ORIGINAL ARTICLE

CONTENTS

Consideration and analysis of exocrine pancreatic insufficiency in assotiative pathology of the digestive tract, unresolved issues

Olesya M. Horlenko, Lyubomyra B. Prylypko, Bohdan M.Halay, Fedir V. Horlenko, Halyna M.Beley, Lyubov A. Halay, Volodymyr M. Bilak
UZHHOROD NATIONAL UNIVERSITY, UZHHOROD, UKRAINIAN

ABSTRACT

Aim: To identify and analyze the patterns of exocrine insufficiency development in patients with assotiative pathology of the digestive tract and its relationship with homeostasis disorders depending on the degree of insufficiency.

Materials and Methods: The total number of patients is 135, aged 50.7±6.2 years, with a diagnosis of Chronic pancreatitis (CP), remission phase with exocrine insufficiency in assotiation with Metabolic-associated steatotic liver disease (MASLD) and gastroesophageal reflux disease (GERD). The divided of patients into groups was based on determining the degree of exocrine pancreatic insufficiency according to the results of the level of fecal elastase-1(FE-1):

Results: In the studied children of the first group, significant differences (p1=0.01-<0.001) were observed in the levels of biochemical indicators, except the values of AST and creatinine levels. Significant intergroup differences were found among the indicators of vitamin D3 (p1<0.001; p2=0.001; p3<0.001), folic acid (p1<0.001; p2<0.001; p3<0.001), Zn (p1=0.001; p2=0.001; p3<0.001), Se (p1<0.001; p2<0.001; p3<0.001) and partly, Na (p1=0.02;) Ca (p2=0.002; p3=0.001), Cl(p3=0.04).

Conclusions: The highest communicative correlations in children of the first group were found for the vitamin D3 level with FE-1 (r=0.64) and fibrinogen in a negative direction (r=-0.30). The value of α1-antitrypsin was correlated in the first group with the minerals Ca (-0.30 at p=0.006), FE-1 (r=-0.26 at p=0.02), while in the second group there was a predominance of communications with inflammatory markers ALT (r=-0.30 at p=0.03), AST (r=-0.29 at p=0.04).

KEY WORDS: exocrine pancreatic insufficiency, Metabolic-associated steatotic liver disease, gastroesophageal reflux disease, correlation, patient

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INTRODUCTION

Chronic pancreatitis is caused by recurrent episodes of inflammation that eventually progress to fibrosis. As a result, both endocrine and exocrine pancreatic functions may be impaired.[1] Proposed mechanisms include theories of toxic metabolism, oxidative stress, obstructive and necrotizing-fibrotic infections.[2,3] The pancreas is a unique organ with a dual function, both endocrine and exocrine. Historically, these two functions have often been studied independently. However, emerging evidence suggests that the complex crosstalk between endocrine and exocrine components plays a critical role in maintaining pancreatic function and has significant implications for various diseases.[4]

Normally, when chyme reaches the duodenum, both secretin and cholecystokinin stimulate the secretion of approximately 1.5 liters of pancreatic fluid, which contains pancreatic enzymes (amylase, lipase, and protease), water, and ions (bicarbonate and phosphate). These enzymes are essential for digestion in the small intestine.[5] Pancreatic insufficiency is often results from impair acinar cell function conditions, which reducing the production of digestive enzymes.[6] Exocrine pancreatic insufficiency (EPI) has long been considered to result from a secretory deficiency of pancreatic enzymes and/or bicarbonate.[7]

As a result, EPI has been observed almost exclusively in the context of pancreatic diseases, mainly chronic pancreatitis (CP) and cystic fibrosis (CF), and more recently, pancreatic cancer (PC) or after pancreatic resection. The first evidence-based guidelines using the Oxford System or the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system to address EPI in the context of CP were published in 2012. [8] Following an award from the United European Gastroenterology (UEG), the first European guidelines were developed and published in 2017 [9].

