ORIGINAL ARTICLE

# EFFECTIVENESS OF HEPATOPROTECTOR IN THE COMPLEX CORRECTION OF CLINICAL MANIFESTATIONS OF CHRONIC PANCREATITIS AND TYPE 2 DIABETES MELLITUS COMORBIDITY

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**Liliya S. Babinets, Iryna M. Halabitska, Iryna O. Borovyk, Olena V. Redkva**
I. HORBACHEVSKY TERNOPIL NATIONAL MEDICAL UNIVERSITY, TERNOPIL, UKRAINE

## ABSTRACT

**The aim:** To investigate the effectiveness of complex protocol treatment with the additional inclusion of a course of the sublingual form of hepatoprotector on the clinical manifestations of patients with chronic pancreatitis in combination with type 2 diabetes mellitus.

**Materials and methods**: We studied 57 outpatients with chronic pancreatitis in the phase of stable or unstable remission in combination with diabetes mellitus in the phase of stable or unstable remission. Two groups were formed according to randomization principles to study the effectiveness of the proposed correction programs: 1st group (30 patients) took protocol treatment for one month, 2nd group (27 patients) – received protocol treatment with a course of hepatoprotector.

**Results:** It was found the results of the impact of two treatment programs on some clinical symptoms and syndromes in patients with chronic pancreatitis. Positive dynamics of clinical symptoms/syndromes were found in both groups of patients, but the therapeutic effect in the 2nd group was more significant. Analysis of the dynamics of the Quality of Life parameters on the scales of a specialized gastroenterological questionnaire under the influence of two treatment programs found statistically significant ($p<0.05$) changes in the group with the inclusion of hepatoprotector for treatment for all parameters in contrast to the group of protocol treatment, where statistically significant changes on three scales (abdominal pain, gastric reflux, and dyspepsia).

**Conclusions:** It is proved that the proposed inclusion in the protocol treatment of a combination of CP and DM2 course of sublingual a demethion in eledtoan increase in its effectiveness in the correction of abdominal pain - by 8.2%, dyspepsia - by 17.8%, constipation - by 7.4% , diarrhea - by 12.9%, astheno-neurotic - by 21.5%, allergic - by 15.9%, autonomic - by 20.1% ($p<0.05$). Found higher efficacy of treatment with the in clusion of a demethion in relation to that in the group of PL on the dynamics of the parameters of the scales of the GSRS questionnaire by a total of 13.7%, $p <0.01$: abdominal pain decreased by 22.6% vs. 16.7%, gastricreflux - by 34.7% against 16.9% ($p <0.05$), diarrhea - by 23.9% against 8.2% ($p<0.001$), constipation - by 20.6% against 5.9% (0.01), dyspepsia - by 32.4% against 17.9% ($p <0.01$), respectively. It proved the feasibility of using sublingual demethion in the complex rehabilitation treatment of patients with comorbidity of CP and diabetes mellitus in order to correct clinical symptoms..

**KEY WORDS:** chronic pancreatitis, type 2 diabetes mellitus, hepatoprotector

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## INTRODUCTION

Most clinicians and researchers believe that the current epidemiology of chronic pancreatitis (CP) is much worse than other diseases. In Ukraine, the incidence of pancreatitis has more than doubled in the last three decades, and the epidemiological rates of CP in our country are 3-4 times worse than in Europe, in Ukraine, there are 880 thousand patients with CP [1, 2]. In 15-20% of cases, patients with CP die from complications arising from exacerbations of pancreatitis, others – due to secondary digestive disorders, infectious complications, and incretory insufficiency of the pancreas in the form of type 2 diabetes mellitus (DM2), which makes CP social and a medically significant problem of medicine [3, 4].

Despite the sufficient number of studies by scientists, the issues of diagnosis, treatment, and rehabilitation of patients with CP with concomitantDM2, which is a global problem of mankind, remain unclear [5]. There is an increase in the number of patients with DM2, which exceeds the mark of two million people. In the world, diabetes is becoming a pandemic [6]. According to WHO experts, the world is projected to increase the number of patients with diabetes to 300 million people. The relationship between exocrine and endocrine function of the pancreas in patients with CP combined with diabetes mellitus has not been fully studied [7].

