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VITAMIN D METABOLISM DISORDERS IN PATIENTS WITH CHRONIC PANCREATITIS WITH CONCOMITANT CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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Abstract

Background. *The comorbid progression of chronic pancreatitis (CP) and chronic obstructive pulmonary disease (COPD) is characterized by chronic systemic inflammation, oxidative stress, and the advancement of structural and functional impairments. These factors can adversely affect vitamin D and calcium homeostasis. Vitamin D deficiency is considered a contributing factor to heightened inflammatory responses, disruptions in mineral metabolism, and the progression of exocrine pancreatic insufficiency.* ***Objective.*** *To investigate the characteristics of vitamin D homeostasis in cases of comorbid CP and COPD compared to the isolated progression of these diseases.* ***Materials and Methods.*** *A total of 145 patients were examined, including 35 with COPD, 35 with CP, and 75 with combined CP and COPD.* ***Study Results.*** *The most significant disruptions in vitamin D and calcium homeostasis were observed in patients with comorbid CP and COPD. The concentration of 25(OH)D was lower than the levels in practically healthy individuals by 24.8% in COPD, 54.4% in CP, and 75.2% with combined CP and COPD ($p<0.05$). Total and ionized calcium content was also lowest in the comorbid group by 13.3% and 14.3%, respectively ($p<0.05$). The highest intensity of systemic inflammation was seen in patients with both CP and COPD, as indicated by 21.5 times increase in C-reactive protein levels compared to healthy individuals ($p<0.05$). Exocrine pancreatic insufficiency was more pronounced in patients with the combined progression of the diseases, evidenced by a twofold reduction in fecal elastase-1 levels ($p<0.05$). A strong inverse correlation was found between 25(OH)D concentration and C-reactive protein levels ($r=-0.68$; $p<0.05$), and a strong direct correlation between 25(OH)D levels and fecal elastase-1 ($r=0.79$; $p<0.05$).* ***Conclusions.*** *The comorbid progression of CP and COPD is associated with the most pronounced vitamin D deficiency and disruption of calcium homeostasis, accompanied by increased systemic inflammation and advancement of exocrine pancreatic insufficiency. The identified correlations suggest the utility of measuring 25(OH)D levels as an additional laboratory marker for systemic inflammation activity and pancreatic functional status, emphasizing the need for routine monitoring of vitamin D sufficiency and calcium metabolism indicators in patients with comorbid CP and COPD.*

Key words: *chronic pancreatitis, chronic obstructive pulmonary disease, vitamin D, calcium, systemic inflammation.*

1. Introduction

The study of vitamin D homeostasis in patients with chronic pancreatitis (CP) and exocrine pancreatic insufficiency with comorbid chronic obstructive pulmonary disease (COPD) is highly significant due to the interconnected disruptions in vitamin D metabolism, malabsorption, and chronic inflammation. In patients with CP, the deficiency of pancreatic lipase and bicarbonate secretion creates conditions for malabsorption of fat-soluble vitamins, particularly vitamin D. A deficiency of this vitamin (25(OH)D level <20 ng/mL) is observed in 60–90% of patients with exocrine pancreatic insufficiency [1–3]. Recent research using precise methods to assess 25(OH)D levels highlights the pathological mechanisms affecting vitamin absorption [4].

In patients with COPD, the role of vitamin D is examined not only in terms of calcium metabolism but also as a crucial immunomodulator. It reduces the production of pro-inflammatory cytokines (IL-6, TNF-α) and enhances the expression of antimicrobial peptides, including cathelicidins, in the respiratory tissues, which is vital for managing infectious exacerbations in COPD [5]. Vitamin D deficiency in CP patients can worsen the course of COPD, increasing the frequency and severity of infectious exacerbations [6, 7].

