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PECULIARITIES OF TREATMENT OF PATIENTS WITH COMORBID PATHOLOGY: CHRONIC PANCREATITIS AND HYPOTHYROIDISM, TAKING INTO ACCOUNT SEPP1 GENE POLYMORPHISM (RS7579)

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Optimization of therapeutic regimens during the treatment of the polymorbid course of chronic pancreatitis combined with hypothyroidism is an important task of modern science.
Aim: *to treat patients with comorbid pathology: chronic pancreatitis and hypothyroidism, taking into account the polymorphism of the SEPP1 gene (RS7579)*
Materials and methods. *During the research, we examined 128 people. Patients were divided into 3 groups. The first group included 48 patients with chronic pancreatitis, the second - 50 patients with chronic pancreatitis in combination with hypothyroidism, and the third - 30 practically healthy people.*
Results. *Symptoms of maldigestion decreased in 72 % of the examined patients. Signs of nutritional deficiency have significantly decreased, and general well-being has improved. Multicomponent therapy also affected mood, sleep, and reduced irritability and symptoms of depression and anxiety disorders. A multisystemic polysyndromic approach to treatment led to improvements in both pancreatic and thyroid function. The effectiveness of the treatment strategy for patients with chronic pancreatitis was dependent on individual characteristics, such as the severity of chronic pancreatitis, the presence of primary hypothyroidism, the degree of selenium deficiency and concomitant symptoms, taking into account polymorphic variants of the SEPP1 (rs7579) gene. Selenoid deficiency decreased, especially in the group with a combination of chronic pancreatitis and hypothyroidism. The improvement in thyroid hormone activity included a 40.46 % decrease in blood TSH and a 2.5-fold increase in free T4.*
Conclusions. *The program of complex therapy led to the normalization of the condition of patients with the G-allele genotype of the SEPP1 gene (rs7579), as evidenced by significant improvements in most of the analyzed indicators. The concentration of fecal elastase 1 and blood selenoprotein P significantly increased, and the level of serum pancreatic α-amylase significantly decreased in carriers of the AA genotype. Under the influence of therapy, there were also changes in the hormonal activity of the thyroid gland, a decrease in the concentration of total metabolites of NO, and an improvement in the health indicators of the cardiovascular system. However, for patients with the AA genotype of the SEPP1 (rs7579) gene, continuation of therapy remains important to achieve an optimal condition, in particular, to manage cholesterol levels and other cardiovascular risk factors*
Keywords: *chronic pancreatitis, hypothyroidism, SEPP1(rs 7579) gene polymorphism, sodium selenite drug*

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1. Introduction

Chronic pancreatitis (CP) is a multifactorial fibro-inflammatory disease, in which repeated episodes of pancreatic inflammation lead to the replacement of normal parenchyma by fibrous tissue and, as a result, to chronic pain, exocrine and endocrine pancreatic insufficiency [1]. Over the past two decades, the number of patients with CP has doubled, which is accompanied by a decrease in the quality of life, a high level of disability and a reduction in life expectancy (mortality is about 15 %, mainly due to oncopathology of the pancreas) [2]. In order to optimize the therapeutic schemes of these nosologies, modern research is aimed at studying the interaction of thyroid hormones with the function of the digestive organs[3, 4]. Currently, it is believed that for the normal functioning of the thyroid gland, in addition to iodine, a number of elements are necessary, including selenium, zinc, copper and calcium [5]. Selenoprotein P (SEPP1) functions as a selenium transport protein and contains approximately half of the total selenium in blood plasma [6–8]. T. Bosschaerts et al. established that the expression of selenoprotein can be associated with resistance to chemotherapy by preventing the induction of ROS in human pancreatic cancer cells [9]. Also, the

expression of SEPP1 changes in the presence of various pathological conditions, and the absence of pathology contributes to the highest level of SEPP1 expression [10]. Jinyuan Mao's study found that selenium status was not associated with SEPP1 rs7579 polymorphism, but SEPP1 rs3877899 was better able to maintain selenium levels during pregnancy [11]. In a study by Lígia Moriguchi Watanabe, SEPP mRNA expression was significantly lower in subjects with the rs7579 GG genotype before and after treatment, thus interindividual differences in Se homeostasis after brazil nut consumption highlight the importance of genetic variability in response to Se intake for health maintenance and prevention of diseases [12]. Therefore, the study of the polymorphism of the SEPP1 gene is very relevant and acquires significant importance for modern medical science, with the aim of forming effective therapeutic schemes for the treatment of polymorbid pathologies.