We found more significant clinical and pathogenetic pathological disorders of inflammatory, intoxication and trophological nature in the comorbid course of CP and diabetes mellitus in comparison with isolated CP motivated us to strengthen the standard treatment of patients with such nosologies by additional therapy, regulated by Orders of the Ministry of Health of Ukraine from 10.09.2014 "On approval and implementation of medical and technological documents on standardization of medical care for chronic pancreatitis" and № 1118 of 21.12.2012 "On approval and implementation of medical and technological documents on standardization of medical care for type 2 diabetes"[8-10].

**Table I.** Comparative analysis of the dynamics of clinical symptoms in the study groups of patients with CP with diabetes mellitus under the influence of PT and PT with the inclusion of ademetionine

| Clinical symptom/syndrome | Comparison Group (number of patients (abs./%)) | | | |
|---|---|---|---|---|
| | 1st group(PT) (n=30) | | 2nd group(PT+AM) (n=27) | |
| | before treatment | after treatment | before treatment | after treatment |
| Abdominal pain syndrome and its equivalents | 30 (100.0) | 8 (26.7)* | 27 (100.0) | 6 (18.5)* |
| Dyspeptic syndrome | 28 (93.3) | 10 (33.3) | 25 (92.6) | 4 (14.8) |
| Diarrhea | 12 (40.0) | 7 (23.3) | 12 (44.4) | 4 (14.8) |
| Constipation | 15 (50.0) | 5 (16.7) | 14 (51.9) | 3 (11.1) |
| Astheno-neurotic syndrome | 25 (83.3) | 7 (23.3) | 26 (96.3) | 4 (14.8) |
| Anemic syndrome | 15 (50.0) | 5 (16.7) | 14 (51.9) | 2 (7.4) |
| Hypovitaminosis | 27 (90.0) | 10 (33.3) | 25 (92.6) | 5 (18.5) |
| Changes in appetite | 16 (53.3) | 9 (30.0) | 14 (51.9) | 5 (18.5) |
| Allergic syndrome | 10 (33.3) | 7 (23.3) | 10 (37.0) | 3 (11.1) |
| Polydipsia | 16 (53.3) | 5 (16.7) | 14 (51.9) | 1 (3.7) |
| Vegetative signs | 25 (83.3) | 11 (36.7) | 22 (81.5) | 4 (14.8) |

Note: * – clinical manifestation in patients with CP with diabetes after treatment was considered to be present in the absence of significant positive dynamics

**Table II.** Comparative analysis of the dynamics of the scales of the questionnaire quality of life GSRS patients with CP with diabetes mellitus under the influence of PT and PT with the inclusion of ademetionine

| GSRS questionnaire scale. score | Comparison group | | | | p |
|---|---|---|---|---|---|
| | 1st group (PT) (n=30) | | 2nd group (PT+AM) (n=27) | | |
| | before treatment | after treatment | before treatment | after treatment | |
| AP (abdominal pain) | 10.29±0.21 | 8.82±0.19 $p_2<0.01$ | 10.50±0.29 $p_1>0.05$ | 7.90±0.14 $p_2<0.001$ | $p_3<0.01$ |
| RS (gastric reflux) | 11.51±0.31 | 9.85±0.27 $p_2<0.01$ | 11.88±0.31 $p_1>0.05$ | 8.82±0.20 $p_2<0.001$ | $p_3<0.05$ |
| DS (diarrhea) | 10.84±0.70 | 10.02±0.60 $p_2>0.05$ | 10.70±0.69 $p_1>0.05$ | 8.63±0.32 $p_2<0.001$ | $p_3<0.001$ |
| CS (constipation) | 8.63±0.61 | 8.15±0.49 $p_2>0.05$ | 8.67±0.51 $p_1>0.05$ | 7.19±0.25 $p_2<0.001$ | $p_3<0.01$ |
| IS (indigestion) | 14.38±0.43 | 12.20±0.39 $p_2<0.01$ | 14.39±0.42 $p_1>0.05$ | 10.87±0.29 $p_2<0.001$ | $p_3<0.01$ |

Notes:
1) $p_1$ – a significant difference in data differences in groups of patients before treatment;
2) $p_2$ – a significant difference in the differences between these patients in their group before and after treatment;
3) $p_3$ – a significant difference in data differences in groups of patients after treatment.