Clearly, the effectiveness of vitamin D replacement therapy remains a significant question. Current studies show that standard doses of cholecalciferol often fail to achieve optimal 25(OH)D levels in patients with CP with exocrine pancreatic insufficiency, mainly due to impaired absorption and increased vitamin metabolism caused by chronic inflammation and oxidative stress [8]. Therefore, dynamic monitoring of 25(OH)D levels and personalized vitamin D3 dosing, alongside enzyme replacement therapy, are crucial for improving calcium metabolism, maintaining bone health, enhancing pulmonary function (specifically FEV1), and reducing systemic inflammation.

Further investigation into effects of vitamin D opens new avenues for developing personalized nutritional support protocols that substantially decrease disability in patients with CP with exocrine pancreatic insufficiency, and COPD.

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The mechanisms by which vitamin D impacts lung tissue include acting as both a nutrient and a hormone through specific vitamin D receptors (VDR) in respiratory epithelial cells and type II alveolocytes, exerting a multifactorial beneficial impact on the lungs [9]. Cholecalciferol stimulates the differentiation of these cells, supporting lung tissue elasticity and integrity, which is critical during the progressive changes seen in COPD [10].

Anti-inflammatory effects of vitamin D are achieved by inhibiting the transcription factor kappa-B (NF-kB), thereby reducing the production of pro-inflammatory cytokines such as IL-6, IL-8, and TNF-α, thus alleviating chronic bronchial inflammation [11]. It also activates genes encoding antimicrobial peptides (cathelicidin LL-37, defensins), which protect the respiratory system against bacterial infections [12]. Chronic deficiency of this vitamin increases the risk of bacterial COPD exacerbations and accelerates obstructive disease progression.

An additional protective mechanism involves inhibiting bronchial remodeling by slowing fibroblast and smooth muscle cell proliferation in the bronchi, preventing irreversible obstruction [13]. The combination of CP with exocrine pancreatic insufficiency and COPD creates a "double hit" effect: limited vitamin D intake due to malabsorption coincides with its increased utilization in response to systemic inflammation and heightened oxidative stress. This requires a comprehensive approach to diagnosis and personalized treatment.

Objective of the study – to explore vitamin D homeostasis characteristics among comorbid CP and COPD compared to the isolated occurrence of these diseases.

2. Materials and methods

145 patients were examined, including 35 with COPD (GOLD II-III), group E, 35 with CP of mixed etiology in the acute phase, and 75 with CP of mixed etiology in moderate acute phase with comorbid COPD (GOLD II-III), group E. The average age was 45.7±6.3 years. The control group consisted of 30 practically healthy individuals of equivalent age and gender.

The diagnosis of CP was established according to the unified clinical protocol approved by the order of the Ministry of Health of Ukraine No. 638 dated September 10, 2014. "On approval and implementation of medical and technological documents for the standardization of medical care in chronic pancreatitis" based on classical clinical, ultrasonographic, biochemical methods, taking into account the Order of the Ministry of Health of Ukraine No. 1204 dated July 4, 2023. "On approval of the Unified Clinical Protocol for Primary and Specialized Medical Care "Chronic Pancreatitis".

Diagnosis and treatment of COPD was carried out in accordance with the recommendations of clinical guidelines (Order of the Ministry of Health of Ukraine No. 555 dated 27.06.2013. taking into account the Adapted Evidence-Based Clinical Guidelines: Chronic Obstructive Pulmonary Disease, 2020). Belonging to groups A, B, E of COPD patients was assessed according to the COPD severity assessment scale according to the AVE (GOLD 2023).

The morphological state of the pancreas was assessed by ultrasonography on the Aloka SS-630 device (Japan). The functional state of the exocrine part of the pancreas was verified by quantitative determination of fecal elastase-1 (ELISA, BIOSERV Diagnostics). The content of total vitamin D (25-OH) in blood serum was examined by enzyme-linked immunosorbent assay. To assess mineral metabolism, the relative ionized calcium content (RICC) index was calculated, which reflects the percentage of the active Ca(i) fraction in the structure of total serum calcium.