It has recently been noted that there is a paucity of studies on EPI in the general population and in patients

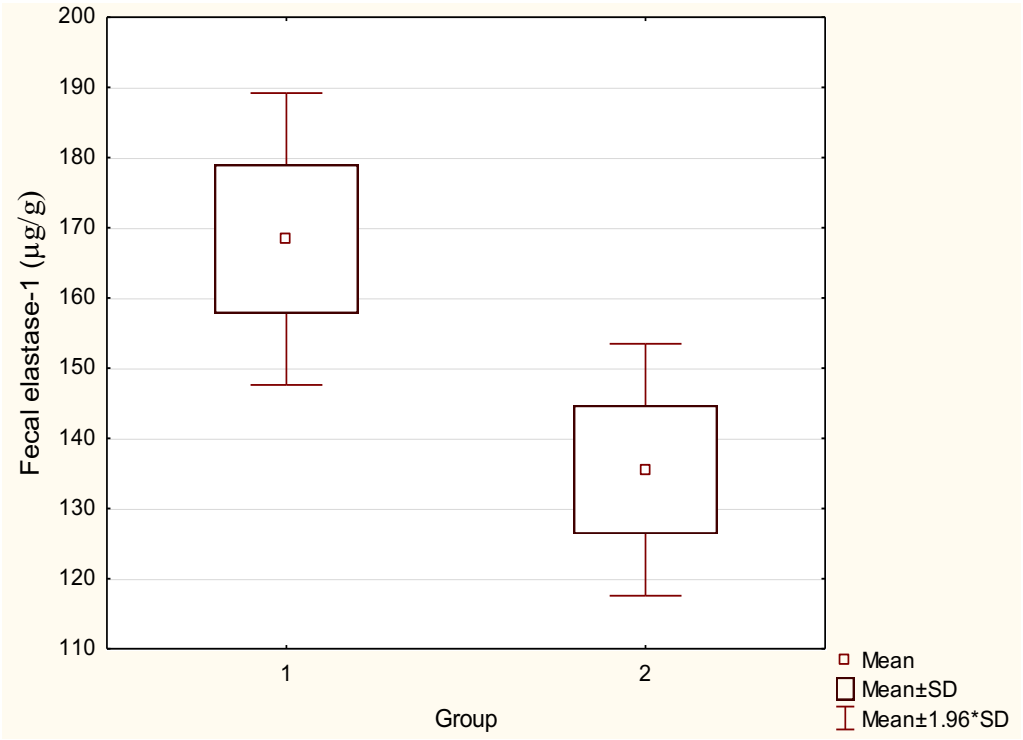

Fig. 1. Gender distribution of patients
Picture taken by the authors

with non-pancreatic diseases, although the number of relevant publications is increasing[10,11].

AIM

The aim is to identify and analyze the patterns of exocrine insufficiency development in patients with assotiative pathology of the digestive tract and its relationship with homeostasis disorders depending on the degree of insufficiency.

MATERIALS AND METHODS

The total number of patients was 135, aged 50.7±6.2 years, diagnosed with Chronic pancreatitis (CP), remission phase with exocrine insufficiency in assotiation with Metabolic-associated steatotic liver disease (MASLD) and gastroesophageal reflux disease (GERD). The divided of patients into groups was based on the determination of the degree of exocrine pancreatic insufficiency according to the results of the level of fecal elastase-1:

Group 1 (n=85) – patients with mild exocrine pancreatic insufficiency (FE-1= 168.40 ± 10.61 µg/g of feces).

Group 2 (n=50) – patients with moderate grade of exocrine pancreatic insufficiency (FE-1 = 135.52 ± 9.16 µg/g of feces) (Fig. 1).

ETHICS

Written informed consent was obtained from all participants. The study protocol was approved by the University Ethics Board of the State Higher Educational Institution "UzhNU". All procedures were performed in accordance with the ethical standards of the Declaration of Helsinki.

