Влияние бенфотиамина на состояние инсулиновой резистентности, содержание некоторых про- и противоспалительных факторов при сахарном диабете и кардиальной автономной нейропатии

Сергиенко В. А.[1], Сергиенко А. А.[1], Сегин В. Б.[2], Ажми С.[1], Сергиенко Л. М.[1]

Цель. Проанализировать влияние бенфотиамина (БФТ) на состояние инсулиновой резистентности, содержание некоторых про- и противовоспалительных факторов у пациентов с диабетом 2 типа (СД2) и клинической стадией кардиальной автономной нейропатии (КАН).

Материал и методы. Обследовано 40 пациентов с СД2 и клинической стадией КАН, возраст 50-59 лет, с длительностью заболевания 1-6 лет с медианой уровня гликированного гемоглобина (HbA_{1c}) 7,16%±0,19%. Пациенты были разделены на 2 группы. Пациенты первой группы получали стандартную гипогликемическую терапию (n=19, контроль) в течение трех месяцев. Пациентам из второй группы (n=21) назначали дополнительно 300 мг в день БФТ в течение 3 месяцев.

В крови определяли уровни глюкозы, HbA_{1c}, иммунореактивного инсулина (ИРИ), С-реактивного белка высокочувствительным методом (вч-СРБ), лептина, фактора некроза опухоли-альфа (ФНО-альфа), интерлейкинов (ИЛ)-6, ИЛ-8 и ИЛ-10. Вычисляли параметры индекса гомеостатической модели (HOMA) оценки резистентности к инсулину (HOMA-IR), соотношение ФНО-альфа/ИЛ-10.

Результаты. Назначение БФТ сопровождалось статистически значимым снижением концентрации ИРИ (Δ=-12,74%±1,42% (p<0,05)); вч-СРБ (Δ=-13,62% ±1,96% (p<0,05)), ФНО-альфа (Δ=-10,24%±1,54% (p<0,05)) и ИЛ-6 (Δ=-15,41% ±2,03% (p<0,05)) по сравнению с контрольной группой. В то же время, назначение БФТ не влияло на концентрацию глюкозы, лептина, ИЛ-8, ИЛ-10; параметры соотношения HOMA-IR и ФНО-альфа/ИЛ-10 (p>0,05).

Заключение. Полученные данные могут указывать на снижение провоспалительной активности иммунного ответа и позволяют рассматривать БФТ в качестве перспективного фармакологического агента в комплексном лечении функциональной стадии КАН.

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[1]Львовский национальный медицинский университет им. Данила Галицкого, Львов; [2]Львовский областной государственный клинический лечебно-диагностический эндокринологический центр, Львов, Украина.

Сергиенко В. А.* — д.м.н., доцент кафедры эндокринологии, ORCID: 0000-0002-6414-0956, Сергиенко А. А. — д.м.н., профессор кафедры эндокринологии, ORCID: 0000-0001-7519-2279, Сегин В. Б. — врач-кардиолог, ORCID: 0000-0003-3871-2196, Ажми С. — ассистент кафедры эндокринологии, ORCID: 0000-0001-8284-102X, Сергиенко Л. М. — к.б.н., доцент кафедры медицинской биологии и генетики, ORCID: 0000-0001-9873-9847.

*Автор, ответственный за переписку (Corresponding author):
serhiyenkoa@gmail.com

AGEs — advanced glycation end-products, ANS — autonomic nervous system, BFT — benfotiamine, BMI — body mass index, CAN — cardiac autonomic neuropathy, CARTs — cardiovascular autonomic reflex tests, COX-2 — cyclooxygenase-2, DN — diabetic neuropathy, HbA_{1c} — glycated hemoglobin A_{1c}, HOMA-IR — Homeostasis Model Assessment (HOMA) insulin resistance (IR) index, hs-CRP — high sensitivity C-reactive protein, IL — interleukin, iNOS — inducible nitric oxide synthase, IRI — immunoreactive insulin, JNK — c-Jun N-terminal kinase, LPS — lipopolysaccharide, NF-κB — nuclear factor kappa-light-chain-enhancer of activated B cells, NO — nitric oxide, OS — oxidative stress, PKC — protein kinase C, T2DM — type 2 diabetes mellitus, TD — thiamine deficiency, TKT — transketolase, TNF-alpha — tumor necrosis factor-alpha, TNF-alpha/IL-10 — tumor necrosis factor-alpha/IL-10 — interleukin 10 ratio.