The RICC coefficient was calculated using the formula:

$$\mathrm{RICC} = \frac{\mathrm{Ca(i)}}{\mathrm{Ca}} \times 100\,\%$$

where: Ca(i) is ionized calcium;
Ca is total calcium.

The study used data on the content of C-reactive protein (CRP) in the blood, the content of elastase-1 in feces according to generally accepted methods.

Statistical analysis of the results was performed in accordance with the type of study and the type of numerical data obtained. The normality of the distribution was checked using the Liliefors, Shapiro-Wilk tests and the method of direct visual assessment of histograms of the distribution of eigenvalues. Quantitative indicators that had a normal distribution are presented in the form of the arithmetic mean (M) and standard deviation (SD), discrete values – in the form of absolute and relative frequencies (percentage of observations to the total number of examined). For comparisons of data that had a normal distribution, parametric tests with the assessment of the Student' t-test or Fisher's F-test were used. The difference $p < 0.05$ was considered statistically significant. To assess

the degree of dependence between variables, Pearson correlation analysis was used in the case of parametric distribution and Spearman rank correlation coefficient in the case of non-normal distribution of indicators. Statistical and graphical processing of the obtained results was performed using the StatSoft Statistica 10.0.1011 Enterprise edition (Stat Soft inc., USA), Microsoft Excel 2007 (Microsoft, USA) software packages.

3. Results and discussion

The analysis of indicators of vitamin D and calcium homeostasis proved that the most pronounced disturbances were observed in patients with a comorbid course of CP and COPD. The concentration of 25(OH)D in blood serum was significantly lower compared to practically healthy individuals in all study groups: by 24.8% in patients with COPD, by 54.4% in patients with COPD, and by 75.2% in the combination of CP and COPD ($p<0.05$). The greatest decrease in the level of vitamin D was found precisely in comorbid pathology, which is probably caused by a combination of malabsorption of fat-soluble vitamins and chronic systemic inflammation (Fig. 1).

Changes in calcium homeostasis were also most pronounced in patients with comorbidities. The level of total calcium in COPD patients improbably decreased by 2.7% ($p>0.05$), while in isolated CP it was lower than control values by 9.0% ($p<0.05$), and in combined CP and COPD by 13.3% ($p<0.05$) (Fig. 2).

Similar changes were established for ionized calcium. In patients with COPD, no significant differences from the control group were found, while in CP its concentration was lower by 10.3% ($p<0.05$), and in comorbid course – by 14.3% ($p<0.05$), which was also significantly different from the indicators of groups of isolated diseases (Fig. 3).

At the same time, the relative content of free ionized calcium remained practically unchanged (48–51%) and did not differ from the indicators of practically healthy individuals, which indicates the preservation of the ratio between calcium fractions even under the conditions of a general decrease in its concentration (Fig. 4).

Assessment of the intensity of systemic inflammation showed a significant increase in the level of C-reactive protein in all studied groups. In patients with CP, the concentration of CRP exceeded the control values by 13.3 times, in patients with COPD – by 17.2 times, while with comorbidity of CP and COPD – by 21.5 times ($p<0.05$), which indicates the maximum activity of systemic inflammation precisely in the combined course of the diseases (Fig. 5).

A more pronounced increase in the content of CRP in the blood of patients with COPD and the maximum in patients with COPD and CP indicates the portion of COPD in the increase of this indicator.

The state of the exocrine function of the pancreas was assessed by the level of fecal elastase-1. In patients with CP, its concentration was lower than the normative values by 1.3 times ($p<0.05$), while when CP was combined with COPD, it was 2.0 times ($p<0.05$), which indicates the progression of exocrine insufficiency of the pancreas in conditions of comorbidity (Fig. 6).