RESULTS

Pancreatic exocrine insufficiency (PEI), defined by insufficient secretion of digestive enzymes, can develop in the setting of metabolic dysfunction even in the absence of overt pancreatic pathology [12]. MASLD is now the most common illness of chronic liver disease in the worldwide. Although the consequences of MASLD on the liver are well documented, its impact on pancreatic function remains poorly understood.

Recent studies have demonstrated a pathophysiological crosstalk between pancreatic dysfunction and hepatic steatosis. FE-1) is a widely accepted noninvasive biomarker for the diagnosis of exocrine insufficiency. A level below 200 µg/g is indicative of exocrine dysfunction [13,14].

Understanding the development and prevalence of metabolic correlates of pancreatic dysfunction in patients with MAFLD is important because the aforementioned pancreatic dysfunction may influenced on nutritional status, glycemic profile, and subsequent progression of liver disease. [15]

A serum biochemical study was performed to interpret the relationship between the results and the degree of exocrine insufficiency (EPI) (Table 1).

There are significant differences (p1=0.01-0.001) in the levels of indicators (total protein, total bilirubin, total

Table 1. Serum biochemical study in the patients

Parameters	Control group (n=23)	1 group (n=85)	2 group (n=50)	Statistical significance of the difference
Total protein , g/l	73.62 ± 3.89	68.60 ± 3.49	66.27 ± 2.91	p_1=0.001; p_2<0.001; p_3<0.001
Total Bilirubin, mkmol/l	10.82 ± 3.85	11.84 ± 6.34	16.02±12.11	p_1=0.01; p_2=0.46; p_3=0.05
AST, mkmol/l	0.44 ± 0.11	0.48 ± 0.20	0.56 ± 0.37	p_1=0.09; p_2=0.36; p_3=0.13
ALT, mkmol/l	0.66 ± 0.15	0.93 ± 0.46	1.05 ± 0.55	p_1=0.19; p_2=0.01; p_3=0.001
Creatinin, mkmol/l	93.59 ± 12.53	104.59 ± 27.89	102.88 ± 35.14	p_1=0.76; p_2=0.07; p_3=0.22
Total Cholosterol mlmol/l	4.25 ± 0.48	5.04 ± 1.11	5.60 ± 0.80	p_1=0.002; p_2=0.001; p_3<0.001
Triglycerides mlmol/l	1.31 ± 0.23	1.75 ± 0.44	1.99 ± 0.30	p_1<0.001; p_2<0.001; p_3<0.001

Notes: p_1 – statistical significance of the difference between the indicators of groups 1 and 2; p_2 – statistical significance of the difference between the indicators of group 1 and the control group; p_3 – statistical significance of the difference between the indicators of group 2 and the control group
Source: compiled by the authors of this study

cholesterol, triglycerides), in addition to the values of AST and creatinine, partly in the levels of total bilirubin and ALT, according to the data in table 1. It is noteworthy that there is a significant decrease in the level of total protein (p_2<0.001; p_3 <0.001) and an increase in total bilirubin in the 1st group of patients in 1.1 times and a significant increase in the 2nd group in 1.6 times (p3=0.05). The indicators level of the vitamin-mineral homeostasis is demonstrated on Table 2.

According to the stude results, which are presented on table II, there are significant differences between the indicators of Vitamin D3 (p1=0.001; p2=0.001; p3=0.001), folic acid ((p1=0.001; p2=0.001; p3=0.001), Zn (p1=0.001; p2=0.001; p3=0.001), Se (p1=0.001; p2=0.001; p3=0.001)) and partly Na (p1=0.02;) Ca (p2=0.002; p3=0.001), Cl (p3=0.04). No differences were found in the values of potassium levels. Significant decreases were noted in the levels of Vitamin D3 (1.1 and 1.6 times), folic acid (1.5 and 1.9 times), Zn (1.2 and 1.4), Se (1.3 and 1.6 times),

The study of inflammatory response markers is informative (Table 3).

A significant increase in the levels of all indicators of the organism's inflammatory response is observed, with a more pronounced in group 2, acording to the results of table III. It should be noted that all indicators varied within the reference values, except for IL-6. Also, the highest comparative values of the decrease were noted in the level of IL-6 (1.5 and 1.6 times, respectively, in the groups).

