silva-Vaz P, Abrantes AM, Morgado-Nunes S, Castelo-Branco M, Gouveia A, Botelho MF, Tralhão JG. Evaluation of prognostic factors of severity in acute biliary pancreatitis. Int J Mol Sci. 2020 Jun 16; 21(12):4300.
9. Chhabra P, Rana SS, Sharma V, Sharma R, Bhasin DK. Hypocalcemic tetany: a simple bedside marker of poor outcome in acute pancreatitis. Ann Gastroenterol. 2016 Apr-Jun;29(2):214-20.
10. Wu D, Lu B, Xue HD, Lai YM, Qian JM, Yang H. A comparison between the revision of Atlanta classification and determinant-based classification in acute pancreatitis. Zhonghua Nei Ke Za Zhi. 2017 Dec 1;56(12):909-13.
11. Pallagi P, Madácsy T, Varga Á, Maléth J. Intracellular Ca^{2+} Signalling in the pathogenesis of acute pancreatitis: Recent advances and translational perspectives. Int J Mol Sci. 2020 Jun 3;21(11):4005.
12. Chvanov M, Voronina S, Zhang X, Telnova S, Chard R, Ouyang Y et al. Knockout of the mitochondrial calcium uniporter strongly suppresses stimulus-metabolism coupling in pancreatic acinar cells but does not reduce severity of experimental acute pancreatitis. Cells. 2020 Jun 5;9(6):1407.
13. Li H, Wen W, Luo J. Targeting endoplasmic reticulum stress as an effective treatment for alcoholic pancreatitis. Biomedicines. 2022 Jan 5;10(1):108.
14. Peng T, Peng X, Huang M, Cui J, Zhang Y, Wu H, Wang C. Serum calcium as an indicator of persistent organ failure in acute pancreatitis. Am J Emerg Med. 2017 Jul;35(7):978-82.
15. Li X, Gan X, Gong J, Mou T, Zhou H, Li M. Association

between vitamin D receptor polymorphisms and acute pancreatitis: A protocol for systematic review and meta analysis. Medicine (Baltimore). 2021 Apr 23;100(16):e25508.
16. Chatterjee R, Parab N, Sajjan B, Nagar VS. Comparison of Acute Physiology and Chronic Health Evaluation II, Modified Computed Tomography Severity Index, and Bedside Index for Severity in Acute Pancreatitis Score in Predicting the Severity of Acute Pancreatitis. Ind J Crit Care Med. 2020 Feb;24(2):99-103.

Received 02.02.2022