Efficiency of Shidnitsa mineral waters in complex rehabilitation of patients with chronic pancreatitis with concomitant diabetes mellitus

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Key words: chronic pancreatitis, diabetes mellitus, ademetionin, drinking mineral waters of the Shidnitsa deposit, exocrine and endocrine pancreatic function

Introduction. As of today, there is an increase in the incidence of chronic pancreatitis (CP) in the general structure of diseases of the digestive system. According to the Research Institute of Gastroenterology NAMS of Ukraine, there are about 1 million patients with CP in the country [4]. Despite the considerable amount of research by domestic and foreign scientists, the issues of diagnosis, treatment and rehabilitation of patients with concomitant diabetes mellitus (DM), which is a global problem of humanity, remain unclear [6]. In particular, the relationship between exocrine and endocrine pancreatic function (pancreas) in patients with CP associated with diabetes has not been fully studied [2]. Although it is known that the basis of endocrine disorders in CP is the morphological features of the location of islets among the acinar tissue, but not isolated from it, which contributes to the interaction between exo- and endocrine cells of the pancreas [7]. Due to the peculiarities of the blood supply to the pancreas, they secrete an insulatory vascular system. In pancreas, blood flow is directed from the islets to the exocrine tissue. Such specific blood supply to the pancreas (its insulatory system) is one of the foundations of functional interaction between endo- and exocrine tissues, i.e. hormones of the pancreas affect its external secretion and vice versa [3]. In addition, changes in the pancreas of patients with CP with diabetes often occur against the background of steatohepatosis or even steatohepatitis, which are the stages of progression of non-alcoholic fatty liver disease (NAFLD) [1].

Modern protocol treatment (PT) of CP is carried out in accordance with the protocols of the Ministry of Health of Ukraine and aims at: eliminating, if possible, aggressive provoking factors (alcohol and tobacco); adherence to a diet taking into account the accompanying pathologies, in particular NAFLD, reduction of pain syndrome; correction of secretory and incretory pancreas failure; treatment of comorbidities; vocational and social rehabilitation; antispasmodics and prokinetics; if necessary — neuroleptics, analgesics, including narcotic; adequate replacement therapy [3, 5].

Oral enzyme therapy has been shown in patients with existing exocrine pancreatic insufficiency (EPI) or other clinical and laboratory evidence of nutrient deficiency. Preference should be given to mini-microspheres or microspheres with enteric-coated coatings, which have shown higher efficacy in the treatment of patients with exocrine malnutrition [2, 5]. Standard basic therapy of CP comorbidity with diabetes is not effective enough for the correction of exocrine and endocrine malnutrition, as well as the correction of dyslipid disorders, insufficient antioxidant defense systems, as well as the condition of the liver as an organ of metabolic detoxification and other vital and vital functions. [5]. Therefore, in such a situation, it is recommended to increase the use of adetionin for the restoration of liver function in case of malnutrition, alcohol consumption or due to the harmful effects of endogenous and exogenous factors. Moreover, it was proposed to receive ademetionine in the most bioavailable non-invasive form — oral sublingual, which is advantageous for the continuation of treatment in the primary care setting. Sublingual form, in which the tablet dissolves under the tongue, provides the main substance easier to get into the bloodstream, bypassing the esophagus and stomach [2, 3].

Rehabilitation of patients with chronic pancreatitis (CP) combined with diabetes mellitus (DM) requires a complex systemic and personified approach, since such comorbidity is characterized by complicated interactions of these nosologies, with more lesions of pancreas as the main organ involved in the

formation and depth pathological manifestations of each patient, as well as the involvement of adjacent organs of the gastrointestinal tract (GIT), other organs and systems. Process of integrated rehabilitation, which purpose is to maximally restore the lost functions of the above organs, especially the pancreas, should include, in addition to standard protocol approaches, the adjuvant effective techniques that showed their practical effectiveness but require research and scientific substantiation. Such techniques include the use of therapeutic mineral water (MW) both in resorts and in outpatient practice according to the place of residence of patients [4].

Aim of research is to investigate the effectiveness of rehabilitation of patients with CP and concomitant DM with the use of the drug ademetionin in the sublingual form (Agepta) and the course of treatment with drinking MW of the Shidnitsa deposit.