Purpose: to treat patients with comorbid pathology: CP and hypothyroidism, taking into account the polymorphism of the SEPP1 gene (RS7579)

2. Materials and methods

During the research, we examined 128 people. Patients were divided into 3 groups. The first group included 48 patients with CP, the second – 50 patients with CP in combination with hypothyroidism, and the third – 30 practically healthy people. All patients received inpatient treatment at the Chernivtsi Regional Clinical Hospital and the Chernivtsi Regional Endocrinological Center. The scientific research was conducted from 2014 to 2016 and from 2020 to 2021.

Diagnosis and treatment of CP was carried out according to the national Unified Clinical Protocol of Primary and Specialized Medical Care "Chronic Pancreatitis" (2023) [13], the National Clinical Guidelines "Chronic Pancreatitis" (2023) [14]. Treatment of hypothyroidism in patients with CP was carried out according to the clinical practice recommendations of the European Thyroid Association for the treatment of thyroid diseases in 2023 and a number of international organizations [15, 16]. They were also guided by certain provisions of the evidence-based domestic Clinical Guidelines "Congenital Hypothyroidism" (2023) [17].

Blood sampling was carried out in the morning on an empty stomach, after a 12-hour fast in a sterile vacuum container. The polymorphism of the gene was determined by the method of polymerase chain reaction (PCR) in the state institution "Reference Center for Molecular Diagnostics of the Ministry of Health of Ukraine" (Kyiv). The functional state of the thyroid gland was assessed by determining the content of hormones: thyroid-stimulating hormone (TSH), free thyroxine (vT4) in venous blood serum using the "Sunrise" (Austria) enzyme immunoassay. In order to determine the state of exocrine insufficiency of the PZ, the level of pancreatic α-amylase was determined according to the Karavey method (mg/s*l) and fecal elastase-1 using the "ELISA Kit Pankrateische Elastase" kit. The level of SEPP was determined using an enzyme-linked immunosorbent assay (ELISA) according to the manufacturer's instructions based on the sandwich technology of a solid-phase enzyme-linked immunosorbent assay with a highly sensitive set of Human SEPP1 (selenoprotein P) "ELISA" (firm. DRG, USA). The concentration of nitrogen monoxide metabolites (NO2-/NO3-) was assessed by a colorimetric method using the Total NO/NO2-/NO3- Assay Kit (RDS, Great Britain).

The study was carried out in accordance with the norms of the European Convention on Human Rights and Biomedicine, principles of GCP, GLP, EUC No. 609 and other EU laws and international legislation on bioethics. The Research Protocol received approval from the Ethics Committee of Bukovinian State Medical University (BSMU) under Protocol №3 dated 19.11.2014.

Each participant signed an informed consent to participate in the study. Statistical analysis was conducted using StatSoft Statistica v.7.0 software (StatSoft Inc., USA). Group differences were assessed through various tests, including the Student's t-test (two-tail distribution and equal variances between the two samples), ANOVA, Pearson's $\chi 2$ test, or the Wilcoxon-Mann-Whitney U-test (in instances of uneven data distribution as indicated by W-Shapiro-Wilk or Kolmogorov-Smirnov test results). Logistic regression analysis was employed to calculate the risk of pathology, reporting relative risk (RelR), risk ratio (RR), odds ratio (OR) with a 95 % confidence interval [95 % CI]. Statistical significance was considered at $P<0.05$.

3. Results of the study

In addition to the basic enzyme replacement therapy and diet according to the treatment protocol, all patients additionally received: selenium preparation (in the form of sodium selenite) in a dose of 100 mcg to 300 mcg per day, depending on the level of selenoprotein P deficiency in the blood; with accompanying hypothyroidism, patients of group 2, the endocrinologist prescribed hormone replacement therapy with L-thyroxine (levothyroxine sodium) in a dose of 25 to 100 μg/day, depending on the individual hormonal imbalance; additional symptomatic therapy (antihypertensive, antispasmodic, anti-inflammatory, antioxidant protection)

Evaluation of the effectiveness of basic enzyme replacement therapy was determined by monitoring the dynamics of clinical symptoms of maldigestion. It was found that these symptoms decreased in 72 % of the examined patients. An excellent improvement was observed in the patient group, which included disappearance of steatorrhea (in 86 % of cases), reduction or complete disappearance of flatulence (70 %), as well as signs of dyspepsia (in 86 % of cases). It is also worth noting, that 27 % of patients achieved normalization of body weight. Significant progress was also recorded in improving nutritional status in general. In addition, there was a significant decrease in the number of people who complained of abdominal pain (90 %) and general weakness (81 %). It is important to note, that the manifestations of indigestion, associated with exocrine insufficiency of the digestive system, significantly improved under the influence of the therapy.