To identify patterns and indicators interdependencies of changes in the secretory function of the pancreas, a correlation analysis was conducted. The correlation communications of indicators in the first group of patients with mild exocrine pancreatic insufficiency are presented in Table 4.

The highest communicative correlations were found for the indicator Vitamin D3 with FE-1 (r=0.64, at p=0.001) and fibrinogen in the negative direction (r=-0.30 at p=0.006), according to the data in table IV. The levels of mineral metabolism components correlated in the following relationships: Ca with α1-antitrypsin (r=-0.30 at p=0.006) and Zn (r=0.41 at p=0.001) and Se (r=0.37 at p=0.001); the level of potassium correlated with the values of folic acid (r=0.30 at p=0.006). Along with this, there were communications of the level of chlorine with the transferrin values (r=0.45 at p=0.001). It should be noted that the severity of clinical symptoms communicated with the studied indicators with a correlation coefficient below 0.30, namely by age categories, pain intensity, disease duration. We present a representative correlogram of the relationships between vitamin D3 in the blood and elastase-1 in feces (Fig. 2) and between the level of Se and Zn in the blood in patients of group 1 (Fig.3).

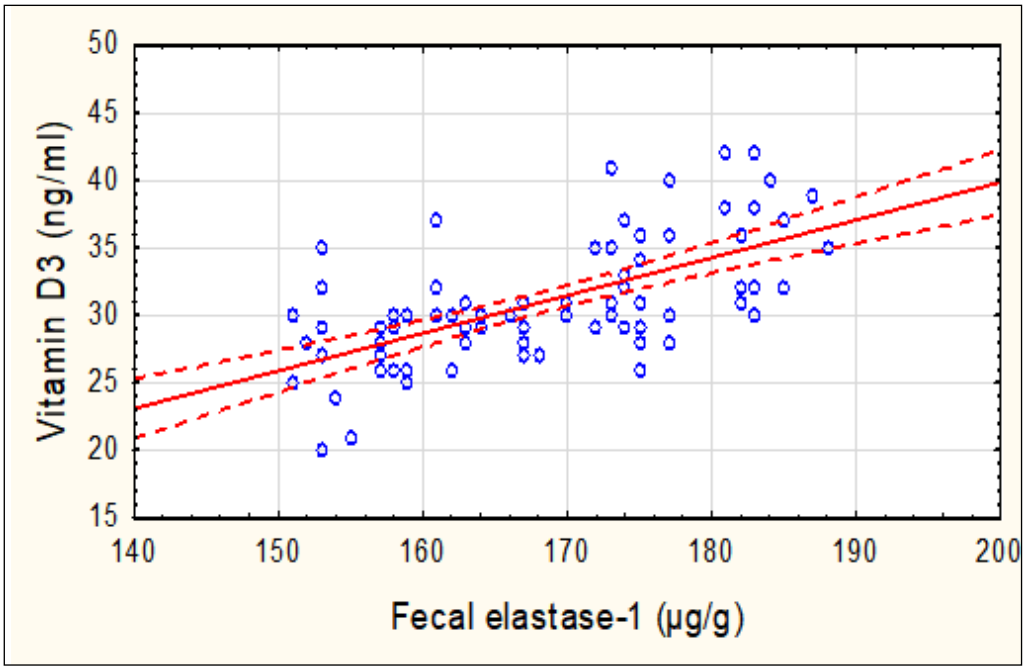

Fig. 2. Correlation between the level of vitamin D3 in the blood and elastase-1 in feces in patients of group 1(r=0,64; p<0,001)
Picture taken by the authors