Materials and methods. We examined 77 patients with CP and concomitant DM who were on dispensary registration in the center of primary health care in Ternopil and on course sanatorium treatment at the resort "Skhidnytsia" (medical and health complex "Tustan"). The source of information for the clinical-anamnestic analysis were “Medical maps of an outpatient patient” (f. 025 / o) and “Spa cards” of patients with CP during 2015–2018. Age of patients varied from 25 to 65 years. The mean age of patients with CP with diabetes was (52.86±0.83) years. The mean disease duration in the group of patients with CP with diabetes was (10.96±0.39) years.

According to treatment programs, patients were divided into 3 groups: Group 1 (protocol treatment (PT) — 26 patients) — received enzyme preparation of pure pancreatin, proton pump inhibitor (pantoprazole 40 mg), anesthetics (mebeverin) and/or prokinetic (motilium), metformin 1000 mg twice a day); Group 2 (PT + ademetionon (AM) — 26 patients) — in addition to PT received a drug ademetionin (sublingual tablets Agepta 400 mg) 1 tablet 2 times per day 30–60 minutes before eating, holding under tongue at least 15–20 min — until complete

dissolution, 1 month course; Group 3 — in addition to PT and Agepta in the above-mentioned scheme, they took the course of treatment by drinking MW of the Shidnitsa deposit according to the proposed scheme.

The low-mineralized MW of Naftusya type (Skhiderny source No 18) enhances the release of pancreatic juice with the activation of pancreatic enzymes in it. MW type "Naftusya" of the Skhidnytskyi field, which has a similar therapeutic effect, differs from Truskavets slightly higher content of hydrocarbons, which positively affects the alkaline-acid balance of patients with diabetes mellitus [4]. Therefore, with CP in the phase of mild exacerbation or unstable remission, especially when combined with diabetes, "Naftusia" was prescribed in a limited dosage of 100–150 ml per intake, heated to 37–40°C, 3 times a day for 60 min before meals. With concomitant hypertension, "Naftusya" was administered with caution, better MW source No 10 (it is slightly weaker, acts more gently) in a similar mode.

In the presence of concomitant problems with the kidneys (the presence of sand in the kidneys) was also prescribed MW source No. 1 for 30 min after eating 150 (later — 200) ml.

60 min after eating, patients with CP, in combination with diabetes, were also assigned a medium-mineralized MB of source 2C (soda) of the Skhidnytsia deposit with a high content of hydrocarbonates that inhibit the secretion of the pancreas, 150 (later — 200) ml [4]. This course of treatment under the supervision of a physician was used for 14 days to assess the condition of patients before and after treatment.

The diagnosis of CP was verified on the basis of protocol No. 638 of September 10, 2014, and the DM — according to protocol No. 1118 of December 21, 2012 [4, 5]. In order to assess the EPI of the pancreas according to the order No. 638 of 10.09.2014, the Ministry of Health of Ukraine used a new non-invasive test — determination of the level of fecal pancreatic elastase-1 by enzyme immunoassay. Detection of fasting blood glucose by the glucose oxidase method

and glycosylated hemoglobin (HbA1c) by ion-exchange chromatography was used to diagnose disorders of endocrine function of the pancreas.

The data obtained were statistically processed using Microsoft Excel and Statistica-6.0. The arithmetic mean (M) with the mean square error (m) was calculated. Hypothesis testing the difference between the two means (p) was performed using the Mann-Whitney U-test. The results were considered significant at the level of their statistical significance $p < 0.05$.

Results and discussion. In the study of the effectiveness of programs of correction for the dynamics of indicators of exocrine and endocrine function of the pancreas, the results are shown in Table 1.

Table 1

Dynamics of indicators of exocrine and endocrine function of pancreas in CP with DM under the influence of various correction programs

Index	Comparison group					
	Group 1 (n=26)		Group 2 (n=26)		Group 3 (n=25)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
α-elastase, mcg/h	97,84±3,17	155,11±6,16 *p<0,05	93,43±3,45	170,57±6,20 *p<0,05 **p<0,05	97,59±3,30	188,74±7,89 *p<0,05 ***p<0,05
Blood glucose, mmol/l	8,93±0,46	8,12±0,26 *p<0,05	8,93±0,43	7,74±0,28 *p<0,05 **p<0,05	8,93±0,43	7,19±0,25 *p<0,05 ***p<0,05
HbA1c, %	7,77±0,32	7,39±0,26 *p<0,05	7,79±0,23	7,07±0,14 *p<0,05 **p<0,05	7,90±0,33	6,94±0,18 *p<0,05 ***p<0,05
Coprogram, scores	4,58±0,18	3,46±0,19 *p<0,05	4,58±0,11	2,81±0,18 *p<0,05 **p<0,05	4,64±0,21	2,08±0,18 *p<0,05 ***p<0,05