Correlation analysis established a strong inverse correlation between the concentration of 25(OH)D and the level of C-reactive protein ($r=-0.68$, $p<0.05$), as well as a strong direct relationship between the content of vitamin D and the level of fecal elastase-1 ($r=0.79$, $p<0.05$). The obtained results indicate that vitamin D deficiency is associated both with an increase in systemic inflammation and with a deterioration of the exocrine function of the pancreas. In patients with a comorbid course of CP and COPD, vitamin D deficiency is caused by the combined effect of interrelated mechanisms: impaired intestinal absorption due to exocrine pancreatic insufficiency and increased consumption in response to chronic systemic inflammation.

The obtained results confirm that the combination of CP and COPD is accompanied by more pronounced disturbances of vitamin D homeostasis compared to the isolated course of each of the diseases. Presumably, this is due to the simultaneous action of two pathogenetic mechanisms. The first consists in impaired absorption of fat-soluble vitamins as a result of progressive exocrine insufficiency of the pancreas and pancreatic lipase deficiency, which is consistent with current literature data [14]. The second mechanism is associated with chronic systemic inflammation, characteristic of COPD and CP, which is accompanied by increased use of vitamin D as one of the regulators of the immune response.

The revealed inverse relationship between the concentration of vitamin D and the level of C-reactive protein is consistent with modern ideas about its immunomodulatory properties. It is known that active metabolites of vitamin D suppress the synthesis of pro-inflammatory cytokines, in particular TNF-α, IL-6 and IL-1β, and thus limit the intensity of the systemic inflammatory response [15].

