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Principles of pathogenetic therapy of diabetic gastroparesis

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Abstract
The therapeutic effectiveness of α-lipoic acid preparations and benfotiamine in treating symptoms of gastroparesis in patients with diabetes mellitus was evaluated. Pathogenetic interrelationships among increasing concentration of peripheral myelin protein and a decrease in the motor-evacuation function of the stomach were determined. The results of a three-month course of pathogenetic therapy demonstrate the effectiveness of combination therapy which is not associated with an improved compensation of carbohydrate and lipid metabolism. It is a result of the direct effect of preparations on the investigated metabolic processes and restoration of myelination of the nerve fibers.

Keywords: *Diabetic Gastroparesis (DG), Peripheral Myelin Protein (PMP), α- Lipoic Acid (α- LA), Benfotiamine*

Introduction
At present, in the scientific literature there are insufficient data on the prevalence of diabetic gastroparesis (DG). Clinicians do not pay sufficient attention to this disease due to the difficulties of its early diagnosis and differences between methods for investigating the motor-evacuation function (MEF) of the stomach in patients with diabetes mellitus (DM) [2, 3]. Progressive damage to peripheral and autonomic nerve endings is considered to be one of the potentially life-threatening chronic complications of DM. Diabetic autonomic neuropathy is a condition characterized by dysfunction of the vagus nerve and nerve endings innervating the stomach and its blood vessels with further development of symptoms of functional dyspepsia. According to the results of many research studies symptoms of gastroparesis are relatively common among patients with DM: 25-60% of patients experience at least one symptom [9, 13]. One third of patients report a combination of several manifestations occurring simultaneously, namely, feeling of fullness, early satiety after eating, and heaviness/discomfort in the epigastric region. Severe clinical course of the disease is characterized by regurgitation and projectile vomiting which do not bring any relief and dramatic weight loss. The diversity of clinical manifestations results in some difficulties in making an accurate diagnosis, unfavourable prognosis and untimely treatment. The problem of timely diagnosis, prevention and treatment of DM is of current importance, and the therapeutic algorithm should be safe and pathogenetically justified.
Chronic hyperglycemia is considered to be one of the major etiopathogenetic factors for the development and progression of DM complications. It inhibits endoneural perfusion leading to the development of hypoxia, impaired metabolism of fatty acids, and activation of free radical oxidation [5, 13]. Under the influence of free radicals the damage to myelin sheath of the nerve fibers progresses resulting in partial opening of the axon. As a result of glucose autoxidation and glycosylation end-product accumulation oxidative stress develops, and the activity of Na-K-ATPase which is known to intensify ischemic neuronal damage decreases. Demyelination of nerve endings and their destruction affect the factors determining the speed of nerve impulse conduction, and intensification of oxidative stress causes apoptosis. Dramatically impaired neuronal activity is also typical in case of increasing clearance of thiamine and its reduced plasma concentration. Impaired sympathoadrenal system activity, progression of vagoinsular denervation, and deterioration of carbohydrate metabolism compensation lead to slowing down of MEF of the stomach in patients with DM. The change in functional properties of peripheral myelin protein 22 (PMP22) should also be considered one of the pathogenic markers of early diagnosis of neuronal damage [1, 7]. Hyperglycocytosis results in progressive disorders of the vagus nerve and nerve endings dysfunction of which results in the development of DM and elevated levels of PMP22 indicate the process of nerve demyelination. At present, there are insufficient data on most properties of PMP22. Therefore, it can be only supposed that there are some pathogenetic relationships between the

concentration of PMP22 and slowing down of gastrointestinal motility in patient with DM.