## THE AIM

The aim of the study is to investigate the effectiveness of complex protocol treatment with the additional inclusion of a course of the sublingual form of ademetionine on the clinical manifestations of patients with chronic pancreatitis in combination with type 2 diabetes mellitus.

## MATERIALS AND METHODS

We studied 57 outpatients with CP in the phase of stable or unstable remission in combination with diabetes mellitus in the phase of stable or unstable remission. Two groups were formed according to randomization principles to study the effectiveness of the proposed correction programs: 1 group (30 patients with CP and DM2) took protocol treatment (PT) for one month, which included normalization of lifestyle and dietary recommendations, enzyme preparation of pure pancreatin inadequate dose (25-40 IU of lipase) during meals, proton pump inhibitor (pantoprazole 40 mg), antispasmodic (mebeverine) and/or prokinetic (motilium) – on-demand, metformin 1000 mg twice daily. The basic components of the PT were the outpatient regime, the diet in accordance with the order of the Ministry of Health of Ukraine dated 29.10.2013. № 931; Group 2 (PT+AM – 27 patients) – received PT with

a course of ademetionine (sublingual tablets Agepta 400 mg) one tablet 2 times a day 30-60 minutes before meals, holding under the tongue for at least 15-20 minutes – until complete dissolution by a course lasting one month.

We analyzed the presence of significant clinical manifestations in% of the total number of patients in the group before treatment. After treatment, the clinical manifestation in patients with CP with diabetes was considered to be present in the absence of significant positive dynamics. The Quality of Life (LQ) was also assessed using the Gastrointestinal Symptom Rating Scale (GSRS) developed by the ASTRA Hassle (I. Wiklund, 1998), which is used to assess the LQ of patients with gastrointestinal disease. It consists of 15 items, grouped into 5 scales: a) abdominal pain (AP); b) indigestion syndrome (IS); c) diarrheal syndrome (DS); d) constipation syndrome (CS); e) gastric reflux syndrome (RS). Each question is evaluated from 1 to 7 points. Lower values correspond to weaker symptoms and higher LQ.

Statistical processing of indicators was performed by the method of variation statistics Fisher-Student with the determination of arithmetic mean (M), standard deviation (q), arithmetic mean error (m). The average values are presented as M± m. An unpaired Student›s t-test was used to compare the two independent samples, and a paired Student's t-test, included in the 2007 Microsoft Excel suite, was used to assess changes in dynamics and treatment effects.

## RESULTS

Table I shows the results of the impact of two treatment programs on some clinical symptoms and syndromes in patients with CP. Positive dynamics of clinical symptoms/syndromes were found in both groups of patients, but the therapeutic effect in the 2nd group was more significant.

According to the dynamics of abdominal pain, the effectiveness of treatment with the inclusion of ademetionine was 81.5% against 73.3% in the protocol treatment group. The dynamics of the effectiveness of dyspeptic syndrome in group 2-1 was 77.8% vs. 60.0%, constipation – 48.2% vs. 40.8%, diarrhea – 29.6% vs. 16.7%, astheno-neurotic – 81.5% vs. 60.0%, allergic – 25.9% vs. 10.0%, for manifestations of autonomic dysfunction – 66.7% vs. 46.6% of that in the group of protocol therapy.

Thus, the analysis of the dynamics of treatment programs on the elimination of the most important clinical symptoms/syndromes in patients with comorbidity of CP and diabetes mellitus proved significantly higher efficiency of the complex with the additional inclusion of ademetionine in protocol therapy, which was also effective ($p<0.05$).

The next stage of the study of the proposed treatment complexes was to study their effectiveness on the state of LQ patients with a combined course of CP and DM 2 on the scales of the international questionnaire GSRS (Table II).

Analysis of the dynamics of LQ parameters on the scales of a specialized gastroenterological questionnaire under the influence of PT and PT+AM found statistically significant ($p<0.05$) changes in the group with the inclusion of ademetionine for treatment for all parameters in contrast to the group of PT, where statistically significant changes on three scales (abdominal pain, gastric reflux, and dyspepsia).

Thus, the method of inclusion in the protocol complex therapy of patients with CP and DM2 outside the exacerbation of the course of the aminoacid drug ademetion in the form of sublingual table tsin order to correct clinical manifestations due to metabolic, antioxidant, anti-inflammatory, and detoxifying restoration of the functional state of the pancreas and liver.