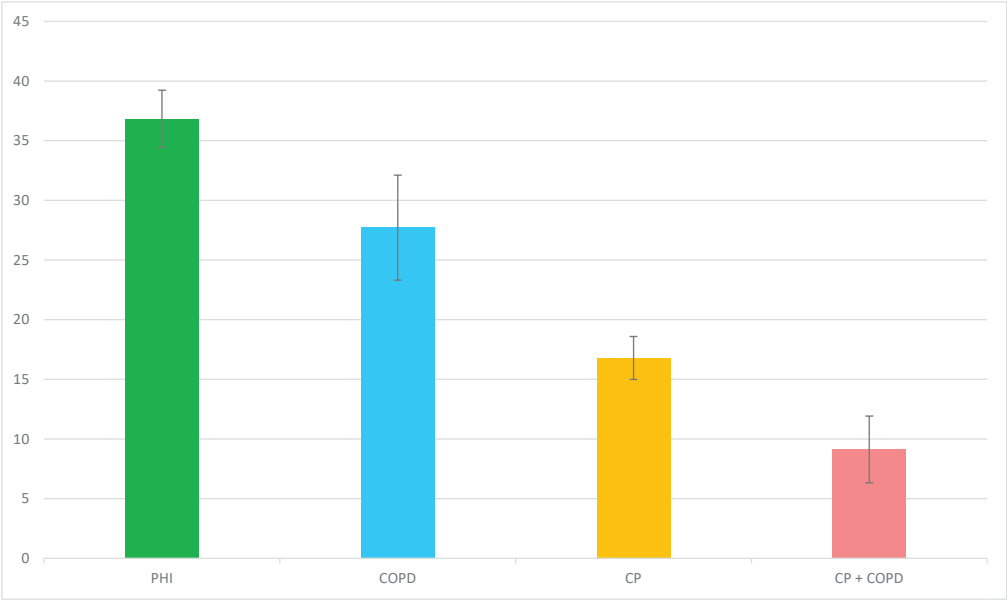


Fig 1. Vitamin D blood content, ng/ml

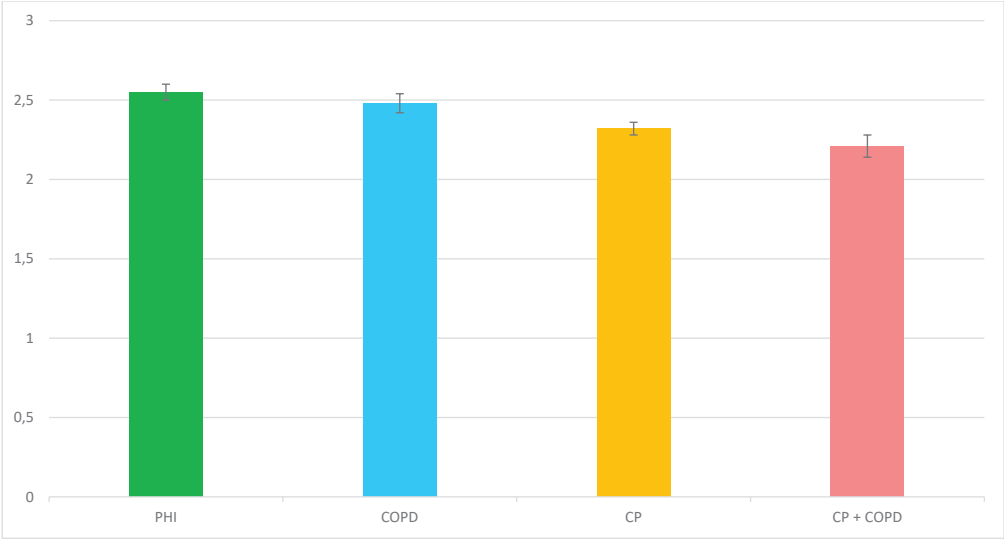


Fig 2. Blood calcium content, mmol/l

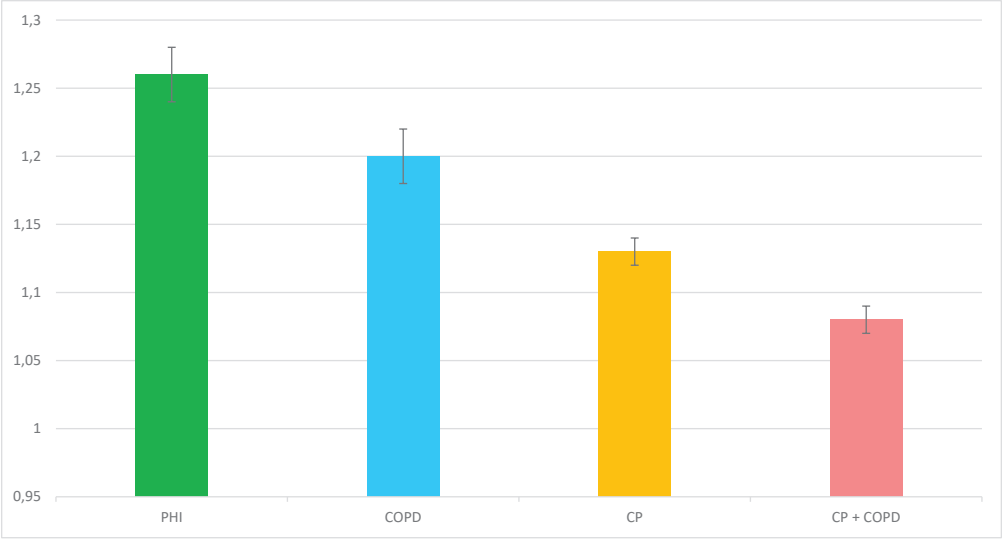


Fig 3. Blood ionized calcium content, mmol/l

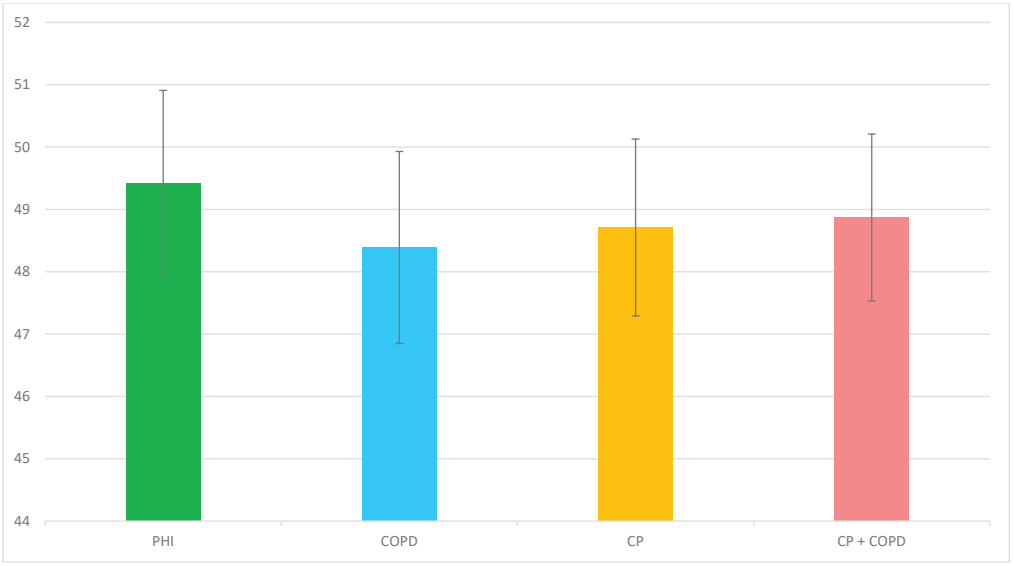


Fig 4. Relative ionized calcium content, %

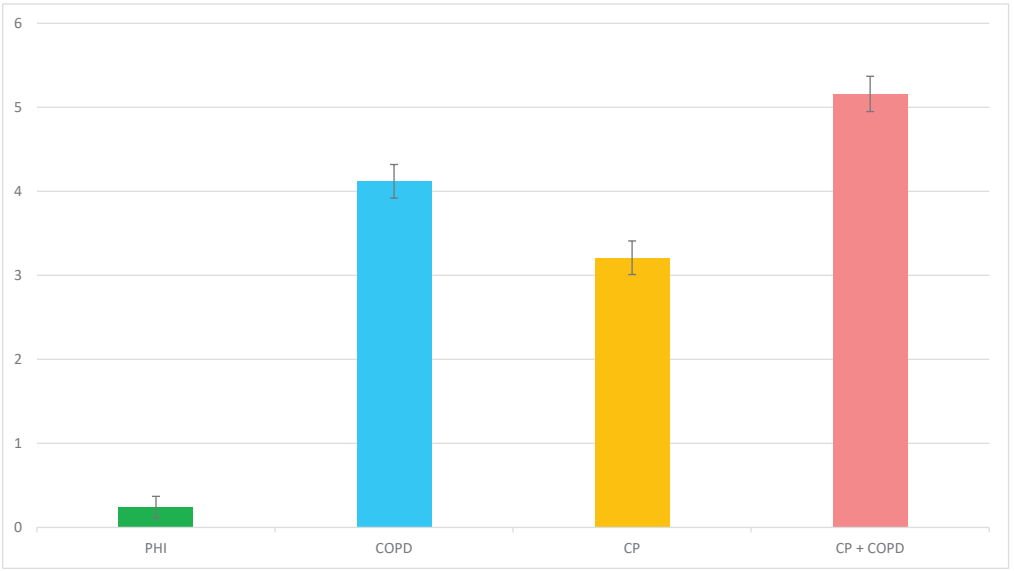


Fig 5. Blood C-reactive protein content, mg/l

No less important is the established direct correlation between the level of 25(OH)D and the concentration of fecal elastase-1. These results indicate that the deterioration of the exocrine function of the pancreas is accompanied by a progressive deficiency of vitamin D, and its deficiency, in turn, can negatively affect the functional state of acinar cells and support structural changes in the tissue of the pancreas [16].