The use of physiological antioxidants and preparations inhibiting the intensity of anaerobic glycolysis is pathogenetically justified and proved after conducting several placebo-controlled trials (ALADIN, SYDNEY, ORPIL, SYDNEY 2, ALADIN III, BENDIP and others) [10, 14, 15]. To prevent the progression of DM it is advisable to use a combination of neurotropic vitamins and alpha-lipoic acid (ALA) preparations. ALA contributes to an increased absorption of glucose influencing glucose transporters in the cell membrane. It is also able to inhibit different pathobiochemical processes of oxidative stress including protein glycosylation preventing the development of complications. Low effectiveness of therapeutic doses of water-soluble forms of thiamine poorly penetrating into the nervous tissue has forced the scientists to look for more effective fat-soluble forms of vitamin B_1 called benfotiamine. 40 mg of benfotiamine have more biological activity than 100 mg of thiamine. Once inside the cell, it is converted to active metabolite of many thiamine derivatives - thiamine pyrophosphate. It is a cofactor being involved in energy metabolism in the nervous tissue at the cellular level. Thiamine pyrophosphate inhibits the formation of advanced glycation end-products slowing down the intensity of anaerobic glycolysis, production of lactate and, thus, slowing the progression of microvascular complications of DM [4, 6, 8, 11, 12].

2. The Aim of the Research

The aim of the research was to evaluate the effectiveness of α-lipoic acid and benfotiamine in treating diabetic gastroparesis.

2.1. Materials and Methods

90 patients at the age of 30-75 years suffering from DM with symptoms of the disorders of MEF of the stomach, disease duration of 5-15 years and glycated hemoglobin levels of 9.80±0.52% were examined. Patients were divided into three groups: Group I included 45 patients with type 1 DM, Group II included 45 patients with type 2 DM, and Group III (the control group) included 15 practically healthy persons (PHP). According to the prescribed treatment all patients with DM were divided into three subgroups: patients (n=15) of subgroup A received medical preparations for the correction of carbohydrate metabolism in combination with 600 mg ALA daily; patients (n=15) of subgroup B were prescribed 300 mg benfotiamine daily in addition to traditional antidiabetic therapy; patients (n=15) of subgroup C were given medical preparations to correct poor glycemic control in combination with medications used in pathogenetic therapy: 600 mg ALA daily and 300 mg benfotiamine. The course of treatment lasted 3 months. To prevent the low efficiency of pathogenetic therapy as a result of the disorders of MEF of the stomach it was recommended to take medications 30-60 minutes before or 2 hours after a meal orally.

After signing the informed consent form to participate in a clinical trial all patients received printed information about the procedures involved in the study and individual treatment algorithm. MEF of the stomach was determined using the ^{13}C-octanoate breath test (OBT). Breath samples were analyzed using infrared spectrometry (IRIS) with the determination of $^{13}CO_2$ concentration. Blood glucose levels were measured by glucose oxidase method. Glycated hemoglobin (HbA_1C) levels were measured using ion exchange liquid chromatography method. Identification of PMP22 was made using ELISA kit designed by Cloud-Clone Corp (the USA).

The state of lipid metabolism was evaluated by the value of total cholesterol (TC), triglycerides (TG), and high-density lipoprotein (HDL) cholesterol fractions, low-density lipoprotein (LDL) cholesterol fractions and very low-density lipoprotein (VLDL) cholesterol fractions. The study was performed in accordance with the Helsinki Declaration and Good Clinical Practice Guideline. The study was approved by the local ethics committee of Ivano-Frankivsk National Medical University and written informed consent was obtained from all patients.

For statistical processing of the material at all stages of the research several Microsoft Excel-based computer programs were developed (calculation of relative values, their deviations, t-test). The mean values were calculated by the statistical software package of Microsoft Excel, in particular, descriptive statistics. The correlation coefficient was determined using a statistical analysis program Statistica 7.0 based on the Pearson Square method, a value of $p<0.05$ was considered significant.

3. Results and Discussion

The research has not revealed any dramatic age-related differences between disease duration and HbA_1C levels ($p>0.05$) (Table 1).

Table 1: General characteristics of study groups, CB±m

Groups	Age	Disease duration	Glycated hemoglobin, %
I A (n=15)	34.13 ± 2.01	13.17 ± 1.24	9.41 ± 0.25
I B (n=15)	32.23±2.01	11.16±1.30	9.31±0.28
I C (n=15)	34.00±2.24	8.19±1.08	8.95±0.26
II A (n=15)	57.15±2.72	12.05±1.82	10.05±0.31
II B (n=15)	62.62±2.86	12.14±1.85	9.42±0.34
II C (n=15)	58.72±2.95	12.83±2.38	10.03±0.33
III (n=15)	49.0±1.36	-	4.42±0.24

The features of changes in lipid metabolism in patients suffering from DM with co-existent disorders of MEF of the stomach after a three-month course of pathogenetic therapy using ALA and benfotiamine are presented in Table 2.