After treatment, it was found that the concentration of pancreatic α-amylase (determined by Caraway) significantly decreased in both observed groups, namely by 38.18 % and 31.63 % respectively ($p<0.001$), reaching reference values. It is worth noting,

that a decrease was noted even in patients with CP, where the concentration remained 20.64 % higher (rCP=0.011). At the same time, the level of fecal pancreatic elastase 1 increased in both groups by 2.11 and 2.15 times (p<0.001), moving from mostly "moderate exocrine insufficiency" to normal content. In addition, complex therapy led to an increase in the amount of selenoprotein P in the blood, both for CP and for the combination of CP and hypothyroidism. The increase was significant and amounted to 32.68 % and 58.57 % (p<0.001). It is important to note, that selenium deficiency remained in patients with comorbidity, as for individuals with isolated CP, although it decreased – by 38.78 % and 26.84 % (p<0.001), respectively as indicated in Table 1. The obtained results indicate the need to continue selenium replacement therapy in patients with CP, especially with accompanying hy-pothyroidism, until the normal level of selenoprotein P in the blood is reached.

Table 1

The level of selenoprotein P and the enzymatic activity of the pancreas in the blood before and after treatment in patients with chronic pancreatitis and in combination with hypothyroidism, M±m.

Groups of patients		Patients with chronic pancreatitis	Patients with chronic pancreatitis and hypothyroidism
Pancreatic α-amylase according to Caraway, mg/(sec*l)	Before treatment	10.58±0.35	11.54±0.29 $p_{XП}$=0.003
	After treatment	6.54±0.27 p<0.001	7.89±0.32 $p_{XП}$=0.011 p<0.001
Pancreatic elastase 1, μg/g	Before treatment	154.17±28.16	140.0±26.15
	After treatment	325.20±32.41 p<0.001	300.55±16.88 p<0.001
Selenoprotein R, ng/ml	Before treatment	4.10±0.45	2.51±0.36 $p_{XП}$<0.001
	After treatment	5.44±0.39 p=0.03	3.98±0.25 $p_{XП}$<0.001 p=0.009

Note: P – the probability of differences in the indicators of patients before treatment within each group; RCP - the probability of differences in indicators of patients with chronic pancreatitis

Moderate-severe enzymatic exocrine insufficiency of the pancreas (PS) was detected in carriers of the AA genotype of the SEPP1 gene (rs7579), which was manifested by a low content of fecal pancreatic elastase 1 (≤100.0 μg/g), an increase in pancreatic α-amylase according to Caraway. This condition was marked by significant selenium deficiency and required high-dose enzyme replacement therapy (ERT), sodium selenite, antioxidant protection, and symptomatic correction as indicated in Table 2.

After the use of complex treatment, a significant increase in the concentration of fecal elastase 1 and selenoprotein P was found. In carriers of the AA genotype, this increase was 2.8 times (p<0.001), while in genotype G it increased by 2.17 times (p<0.001). Note that in the G-allele group, there was also an increase of 46.15 % (p=0.039), and in the AA group – by 42.01 % (p=0.049). Patients, regardless of polymorphic variants of the SEPP1 gene, were marked by a decrease in the content of pancreatic α-amylase according to Caraway to normal values by 38.89 % and 37.09 %, respectively (p<0.001). Thus, the results indicate the effectiveness of the use of complex treatment in carriers of the AA and G genotype of the SEPP1 gene for the correction of enzymatic exocrine insufficiency of the pancreas and selenodeficiency.

Table 2

The enzymatic activity of the pancreas and blood selenoprotein P level before and after treatment in patients with chronic pancreatitis taking into account polymorphic variants of the SEPP1 gene (rs7579)

Indicators	Treatment	Patients, n=49 (%)	
		AA-genotype	G-allele
Pancreatic α-amylase according to Caraway, mg/(sec*l)	Before treatment	11.70±0.35	11.0±0.53
	After treatment	7.15±0.40 p<0.001	6.92±0.32 p<0.001
Pancreatic elastase 1, μg/g	Before treatment	100.0	152.54±28.30 p_{AA}<0.001
	After treatment	280.46±30.25 p<0.001	331.05±23.87 p<0.001
Selenoprotein R, ng/ml	Before treatment	2.60±0.31	3.38±0.55
	After treatment	3.80±0.47 p=0.039	4.80±0.44 p=0.049

Note: P – the probability of differences in the indicators of patients before treatment within each group; RAA - the probability of differences in indicators of carriers of the AA genotype of the SEPP1 gene (rs7579)

No significant changes in thyroid function (TSH) were found in patients with chronic pancreatitis (CP) both before and after treatment, as shown in Table 3. Instead, the concentration of total nitrogen compounds NO in these patients after treatment was found to be reduced from high values to the upper limit of normal – by 11.89 % (p=0.005).