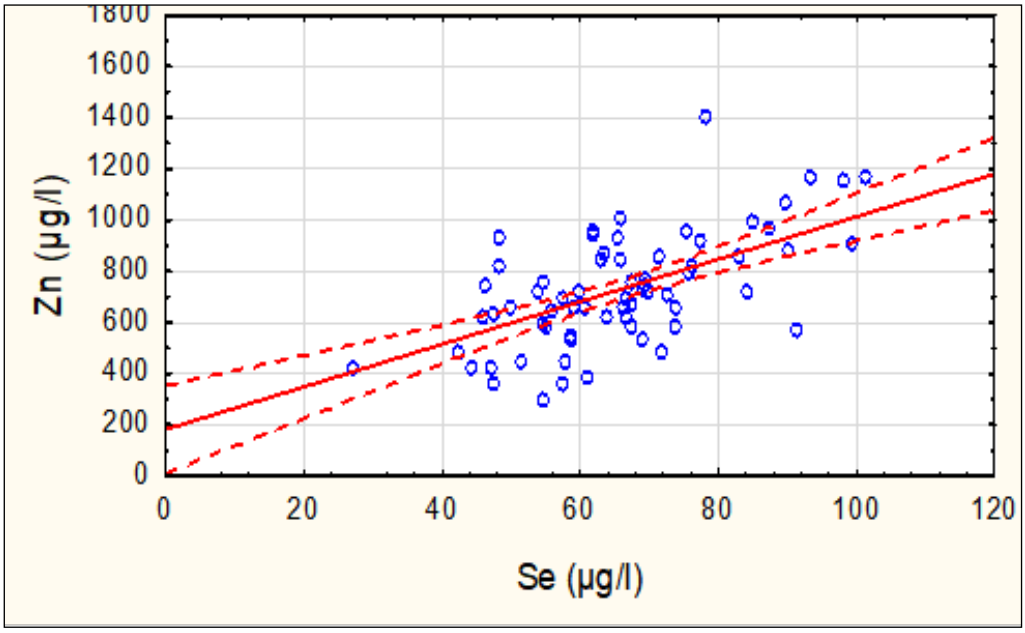

Fig. 3. Correlation between Se and Zn levels in the patients blood of group 1(r=0,58; p<0,001)
Picture taken by the authors

We inform about correlations between the indicators values in the studied contingent of the group 2 (Table 5).

The numerous relationships between the levels of indicators are noted, according to the data in table 5. The correlation coefficient of FE-1 with vitamin D3 is higher than in the first group (r=0.67 at p=0.001) and a new communication with creatinine was detected (r=0.29 at p=0.04). α1-antitrypsin, which is responsible for inhibiting the number of enzymes activity, correlated in the first group with the minerals Ca (-0.30 at p=0.006) and in low correlation coefficient with the levels of K (r=0.24 at p=0.03), Zn (r=0.23 at p=0.03)) and FE-1 (r=0.26 at p=0.02). While in the second group there were a predominance of communications with inflammatory markers ALT (r=0.30 at p=0.03), AST (r=0.29 at p=0.04), which are markers of liver and heart cell damage. Communicative relationships of α1-antitrypsin were also observed with transferrin (r=0.34 at p=0.01) and potassium ions (r=0.47 at p=0.001). Alpha-1 antitrypsin is an acute phase protein, a circulating glycoprotein synthesized primarily by the liver. Its concentration increases in response to acute infection. The accumulation of unfolded or misfolded proteins and their polymers in the lumen of the endoplasmic reticulum has a toxic effect of increasing function, leading to a stress response of cells associated with the endoplasmic reticulum and likewise ultimately causes chronic liver damage in some