The use of 600 mg ALA daily for a 3 month period did not affect lipidogram parameters in patients with type 1 DM while in patients of Group II A significant efficiency of the levels of TC, AI ($p<0.05$), VLDL cholesterol ($p<0.01$) was observed, and when using 300 mg benfotiamine significant reduced levels of TC, AI ($p<0.05$) were found in patients of both groups. After treatment there was a significant difference in the level of TC and VLDL cholesterol ($p<0.05$) among patients of Group II B (Table 2). The use of combination of ALA preparations and benfotiamine was more effective for most parameters of lipid metabolism (subgroups I C and II C).

The changes in the parameter of the state of compensation of carbohydrate metabolism (HbA_1C) in patients 3 months after treatment are presented in Figure 1. It reduced by 1.1 times in patients of subgroups I C (8.19±0.26%) and II C (9.05±0.35) ($p<0.05$). Many researchers have described how to provide the state of compensation of DM using basic therapy in combination with preparations of pathogenetic therapy [11, 12, 15], however, the mechanism of direct action of ALA and benfotiamine on lipid metabolism parameters remains controversial.

Table 2: Dynamics of lipidogram parameters in patients of study groups before and after treatment, CB±m

Paremeters	TC, mmol/l		Triglycerides, mmol/l		HDL cholesterol, mmol/l		LDL cholesterol, mmol/l		VLDL cholesterol mmol/l		AI	
Groups	before	after	before	after	before	after	before	after	before	after	before	after
	treatment		treatment		treatment		treatment		treatment		treatment	
I A (n=15)	5.5± 0.21	5.20± 0.18	2.75± 0.27	2.55± 0.25	1.00± 0.06	1.06± 0.06	5.34± 0.32	4.85± 0.29	0.79± 0.12	0.70± 0.11	2.79± 0.27	1.52± 0.25**
I B (n=15)	6.21± 0.27	5.38± 0.27*	2.32± 0.41	1.96± 0.38	1.06± 0.05	1.18± 0.06	6.11± 0.41	5.40± 0.39	1.06± 0.19	0.89± 0.17	2.21± 0.38	1.16± 0.30*
I C (n=15)	6.38± 0.31	5.44± 0.29*	2.84± 0.29	2.04± 0.12*	1.04± 0.05	1.26± 0.07**	6.65± 0.37	5.55± 0.35*	1.20± 0.13	0.97± 0.12	2.89± 0.37	1.80± 0.26*
II A (n=15)	6.67± 0.48	5.18± 0.48*	3.25± 0.37	2.69± 0.35	1.00± 0.06	1.06± 0.06	6.54± 0.65	6.06± 0.63	1.48± 0.17	1.39± 0.16**	3.94± 0.24	2.54± 0.64*
II B (n=15)	6.83± 0.36	5.52± 0.36*	3.59± 0.37	2.52± 0.36*	1.04± 0.06	1.20± 0.07	6.12± 0.45	5.51± 0.45	1.33± 0.17	1.20± 0.16*	3.85± 0.35	2.88± 0.31*
II C (n=15)	6.29± 0.41	5.06± 0.41*	3.46± 0.33	2.00± 0.32**	1.01± 0.05	1.32± 0.06∞	6.05± 0.46	4.95± 0.48*	1.12± 0.15	0.91± 0.14	3.55± 0.35	2.58± 0.29*
III (n=15)	4.49± 0.14		1,54± 0,28		1.75± 0.07		2.56± 0.03		0.93± 0.06		0.16± 0.05	

Note: *, **, ∞ - p <0.05, p<0.01, p<0.001 compared with those before and after treatment