In the group of patients with CP and hypothyroidism, more pronounced changes in thyroid function were observed, both before and after treatment: the level of thyroid-stimulating hormone (TSH) decreased under the influence of complex therapy by 40.46 % (p=0.002), and free thyroxine 4 (T4) increased by 2.5 times (p=0.006), reaching the normal limit. These indicators differed from

similar ones in people with CP - the TSH content exceeded this indicator by 34.74 % (pHP=0.045), and free T4 was lower by 33.33 % (pHP=0.03), respectively.

In addition, the content of total NO metabolites decreased as a result of therapy in patients with CP and hypothyroidism by 24.90 % (p<0.001), although it still remained higher than the upper limit of normal by 16.16 % and in the group with isolated CP by 13 .26 % (rCP<0.01).

Changes in the hormonal activity of the thyroid gland and the level of total metabolites of nitrogen monoxide (NO) in the blood of patients under the influence of treatment, taking into account the allelic status of the SEPP1 gene (rs7579), are highlighted in Table 4.

Before treatment, a marked hormonal imbalance of the thyroid gland was observed in patients with CP, carriers of the AA genotype of the SEPP1 gene (rs7579), manifested by an increased concentration of thyroid-stimulating hormone (TSH) and a reduced level of free thyroxine 4 (T4). In this group, there was an increase in the level of total stable NO metabolites in the blood by 52.24 % (p<0.001), reaching possibly harmful values. These changes were visible only in patients with the AA genotype and indicate a possible compensation by an increased level of antioxidant protection, anti-inflammatory factors and stabilization of the activity of inducible NO-synthase.

After treatment, a decrease in TSH and an increase in free T4 by 30.17 % (p=0.002) and 2.6 times (p<0.001) were found in the group of patients with the AA genotype. These changes partially normalized the indicators in most patients, indicating the need for further treatment. Owners of the G genotype showed a complete average statistical normalization of indicators under the influence of treatment, although in general the changes were unclear. It should be noted, that the number of patients with comorbidity (CP and hypothyroidism) was the same among owners of the G genotype (24 vs. 20), while there were only such patients with the AA genotype.

The reatment contributed to a decrease in the level of total metabolites of NO in the AA group by 21.49 % (p<0.001) and in the G group by 25.34 % (p=0.005). However, despite treatment, the level of NO metabolites in owners of the AA genotype continued to exceed the upper limit of normal by 19.52 %.

Table 3

The hormonal activity of the thyroid gland and the content of total metabolites of nitrogen monoxide in the blood before and after treatment of patients with chronic pancreatitis and in combination with hypothyroidism, M±m

Groups of patients		Patients with chronic pancreatitis	Patients with chronic pancreatitis and hypothyroidism
Total Metabolites NO, μmol/l	Before treatment	29.10±0.86	38.67±0.90 $p_{XП}$<0.001
	After treatment	25.64±0.80 p=0.005	29.04±0.65 $p_{XП}$<0.01 p<0.001
TSH, mk MO/ml	Before treatment	3.0±0.32	6.97±0.33 $p_{XП}$<0.001
	After treatment	3.08±0.24	4.15±0.46 $p_{XП}$=0.045 p=0.002
Free T4, ng/dl	Before treatment	1.39±0.12	0.36±0.07 $p_{XП}$<0.001
	After treatment	1.35±0.16	0.90±0.12 $p_{XП}$=0.03 p=0.006

Note: P – the probability of differences in the indicators of patients before treatment within each group; RCP - the probability of differences in indicators of patients with chronic pancreatitis

Table 4

The content of total metabolites of nitric oxide and hormonal activity of the thyroid gland in patients with chronic pancreatitis before and after treatment, taking into account polymorphic variants of the SEPP1 gene (rs7579)

Indicators	Treatment	Patients, n=49 (%)	
		AA-genotype	G-allele
Total metabolites NO, μmol/l	Before treatment	38.06±0.31	33.50±2.31 p_{AA}<0.001
	After treatment	29.88±0.60 p<0.001	25.01±1.55 p_{AA}=0.025 p=0.005
TSH, mk MO/ml	Before treatment	7.69±0.21	4.73±0.82 p_{AA}<0.001
	After treatment	5.37±0.38 p=0.002	3.65±0.41 p_{AA}=0.003
Free T4, ng/dl	Before treatment	0.34±0.05	0.93±0.24 p_{AA}<0.001
	After treatment	0.88±0.14 p<0.001	1.33±0.17 p_{AA}=0.047

Note. P – the probability of differences in the indicators of patients before treatment within each group; RAA - the probability of differences in indicators of carriers of the AA genotype of the SEPP1 gene (rs7579)

4. Discussion of research results

During our scientific research, for the first time in Ukraine, the treatment of patients with CP and hypothyroidism was studied, taking into account the polymorphism of the SEPP1 gene (RS7579) in patients with CP, combined with hypothyroidism in residents of Northern Bukovyna.