Table 2. Investigation of vitamin-mineral cmpositions in the patients

Parameters	Control group (n=23)	1 group (n=85)	2 group (n=50)	Statistical significance of the difference
Vitamin D3 (30-70, ng/ml)	35.52 ± 5.16	31.02 ± 4.61	19.28 ± 3.45	p_1<0.001; p_2=0.001; p_3<0.001
Folic acid (3,89-26,8 ng/ml)	12.07 ± 3.78	7.83 ± 2.06	6.27 ± 2.30	p_1<0.001; p_2<0.001; p_3<0.001
Zn (543-1130 mkg/л)	895.27 ± 189.44	729.05 ± 209.72	620.94 ± 127.44	p_1=0.001; p_2=0.001; p_3<0.001
Sel(23-190 mkg/l)	85.93 ± 12.5	65.81 ± 14.64	53.52 ± 10.70	p_1<0.001; p_2<0.001; p_3<0.001
Na (135-155mmol/l)	143.38 ± 3.27	143.58 ± 3.16	142.26 ± 2.81	p_1=0.02; p_2=0.79; p_3=0.14
Ca (2,1-2,6mmol/l)	2.33 ± 0.11	2.16 ± 0.25	2.14 ± 0.27	p_1=0.75; p_2=0.002; p_3=0.001
K (3,6-5,5 mmol/l)	4.49 ± 0.37	4.43 ± 0.33	4.31 ± 0.43	p_1=0.07; p_2=0.45; p_3=0.09
Cl (95-108 mmol/l)	103.2 ± 2.64	101.83 ± 3.30	101.70 ± 2.90	p_1=0.81; p_2=0.07; p_3=0.04

Notes: p_1 – statistical significance of the difference between the indicators of groups 1 and 2; p_2 – statistical significance of the difference between the indicators of group 1 and the control group; p_3 – statistical significance of the difference between the indicators of group 2 and the control group
Source: compiled by the authors of this study

individuals [16,17]. Scientists believe that there are next interrelated issues with EPI. The diagnosis and treatment of EPI must go beyond the pancreas and require a more holistic approach. Many other EPI conditions are being considered in this direction, some of which have an anatomically intact pancreas but impaired pancreatic enzyme activity in the lumen. For "normal" digestion, food and pancreatic enzymes must meet at the right time, place, and environment [18,19].

DISCUSSION

The common clinical pancreatic secretion scenario is about reduced but sufficient for normal nutrient digestion cannot be defined as insufficiency but as pancreatic exocrine dysfunction. Although its hepatic complications are well documented, emerging evidence suggests that MAFLD may also be associated with EPI, a condition in which the pancreas does not produce or supply sufficient digestive enzymes [12].

The varying probabilities of developing EPI in different clinical settings significantly influence the diagnostic approach and management in clinical practice [20]. EPI always requires treatment, and symptom relief and normalization of nutritional status are therapeutic goals. Other clinical consequences of EPI depend on the disease [21].

The results of our study demonstrated that the presence of comorbidities of the digestive tract are interconnected by common pathophysiological links and influences. These results are consistent with previous studies by Niriella et al. [22] and Yu et al. [23]

Liver function tests in our study showed elevated liver enzymes in the study group. Nguyen et al. [24] and Zdanowicz et al. [25] also found an increase in ALT compared with the control group ($p < 0.001$).The most significant finding of our study was a reliable reduced level of FE-1 in the MAFLD study group, suggesting impaired pancreatic exocrine function. Our findings are consistent with those of Herzig et al. [26], who reported that 21.7% of elderly subjects without gastrointestinal disease or diabetes had fecal elastase levels below 200 μg/g, suggesting subclinical pancreatic dysfunction. Similarly, Naruse et al. [14] confirmed that fecal elastase is a specific marker of severe exocrine pancreatic insufficiency. No significant age, gender, or

Table 3. Inflammatory response markers in the study children

Parameters	Control group (n=23)	1 group (n=85)	2 group (n=50)	Statistical significance of the difference
Fibrinogen (1,8-3,5 g/l)	2.47 ± 0.39	2.85 ± 0.54	3.10 ± 0.55	p_1=0.01; p_2=0.002; p_3<0.001
Transferrin (2,0-3,6 g/l)	2.16 ± 0.27	2.35 ± 0.30	2.76 ± 0.34	p_1<0.001; p_2=0.007; p_3<0.001
α1- antitrypsin (0,9-2,0 g/l)	1.35 ± 0.18	1.49 ± 0.24	1.80 ± 0.22	p_1<0.001; p_2=0.01; p_3<0.001
IL-4 (0-4 pg/ml)	1.41 ± 0.57	1.92 ± 0.20	2.13 ± 0.33	p_1<0.001; p_2<0.001; p_3<0.001
IL-6 (0-10 pg/ml)	7.97 ± 1.84	12.09 ± 1.61	13.08 ± 1.63	p_1=0.001; p_2<0.001; p_3<0.001