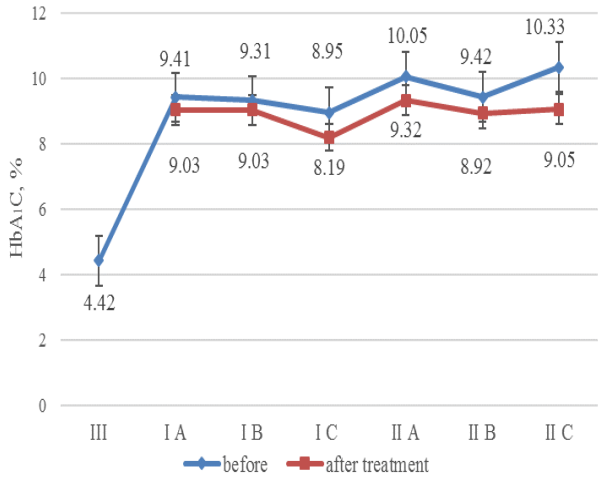

Fig 1: Dynamics of HbA_1C levels (%) in study groups before and after treatment

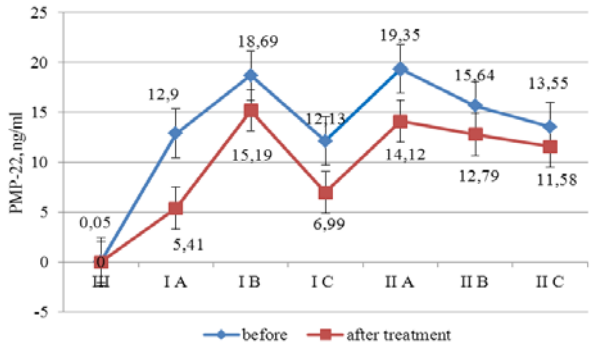

Fig 2: Dynamics of PMP levels in study groups before and 3 months after treatment

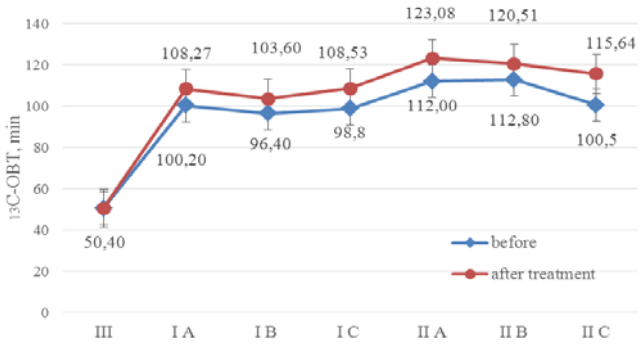

Fig 3: Results of the ^{13}C- OBT in study groups before and after treatment

To determine the extent of damage to the myelin sheath and progression of symptoms of diabetic neuropathy the concentration of PMP22 indicating the degree of demyelination of nerve endings was determined. This parameter increased by 200-300 times in patients with types 1 and 2 DM compared to that in PHP. Positive dynamics of patients' subjective complaints was observed 3 months after performing pathogenetic therapy using ALA preparations and benfotiamine separately and in combination. It was confirmed by the results of the ^{13}C- OBT indicating restoration of MEF of the stomach (Figures 2, 3).

The results of the study have revealed a moderate positive correlation between the levels of glycated hemoglobin and concentration of PMP22 in blood serum r=0.68±0.02 (p<0.01) indicating direct action of chronic hyperglycemia on the extent of damage to the myelin sheath. A strong direct relationship between the level of PMP22 and the results of the ^{13}C- OBT r=0.87±0.08 (p<0.001) has also been found.

Therefore, decompensation of carbohydrate metabolism and demyelination of nerve endings as a result of increased levels of PMP22 can be considered to be the main pathogenetic factors for the development and progression of DM while the manifestations of dyslipidemia do not have any direct action on these parameters.

4. Conclusions

Administration of 600 mg ALA and 300 mg benfotiamine daily when treating patients with types 1 and 2 DM did not significantly affect lipid metabolism parameters; it contributed, however, to significant reduction in the concentration of PMP22 indicating the suppression of demyelination of nerve endings and, thus, preventing reduced MEF of the stomach.