## DISCUSSION

The evidence base for the use of ademetionine in liver disease is quite large – more than 8,000 publications and more than 200 clinical studies. In particular, a meta-analysis was conducted based on 12 randomized clinical trials involving 705 patients with chronic liver disease (cholestasis of pregnant women, toxic hepatitis, viral hepatitis with intrahepatic cholestasis, alcoholic liver disease, nonalcoholic fatty liver disease). liver disease), where the safety of ademetionine was studied (frequency of side effects, long-term prognosis, mortality rate, number of liver transplants, as well as the level of total bilirubin, ALT, AST, etc.)[11-14]. The results obtained after data analysis and independent comparisons show a significant reduction in total bilirubin and ACT levels with ademetionine treatment. A meta-analysis confirmed that a proven level of safety and effect on liver function is the basis for the use of ademetionine as a basic drug in the treatment of chronic liver disease. The level of side effects of the drug corresponded to the level of placebo[15, 16].

However, due to the tendency of the liver to retain approximately 60% of the dose of ademetionine, the likelihood of using SAMe to take it orally in the form of gastro-resistant tablets is complicated by its lack of bioavailability, which necessitates very high oral doses (1600 mg/day). or administered by intramuscular injection, which is not always convenient due to invasiveness, pain, and discomfort in an outpatient setting[17]. The possibility of taking SAMe in the form of tablets for absorption allows achieving significant levels of bioavailability also by oral administration. The use of SAMe by sublingual absorption ensures that the first passage through the liver is overcome. From the moment venous blood passes from the sublingual plexus, it flows directly into the superior vena cava. A study of 6 healthy volunteers compared the pharmacokinetic absorption parameters of SAMe taken orally in the form of gastro-resistant tablets (200 mg of the active substance SAMe) or in the form of lozenges (119.76 mg of the active substance)[18, 19]. The results showed that the levels of bioavailability obtained by taking the lozenges were approximately twice as high as those determined with the use of gastro-resistant tablets. Thus, the results showed that the use of tablets for resorption allowed when taking SAMe orally can provide the same levels of bioavailability as when administered intramuscularly[20, 21]. This has attracted our attention in terms of possible use for positive effects on the liver as an organ of metabolic detoxification and other pleiotropic effects, but requires scientific justification for use in patients with CP in comorbidity with diabetes, as we have not found similar studies.

## CONCLUSIONS

1) it is proved that the proposed inclusion in the protocol treatment of a combination of CP and DM2 course of sublingual a demethion in eledtoan increase in its effectiveness in the correction of abdominal pain – by 8.2%, dyspepsia – by 17.8%, constipation – by 7.4% , diarrhea – by 12.9%, astheno-neurotic – by 21.5%, allergic – by 15.9%, autonomic – by 20.1% ($p<0.05$); 2) found higher efficacy of treatment with the in clusion of a demethion in relation to that in the group of PL on the dynamics of the parameters of the scales of the GSRS questionnaire by a total of 13.7%, $p <0.01$: abdominal pain decreased by 22.6% vs. 16.7%, gastricreflux – by 34.7% against 16.9% ($p <0.05$), diarrhea – by 23.9% against 8.2% ($p<0.001$), constipation – by 20.6% against 5.9% (0.01), dyspepsia – by 32.4% against 17.9% ($p <0.01$), respectively; 3) it proved the feasibility of using sublingual demethion in the complex rehabilitation treatment of patients with comorbidity of CP and diabetes mellitus in order to correct clinical symptoms.