Notes: p_1 – statistical significance of the difference between the indicators of groups 1 and 2; p_2 – statistical significance of the difference between the indicators of group 1 and the control group; p_3 – statistical significance of the difference between the indicators of group 2 and the control group
Source: compiled by the authors of this study

comorbidity was found, which is in agreement with Zsóri [27], who suggested that EPI in metabolic liver disease results from complex metabolic dysfunctions rather than traditional risk factors. Numerous studies [28,29] have linked low levels FE-1 to altered glycemic profiles. In particular, Rathmann et al. [30] demonstrated a negative correlation between HbA1c and pancreatic elastase even in nondiabetic patients, suggesting that exocrine pancreatic dysfunction may develop early [31] with metabolic abnormalities. Fatty infiltration of the pancreas may contribute to exocrine dysfunction, linking these two conditions as part of a systemic metabolic disorder, as highlighted in recent studies by Maetzel et al. [32].

Multivariate regression analysis identified MAFLD as an independent predictor of EPI by Boga et al. [12], who similarly found NAFLD to be a major predictor of reduced pancreatic function.

FE-1, although validated as a noninvasive marker of pancreatic exocrine function, is subject to potential confounding factors, namely the presence of diarrhea, which may dilute the enzyme concentration, and technical problems associated with sample collection. These factors may affect the accuracy of the measurement. [33]

CONCLUSIONS

1. Indicative correlations of the levels vitamin D3 with FE-1 (r=0.64, at p=0.001) and fibrinogen in a negative direction were found (r=-0.30 at p=0.006) in ccordance of communicative relationships in the 1st study group.
2. The levels of mineral metabolism components correlated in the following relationships: Ca with α1-antitrypsin (r=-0.30 at p=0.006) and Zn (r=0.41 at p<0.001) and Se (r=0.37 at p<0.001); the potassium level correlated with the values of folic acid (r=0.30 at p=0.006). Along with this, communications of the chlorine level with the values of transferrin (r=0.45 at p=0.001) were noted. It should be noted that the severity of clinical symptoms communicated with the studied indicators in coefficient less then 0.30, namely by age categories, pain intensity, disease duration.
3. In group 2, numerous relationships between the levels of indicators are noted. The correlation coefficient of FE-1 with Vitamin D3 is higher than in the first group (r=0.67 at p<0.001) and a new communication with creatinine was detected (r=0.29 at p=0.04).
4. α-1-antitrypsin, as a substance synthesized in the liver and responsible for inhibiting the activity of a number of enzymes, correlated in the levels of date first group with the minerals Ca (r=-0.30 at p=0.006) and with a low correlation coefficient with the levels of K (r=0.24 at p=0.03), Zn (r=-0.23 at p=0.03)) and FE-1 (r=-0.26 at p=0.02), while in the 2 group there was a communication predominance with inflammatory markers ALT (r=-0.30 at p=0.03), AST (r=-0.29 at p=0.04), which are markers of liver and heart cell damage. Communicative relationships with transferrin (r= 0.34 at p=0.01) and potassium ions (r=0.47 at p=0.001) were also observed.
5. Our results highlight a significant association

Table 4. Date correlations in cildren (1 groupe)