Notes:

* p — reliability of the difference regarding such indices of their group of patients before treatment;

** p — reliability of the difference regarding such indices of Group I of patients;

*** p — reliability of the difference regarding such indices of Group II patients.

Positive dynamics in all groups of comparison was revealed, but its intensity differed in those groups. Improvement of exocrine and endocrine pancreatic function was found: level of fecal α-elastase increased by 58.5% in Group 1, by 82.6% in Group 2, by 93.4% in Group 3; level of blood glucose decreased by 9.2% in Group 1, by 13.3% in Group 2, by 19.5% in Group 3; level of HbA1c — by 4.9% in Group 1, by 9.2% in Group 2, by 12.2% in Group 3; changes in the coprogram — by 24.5% in Group 1, by 38.6% in Group 2, by 55.2% in Group 3.

Therefore, a statistically significant improvement was observed in the 2nd group of patients with respect to the 1st ($p < 0.05$) testimony to the efficacy of the use of adetionin (sublingual Ahepta tablets) in a comprehensive program of correction in patients with CP with PD. However, the most pronounced dynamics in terms of exocrine and endocrine function of the pancreas was found in the 3rd group of patients with respect to the 2nd and 1st respectively, which indicates the feasibility of additional appointment of a course of drinking MW of the Skhidnytsia field according to the proposed scheme.

Conclusion. The effectiveness of inclusion of AM in complex standard protocol program of treatment of patients with CP with concomitant DM in sublingual tablets (Agepta) with 400 mg twice a day during 1 month and 14-day course of treatment with drinking MW of the Shidnitsa deposit according to the proposed scheme was proved by statistically significant improvement of the indices of exocrine and endocrine pancreatic function ($p<0.05$).

In future research, we plan to determine the dynamics of endogenous intoxication and antioxidant systems under the influence of various treatment programs.

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Relevance. Rehabilitation of patients with chronic pancreatitis (CP) combined with diabetes mellitus (DM) requires a complex systemic and personified approach, since such comorbidity is characterized by complicated interactions of these nosologies, with more lesions of pancreas as the main organ involved in the formation and depth pathological manifestations of each patient, as well as the involvement of adjacent organs of the gastrointestinal tract (GIT), other organs and systems. Process of integrated rehabilitation, which purpose is to maximally restore the lost functions of the above organs, especially the pancreas, should include, in addition to standard protocol approaches, the adjuvant effective techniques that showed their practical effectiveness but require research and scientific substantiation. Such techniques include the use of therapeutic mineral water (MW) both in resorts and in outpatient practice according to the place of residence of patients.

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Results. Positive dynamics in all groups of comparison was revealed, but its intensity differed in those groups. Improvement of exocrine and endocrine pancreatic function was found: level of fecal α-elastase increased by 58.5% in Group 1, by 82.6% in Group 2, by 93.4% in Group 3; level of blood glucose decreased by 9.2% in Group 1, by 13.3% in Group 2, by 19.5% in Group 3; level of HbA1c — by 4.9% in Group 1, by 9.2% in Group 2, by 12.2% in Group 3; changes in the coprogram — by 24.5% in Group 1, by 38.6% in Group 2, by 55.2% in Group 3.

Discussion. There was a statistically significant improvement in the results of Group 2 as compared to Group 1 ($p<0.05$), which indicates the effectiveness of use of AM (agepta sublingual tablets) in a comprehensive correction program for patients with CP and DM. However, the most evident dynamics of indicators of exocrine and endocrine pancreatic function was found in Group 3 as compared to Groups 2 and 1, respectively, indicating the expediency of the additional appointment of the therapeutic course of drinking MW of the Shidnitsa deposit according to the proposed scheme.

Conclusion. The effectiveness of inclusion of AM in complex standard protocol program of treatment of patients with CP with concomitant DM in sublingual tablets (Agepta) with 400 mg twice a day during 1 month and 14-day course of treatment with drinking MW of the Shidnitsa deposit according to the proposed scheme was proved by statistically significant improvement of the indices of exocrine and endocrine pancreatic function ($p<0.05$).