As a result of taking 600 mg ALA daily for a 3 month period the level of PMP22 reduced by 1.4 times (p<0.05) in patients with types 1 and 2 DM. When taking 300 mg benfotiamine the level of PMP22 reduced by 1.2 times, respectively. The use of combination of ALA preparations and benfotiamine simultaneously was more effective, since the level of PMP22

reduced by 1.7 times in patients with type 1 DM while in patients with type 2 DM it reduced by 1.2 times only.

The obtained results allow us to assume that the effectiveness of combination therapy using ALA and benfotiamine is not associated with an improved compensation of carbohydrate metabolism in patients with types 1 and 2 DM with co-existent disorders of MEF of the stomach. It is a result of the direct effect of investigated preparations on the pathogenetic metabolic processes and restoration of myelination of the nerve fibers.

5. References

1. Amici SA, William DA, Murphy AJ. Peripheral Myelin Protein 22 Is in Complex with α6β4 Integrin, and Its Absence Alters the Schwann Cell Basal Lamina. The Journal of Neuroscience. 2006; 26(4):1179 -1189.
2. Camilleri M, Parkman HP, Shafi MA, Abell TL, Gerson L. Clinical guideline: management of gastroparesis. American College of Gastroenterology. American Journal of Gastroenterology 2013; 108(1):18-37.
3. Kyryliuk DB, Shyshin AN. Diabetic gastropathy (review). Bulletin of Saint-Petersburg University, Series – Medicine 2006; 1:5-15.
4. Mankovskyi BN. Treatment of diabetic polyneuropathy: what are evidence-based guidelines? Medicines of Ukraine 2011; 10(156):30-33.
5. Martin CL, Albers J, Herman WH. Neuropathy Among the Diabetes Control and Complications Trial Cohort 8 Years After Trial Completion. Diabetes Care 2006; 29:340-344.
6. Novikov VI, Novikov KY. Benfotiamine and pyridoxine: new horizons in treatment of diabetic complications. International Journal of Endocrinology. 2013; 7(55):39-44.
7. Ohsawa Y, Murakami T, Miyazaki Y. Peripheral myelin protein 22 is expressed in human central nervous system. Journal of the Neurological Science. 2006; 247(1):11-15.
8. Pankiv VI. The effectiveness of using alpha-lipoic acid in diabetic neuropathy. International Journal of Endocrinology. 2015; 2(66):59-65.
9. Pogromov AP, Baturova VY. Diabetic autonomic neuropathy and digestive organs. Pharmateca 2011; 5:42-45.
10. Stracke H, Gaus W, Achenbach U, Federlin K, Bretzel RG. Benfotiamine in Diabetic Polyneuropathy (BENDIP): Results of a Randomised, Double Blind, Placebocontrolled Clinical Study. Experimental and Clinical Endocrinology & Diabetes, DOI 10.1055/s-2008-1065351, 2008.
11. Shay K, Moreau R, Smith E. Alpha–lipoic acid as a dietary supplement: Molecular mechanisms and therapeutic potential. Biochimica et Biophysica Acta 2009; 1790(10):1149-1160.
12. Stirban A, Negrean M, Stratmann B. Benfotiamine prevents macro- and microvascular endothelial dysfunction and oxidative stress following a meal rich in advanced glycation end products in individuals with type 2 diabetes. Diabetes Care 2006; 29(9):2064-2071.
13. Tsymmerman YS, Zinatullin MR. Diabetes mellitus and functional and structural changes in the gastroduodenal region: clinical and epidemiological research. Therapeutic Archive 2011; 2:71-75.
14. Ziegler D, Phillip AL, William JL. Efficacy and safety of antioxidant treatment with α-Lipoic acid over 4 years in diabetic polyneuropathy. Diabetes Care 2011; 34:2054-2060.
15. Ziegler D, Ametov A, Barinov A. Oral treatment with α-lipoic acid improves symptomatic diabetic polyneuropathy: the SYDNEY 2 trial. Diabetes Care 2006; 29:2365-2370.