Parameters		r	p
FE-1	Total bilirubin.	-0.25	0.02
	Fibrinogen	-0.26	0.02
	Zn	0.24	0.03
	Vitamin D3	0.64	<0.001
	α1-antitrypsin	-0.26	0.02
	Pain intensity	-0.25	0.02
Transferrin	AST	-0.22	0.04
	Cl	0.45	<0.001
Fibrinogen	Vitamin D3	-0.30	0.006
	FE-1	-0.26	0.02
	Pain intensity	0.28	0.01
α1-antitrypsin	Ca	-0.30	0.006
	K	0.24	0.03
	Zn	-0.23	0.03
	FE-1	-0.26	0.02
IL-4	ALT	-0.24	0.02
IL-6	Ca	0.28	0.01
	K	-0.26	0.02
Folic acid	K	0.29	0.005
Vitamin D3	Fibrinogen	-0.30	0.006
	FE-1	0.64	<0.001
Zn	Ca	0.41	<0.001
	Se	0.58	<0.001
	FE-1	0.24	0.02
	α1-antitrypsin	-0.23	0.03
	Age	-0.23	0.03
Se	Total cholesterol	0.23	0.03
	Ca	0.37	<0.001
	K	-0.27	0.01
	Zn	0.58	<0.001
Ca	Zn	0.41	<0.001
	Se	0.37	<0.001
	α1-antitrypsin	-0.30	0.006
	IL-6	0.28	0.009
	Age	-0.25	0.02
K	-0,30	-0.30	0.006
	Folic acid	0.30	0.006
	Se	-0.27	0.01
	α1-antitrypsin	0.24	0.02
	IL-6	-0.26	0.02
	Pain intensity	0.26	0.02
Cl	Disease duration	0.22	0.05
	Age	-0.22	0.05
	Transferrin	0.45	<0.001

Source: compiled by the authors of this study

Table 5. Date correlations in cildren (2 groupe)

Parameters		r	p
FE-1	Creatinine	0.29	0.04
	Vitamin D3	0.67	<0.001
Transferrin	α1-antitrypsin	0.34	0.01
Fibrinogen	-	-	-
α1-antitrypsin	Transferrin	0.34	0.01
	ACT	-0.29	0.04
	ALT	-0.30	0.03
	K	0.47	0.001
IL-4	Total bilirubin	0.28	0.05
	Ca	0.34	0.01
	Cl	0.32	0.02
IL-6	-	-	-
Folic acid	Na	0.30	0.03
Vitamin D3	FE-1	0.67	<0.001
	Creatinine	0.38	0.006
Zn	AST	0.38	0.006
	Se	0.29	0.04
	Age	-0.38	0.006
Se	Ca	0.35	0.01
	Zn	0.29	0.04
	Total bilirubin	0.34	0.01
Ca	Se	0.35	0.01
	IL-4	0.34	0.01
K	AST	-0.28	0.05
	ALT	-0.35	0.01
	Total cholesyerol	-0.40	0.004
	Triglycerides	-0.60	<0.001
	α1- antitrypsin	0.47	0.001
	Age	0.32	0.02
Na	Folic acid	0.30	0.03
Cl	Total bilirubin	-0.31	0.02
	Il-4	0.32	0.02

Source: compiled by the authors of this study

between GERD, MAFLD, and EPI, with FE-1 levels serving as a reliable marker for detecting pancreatic dysfunction in this population. The definition, pathogenesis, clinical consequences, diagnosis, and treatment of EPI in different clinical conditions require further investigation and proper patient monitoring to reduce the risk of complications and improve the quality of life of patients with EPI.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

CORRESPONDING AUTHOR

Olesya M. Horlenko
Uzhhorod National University
14 Universytetska St, 88000 Uzhhorod, Ukraine
e-mail: ohorlenko@gmail.com

ORCID AND CONTRIBUTIONSHIP

Olesya M. Horlenko: 0000-0002-2210-5503 A B C E F
Lyubomyra B. Prylypko: 0000-0002-4131-55450 A B E F
Bohdan M. Halay: 0000-0002-7566-4982 A F
Fedir V. Horlenko: 0000-0002-0496-2069 A F
Halyna M. Beley: 0000-0002-0496-2069 E F
Lyubov A. Halay: 0000-0002-0496-2069 A F
Volodymyr M. Bilak: 0000-0002-2045-8460 A D

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