Some works report that the rs7579 polymorphism is located in the untranslated region (3'UTR) of the SEPP1 gene and can potentially affect the incorporation of selenocysteine during protein synthesis [18]. On the other hand, rs7579 in the 3'UTR of mRNA can affect miRNA functions through the secondary structure of the 3'UTR and the thermodynamic characteristics of the hybridization site [19]. This single nucleotide polymorphism (SNP) rs7579 can also deregulate the expression of the target gene SEPP1 by changing the binding capacity of microRNA (miRNA). The question arises as to how this SNP of the SEPP1 gene can be associated with the course of CP and in combination with hypothyroidism. In addition, separate links of the pathogenesis of CP need to be systematized and detailed, depending on concomitant risk factors, enzymatic activity of the pancreas, and hormonal changes of the thyroid gland in the context of pathogenetically based personalized treatment and secondary prevention of CP, including when combined with hypothyroidism.

5. Conclusions

1. Integrated treatment of patients with chronic pancreatitis led to the improvement of the exocrine function of the pancreas and reduction of clinical manifestations of maldigestion. In 72 % of cases, the disappearance or significant reduction of symptoms of maldigestion was observed, including flatulence and dyspeptic syndrome in 86 % and 70 %, respectively. In 27 % of patients, body weight was normalized, in 90 % of cases abdominal pain disappeared, and the rest experienced significant relief. Signs of nutritional deficiency have significantly decreased, and general well-being has improved. Multicomponent therapy also affected mood, sleep, and reduced irritability and symptoms of depression and anxiety disorders.

2. A multisystem polysyndromic approach to treatment led to the improvement in the functions of both the pancreatic and thyroid glands. An increase in the concentration of fecal pancreatic elastase 1 by 2.11 and 2.15 times was noted from "moderate exocrine insufficiency" to the normal level. In addition, there was a decrease in the level of pancreatic α-amylase to the reference values by 38.18 % and 31.63 %, respectively. Selenium deficiency decreased, especially in the group with a combination of chronic pancreatitis and hypothyroidism. The improvement in thyroid hormone activity included a 40.46 % decrease in blood TSH levels and a 2.5-fold increase in free T4. The number of total metabolites of NO decreased, but remained higher than normal.

3. The effectiveness of the treatment strategy for patients with chronic pancreatitis (CP) was dependent on individual characteristics, such as the severity of CP, the presence of primary hypothyroidism, the degree of selenium deficiency and concomitant symptoms, taking into account polymorphic variants of the SEPP1 (rs7579) gene. The most severe course of CP before therapy was in those who were carriers of the AA genotype of the SEPP1 gene (rs7579).

These patients had "moderate/severe enzymatic exocrine insufficiency" with low faecal pancreatic elastase 1, elevated pancreatic α-amylase, significant selenium deficiency, and required higher doses of pharmacotherapy. Primary hypothyroidism was also observed in this group of patients, which was associated with an increase in total NO metabolites in the blood. This required an individual approach to treatment, including adjusting the doses of L-thyroxine and antioxidant drugs.

4. The program of complex therapy led to the normalization of the condition of patients with the G-allele genotype of the SEPP1 gene (rs7579), which is evidenced by the significant improvements in most of the analyzed indicators. The concentration of fecal elastase 1 and blood selenoprotein P significantly increased, and the level of serum pancreatic α-amylase significantly decreased in carriers of the AA genotype. Under the influence of therapy, there were also changes in the hormonal activity of the thyroid gland, the decrease in the concentration of total metabolites of NO, and the improvement in the health indicators of the cardiovascular system. However, for patients with the AA genotype of the SEPP1 (rs7579) gene, continuation of therapy remains important to achieve an optimal condition, in particular, to manage cholesterol levels and other cardiovascular risk factors.

Conflict of interest

The authors declare that they have no conflict of interest in relation to this research, whether financial, personal, authorship or otherwise, that could affect the research and its results, presented in this paper.

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Data availability

Data will be provided upon reasonable request.

Use of artificial intelligence

The authors confirm that they did not use artificial intelligence technologies when creating the presented work.

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