Thus, the level of 25(OH)D can be considered not only as an indicator of the body's supply of vitamin D, but also as a potential laboratory marker of the activity of systemic inflammation and the degree of pancreatic exocrine insufficiency in patients with a comorbid course of CP and COPD. The obtained results justify the expediency of routine determination of 25(OH)D and ionized calcium concentration in this category of patients for timely detection of mineral metabolism disorders and their subsequent correction.

4. Conclusions

Patients with chronic pancreatitis have a significant deficiency of vitamin D in the blood, which reliably increases in comorbidity of chronic pancreatitis with chronic obstructive pulmonary disease, contributes to calcium metabolism disorders and is strongly correlated with the increase in the intensity of systemic inflammation and the degree of exocrine pancreatic insufficiency.

Prospects for further research. Further studies should focus on the treatment of vitamin D metabolism disorders associated with exocrine

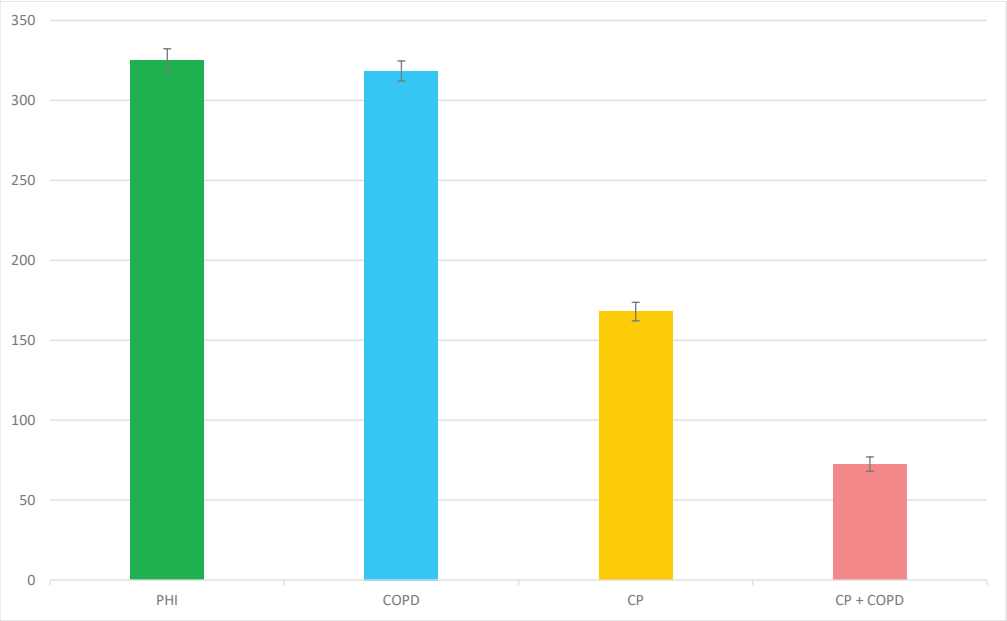


Fig 6. Fecal elastase-1 content, µg/l

pancreatic insufficiency in patients with chronic pancreatitis and comorbid chronic obstructive pulmonary disease.

Conflict of interest

The authors declare that they have no conflict of interest.

Use of artificial intelligence

An artificial intelligence tool was used to check grammar and edit the style of the manuscript during preparation of the article. The use of artificial intelligence was limited to text editing and did not affect the interpretation of the scientific data, the formulation of the conclusions, or the substantive content of the study.

Primary data and materials

The primary data of the study are retained by the authors and may be provided upon reasonable request, subject to confidentiality requirements and ethical standards regarding the personal data of the study participants.

Financing

The study was conducted without specific financial support.

Authors' contribution

Inna Dudka: data analysis and interpretation, writing of the article. Oksana Khukhlina: study concept and design, final approval of the article. Tetiana Dudka: data collection, editing of the article.

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