## REFERENCES


1. Bellin M.D., Whitcomb D.C., Abberbock J. et al. Patient and disease characteristics associated with the presence of diabetes mellitus in adults with chronic pancreatitis in the United States. Am J Gastroenterol. 2017;112(9):1457.
2. Dite P., Novotny I., Nechutova H., Trna J. Chronic pancreatitis-classification, diagnosis and therapy. RozhlChir. 2012;91(12):684.
3. Dominguez-Munoz J.E., Lucendo A., Carballo L.F. et al. A Spanish multicenter study to estimate the prevalence and incidence of chronic pancreatitis and its complications. Rev EspEnferm Dig. 2014;106(4):239.
4. Issa Y., Bruno M.J., Bakker O.J. et al. Treatment options for chronic pancreatitis. Nat Rev Gastroenterol Hepatol. 2014;l l(9):556-64. doi: 10.1038/nrgastro.2014.74.
5. Ito T., Ishiguro H., Ohara H. et al. Evidencebased clinical practice guidelines for chronic pancreatitis 2015. J Gastroenterol. 2016;51 (2):85-92. doi: 10.1007/s00535-015-l 149-x.
6. Lohr J.M., Oliver M.R., Frulloni L. Synopsis of recent guidelines on pancreatic exocrine insufficiency. United European Gastroenterol J. 2013;l(2):79-83. doi: 10.1177/2050640613476500.
7. Turner R. Chronic pancreatitis: Negotiating the complexities of diagnosis and management. Aust Fam Physician. 2015;44(10):718.
8. Babinets L.S., Sasyk H.M., Halabitska I.M., Mykuliak V.R. Possibilities of complex rehabilitation of patients with type 2 diabetes and concomitant chronic pancreatitis in ambulatory practice. Balneologia. 2021(1):12-15.
9. Babinets L.S., Halabitska I.M., Borovyk I.O. et al. The influence of exocrine pancreatic in sufficiency in the formation of osteopenia in patients with primary osteoarthritis. Wiadomosci lekarskie. 2020;3(10), 2238-2240.
10. Babinets L.S., Halabitska I.M. Characteristics of joint pain in patients with primary osteoarthritis and comorbid conditions with exocrine pancreatic insufficiency. LekarskyObzor. 2021;70 (2): 62-64.
11. Babinets L.S., Halabitska I.M. Chronic in flammatory process and bone tissue changes in patients with osteoarthritis and exocrine pancreatic insufficiency. LekarskyObzor. 2020;69 (1):7-10.
12. Whitcomb D.C. Primer on precision medicine for complex chronic disorders. Clin Trans Gastroenterol. 2019;10(7): e00067.
13. Schrader H. Et al. Determinants of glucose control in patients with chronic pancreatitis. Diabetologia. 2019, 47p.
14. Yadav D. et al. Incidence, prevalence, and survival of chronic pancreatitis: a population-basedstudy. The American journal of gastroenterology. 2011;106;(12):2192.
15. Yang D., Forsmark C.E. Chronic pancreatitis. CurrOpinGastroenterol. 2017;33(5):396-403. doi: 10.1097/MOG.0000000000000377.
16. Wang F.S., Fan J.G., Zhang Z. et al. The global burden of liver disease: the major impact of China. Hepatol. 2014;60(6):2099-108.
17. The burden of liver disease in Europe -a review of available epidemiological data. http://www.easl.eu/medias/EASLimg/Discover/EU/54ae845caec619f_file.pdf. [date access 12.02.2021]
18. American liver foundation. The liver low down-liver disease: the big picture. http://www.liverfoundation.org/education/liverlowdown/ll1013/bigpicture. [date access 12.02.2021]
19. WHO. World Health Rankings. https:World_Health_Organization_ranking_of_health_systems_in_2000 [date access 12.02.2021].
20. Zakhari S. Bermuda triangle for the liver: alcohol,obesity, and viral hepatitis. Gastroenterol Hepatol. 2013;28(1):18-25.
21. World gastroenterology organization: e-WGN expert point of view articles collection, 2017:global burden of liver disease: a true burden on health sciences and economies. http://www.worldgastroenterology.org/publications/e-wgn/e-wgn-expert-point-of-view-articles-collection/global-burden-of-liver-disease-a-true-burden-on-health-sciences-and-economies. [date access 12.02.2021].


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**ORCID and contributionship:**
*Liliya S. Babinets: 0000-0002-0560-1943* A-F
*Iryna M. Halabitska: 0000-0002-9028-7230* A-F
*Iryna O. Borovyk: 0000-0003-0114-2935* A-F
*Olena V. Redkva: 0000-0002-3572-1583* A-F

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## CORRESPONDING AUTHOR

**Liliya S. Babinets**
I. Horbachevsky Ternopil National Medical University
14 Kupchyns'ky St., 46400 Ternopil, Ukraine
tel: +380673520743
e-mail: lilyababinets@gmail.com

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