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Effects of benfotiamine on the insulin resistance state, some pro- and anti-inflammatory factors content in patients with type 2 diabetes mellitus and cardiac autonomic neuropathy

Sergienko V. A.[1], Sergienko A. A.[1], Segin V. B.[2], Ajmi S.[1], Sergienko L. M.[1]

Aim. The aim of the study was to analyze the effect of benfotiamine (BFT) on the insulin resistance state, the content of some pro- and anti-inflammatory factors in patients with type 2 diabetes mellitus (T2DM) and advanced stage of cardiac autonomic neuropathy (CAN).

Material and methods. 40 patients with T2DM and advanced stage of CAN, aged between 50-59 yrs with disease term 1-6 yrs and average glycated hemoglobin A_{1c} (HbA_{1c}) 7,16%±0,19% were examined. Patients were divided into 2 groups. The patients from first group received standard hypoglycemic treatment (n=19, control) for three mo. To patients from the second (n=21, treatment group) was prescribed 300 mg/q.d. of the BFT in addition for three mo.

The levels of blood glucose, HbA_{1c}, immunoreactive insulin (IRI), high sensitivity C-reactive protein (hs-CRP), leptin, tumor necrosis factor-alpha (TNF-alpha), interleukins (IL)-6, IL-8 and IL-10 were determined. The Homeostasis Model Assessment (HOMA) insulin resistance (IR) index (HOMA-IR) parameters, TNF-alpha/IL-10 ratio were calculated.

Results. Treatment with BFT led to significant decrease in the concentration of IRI [Δ=-12,74%±1,42% (p<0,05)]; hs-CRP (Δ=-13,62%±1,96% (p<0,05)), TNF-alpha (Δ=-10,24%±1,54% (p<0,05)) and IL-6 (Δ=-15,41%±2,03% (p<0,05)) compared to the control group. At the same time, prescription of BFT does not affect the concentration of glucose, leptin, IL-8, IL-10; HOMA-IR and TNF-alpha/IL-10 ratio parameters (p>0,05).

Conclusion. Obtained data may indicate a decrease in the activity of the proinflammatory link of the immune response and allow us to consider BFT as a promising pharmacological agent in the complex treatment of the advanced stage of CAN.

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Key words: benfotiamine, type 2 diabetes mellitus, cardiac autonomic neuropathy, insulin resistance, pro- and anti-inflammatory factors.

Conflicts of Interest: the research was carried out within the frame of the scientific work of Lviv National Medical University named after Danylo Halytsky (№ 0111U000131).

[1]Danylo Halytsky Lviv National Medical University, Lviv; [2]Lviv Regional State Clinical Medical and Diagnostic Endocrinology Center, Lviv, Ukraine.

Sergienko V. A. ORCID: 0000-0002-6414-0956, Sergienko A. A. ORCID: 0000-0001-7519-2279, Segin V. B. ORCID: 0000-0003-3871-2196, Ajmi S. ORCID: 0000-0001-8284-102X, Sergienko L. M. ORCID: 0000-0001-9873-9847.

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Diabetic autonomic neuropathy (DAN) is often underestimated and indeed is a serious complication of diabetes mellitus (DM), as can potentially affect any circuit/tract of autonomic nervous system (ANS). The most studied and common form of DAN is cardiac autonomic neuropathy (CAN), owing to its relation with other microangiopathic comorbidities and life-threatening complications. Development of CAN is characterized by lesion of nerve fibers in the parasympathetic and sympathetic divisions of the ANS [1, 2].

The broad term that describes any malfunction or disease of the ANS is dysautonomia. It has been proved that functional changes in the ANS are associated with various forms of mild to moderate vitamin deficiencies. Mild to moderate thiamine deficiency (TD) and/or hypoxia both give rise to exaggeration of centrally controlled mechanisms involved in all survival reflexes, mediated normally through a balanced reaction of the endocrine system and ANS [3]. Due to increased requirements deriving from amplified and accelerated glucose metabolism in non-insulin dependent tissues, DM might be considered as TD state [3, 4]. The TD in clinical diabetes may increase the fragility of vascular cells to the adverse effects of hyperglycemia and there by the increase of the risk of microvascular complications development [2, 3]. Chronic exposure to moderate and severe hypoxia increases the activity of the sympathetic nervous system and adrenal medulla, and TD induces an early functionally significant central muscarinic cholinergic lesions [3]. It was showed in several studies that prescription of benfotiamine (BFT), is associated with reduction of oxidative stress (OS) and diabetic micro-macrovascular complications. OS was considered as the main pathophysiological pathway of CAN development. Elevated intracellular levels of glucose lead to activation of polyol pathway, formation of advanced glycation end-products (AGEs), resulting in subsequent formation of reactive oxygen species (ROS) [4].

It is clear that the correction of TD must be performed using exogenous vitamin B_1, or BFT (high-bioavailable liposoluble vitamin B_1 derivatives). Results of experimental and clinical studies suggest a positive effect of BET prescription on prevention of diabetic vascular disease progression. BFT broad therapeutic potential has a good efficiency on medications containing soluble thiamine derivatives for the purpose of regulating the activity of free radical processes; correction of endothelial dysfunction in case of cardiovascular diseases (CVD), stabilization of clinical and antioxidants effects [5].

The aim of this study is to analyze the effect of BFT on the insulin resistance, the content of some pro- and anti-inflammatory factors in patients with type 2 DM (T2DM) and advanced stage of CAN.

Material and methods

Forty patients with T2DM and advanced stage of CAN, aged between 50-59 years with disease duration 1-6 years, median body mass index (BMI) 27,2±0,34 kg/m^2 and median glycated hemoglobin A_{1c} (HbA_{1c}) 7,16±0,19% were examined. The standard hypoglycemic treatment of DM included dietary regime, appropriate physical activity, and oral antihyperglycemic drugs.

Patients with T2DM and CAN were divided into 2 groups. Patients in groups did not differ significantly in age, sex distribution, BMI, duration of the disease which made them as homogeneous as possible. First group received traditional antihyperglycemic therapy (n=19, control group) for three months; patients in group 2 (n=21, treatment group), received in addition to standard treatment 300 mg/q.d. BFT for three months. To determine the effects of BFT on the investigated parameters all measurements were performed initially and after the end of treatment period. Each patient examined before the beginning of the study did not take BFT and was on stable regime of hypoglycemic and antihypertensive treatment for 6 months.

Study inclusion criteria: age: 50-60 yrs old; T2DM with optimal or suboptimal glycemic control; T2DM patients with advanced stage of CAN; clinical stages of diabetic polyneuropathy; BMI within 20-30 kg/m^2; consent to maintain appropriate physical activity.

T2DM was diagnosed according to [6], and CAN [1]. All patients underwent screening for CAN that included five cardiovascular autonomic reflex tests (CARTs). Resting 12-lead surface electrocardiography (ECG) and Holter-ECG ((ECG "EC-3H" ("Labtech," Hungary)) analysis included measurement of 24 hours ECG, circadian indexes and heart rate variability parameters. The severity of CAN was determined on the condition that all five CARTs were performed. The results were considered according to scores obtained in individual tests. Physiological values were evaluated as "0" scores, borderline values — as "0,5" scores, pathological values — as "1" score [1]. The scores were summed up and the median score for studied patients was 2,8±0,29.

The concentration of glucose in the blood was determined by the glucose oxidase method while HbA_{1c} was assessed using a highly sensitive method of ion-exchange liquid chromatography with D-10 analyzer and BIO-RAD reagents (USA). Determination of immunoreactive insulin (IRI) was performed using commercial kits from immunogen insulin immuno-

Table 1

The glucose, IRI concentrations and HOMA-IR parameters after 3-months of BFT therapy (Δ%, Mean±SEM)

Parameter	Patients with T2DM and advanced stage of CAN (n=40)				
	Groups	Before treatment	After treatment	% change	p
Fasting blood glucose (mmol/L)	Control (n=19)	7,03±0,26	7,05±0,30	+0,89%±3,1%	>0,05
	Treatment (n=21)	6,64±0,42	6,69±0,38	+2,19%±2,96%	>0,05
Fasting IRI (μIU/mL)	Control (n=19)	27,76±2,11	26,01±2,19	-6,7%±2,0%	>0,05
	Treatment (n=21)	26,84±1,39	23,21±0,86	-12,74%±1,42%	<0,05
HOMA-IR	Control (n=19)	9,03±0,98	8,39±0,91	-7,15%±1,8%	>0,05
	Treatment (n=21)	8,06±0,89	6,99±0,6	-11,91%±2,68%	>0,05

Note: The results are presented as absolute values and as % change from baseline, (Δ%, Mean±SEM); p<0,05, compared to baseline.

Abbreviation: BFT — benfotiamine, CAN — cardiac autonomic neuropathy, HOMA-IR — Homeostasis Model Assessment of insulin resistance, IRI — immunoreactive insulin, T2DM — type 2 diabetes mellitus.

Table 2

Changes of the hs-CRP, leptin and TNF-alpha concentrations after 3-months of BFT therapy (Δ%, Mean±SEM)

Parameter	Patients with T2DM and advanced stage of CAN (n=40)				
	Groups	Before treatment	After treatment	% change	p
hs-CRP (mg/L)	Control (n=19)	2,88±0,48	2,69±0,48	-7,2%±1,64%	>0,05
	Treatment (n=21)	2,91±0,19	2,48±0,1	-13,62%±1,96%	<0,05
Leptin (μg/L)	Control (n=19)	21,06±1,69	19,52±1,58	-7,1%±1,81%	>0,05
	Treatment (n=21)	20,87±1,85	19,61±1,84	-6,41%±1,33%	>0,05
TNF-alpha (pg/mL)	Control (n=19)	5,82±0,44	5,49±0,42	-6,1%±1,02%	>0,05
	Treatment (n=21)	5,38±0,2	4,75±0,13	-10,24%±1,54%	<0,05

Note: The results are presented as absolute values and as % change from baseline, (Δ%, Mean±SEM); p<0,05, compared to baseline.

Abbreviation: BFT — benfotiamine, CAN — cardiac autonomic neuropathy, hs-CRP — high sensitivity C-reactive protein, T2DM — type 2 diabetes mellitus, TNF-alpha — tumor necrosis factor-alpha.

radiometric assay reagents (Czech Republic); leptin level-from Immunotech Leptin (Czech Republic) test kits; tumor necrosis factor-alpha (TNF-alpha), interleukin (IL)-6, IL-8 and IL-10-from Vector-Best (Russia); high-sensitivity C-reactive protein (hs-CRP) — from diagnosis-related group (USA). TNF-alpha/IL-10 ratio and homeostasis model assessment (HOMA) insulin resistance (IR) index (HOMA-IR) were calculated.

The work was done according to the principles of the Declaration of Helsinki (2004).

All patients signed an informed consent prior their inclusion in the study.

The normality of presented data were checked by using Shapiro-Wilk test, all the studied variables had a normal distribution. Absolute values were compared with calculation of mean values, errors of means, using Student's t-test. Data are presented as mean±standard error of the mean (Δ%, Mean±SEM). Statistical significance was set at p<0,05. All tests were performed using the ANOVA (MicroCal Origin v. 8.0) software.

Results

The level of HbA_{1c} in patients with T2DM and advanced stage of CAN did not change significantly after treatment (p>0,05). Changes of glucose, IRI concentrations and HOMA-IR parameters in patients with T2DM and advanced stage of CAN after 3-months of BFT therapy are given in table 1.

As can be seen from table 1 prescription of BFT to patients with T2DM and advanced stage of CAN contributes to a statistically significant reduction in IRI levels (Δ=-12,74%±1,42% (p<0,05)). At the same time, prescription of BFT does not affect the concentration of fasting glucose and HOMA-IR parameters (p>0,05). Investigated parameters did not change significantly in the control group (p>0,05).

Changes of hs-CRP, leptin and TNF-alpha concentrations in blood of patients with T2DM and advanced stage of CAN after 3-months of BFT therapy are given in table 2.

It is shown in table 2 that the outcome of treatment group was better than of control group. In particular, BFT prescription to patients with T2DM and advanced stage of CAN contributes to a statistically significant reduction in hs-CRP (Δ=-13,62%±1,96% (p<0,05)) and TNF-alpha (Δ=-10,24%±1,54% (p<0,05)) levels compared to the control group. Prescription of BFT does not affect on the concentration of leptin (p>0,05).

Changes of some IL's concentrations and TNF-alpha/IL-10 ratio of patients with T2DM and advanced

Table 3

IL-6, IL-8, IL-10 concentrations and TNF-alpha/IL-10 ratio after 3-months of BFT therapy (Δ%, Mean±SEM)

Parameter	Patients with T2DM and advanced stage of CAN (n=40)				
	Groups	Before treatment	After treatment	% change	p
IL-6 (pg/mL)	Control (n=19)	5,54±0,52	5,14±0,44	-5,81%±1,79%	>0,05
	Treatment (n=21)	5,74±0,31	4,79±0,22	-15,41%±2,03%	<0,05
IL-8 (pg/mL)	Control (n=19)	7,26±0,49	6,94±0,48	-3,9%±1,59%	>0,05
	Treatment (n=21)	7,12±0,48	6,64±0,43	-6,32%±2,03%	>0,05
IL-10 (pg/mL)	Control (n=19)	16,73±2,53	15,66±2,28	-3,7%±2,33%	>0,05
	Treatment (n=21)	16,17±1,86	14,78±1,49	-6,19%±2,73%	>0,05
TNF-alpha/IL-10 (%)	Control (n=19)	42,51±5,49	41,5±4,79	-0,51%±2,32%	>0,05
	Treatment (n=21)	38,61±4,27	35,91±3,33	-4,34%±2,77%	>0,05

Note: The results are presented as absolute values and as % change from baseline, (Δ%, Mean±SEM); p<0,05, compared to baseline.

Abbreviation: BFT — benfotiamine, CAN — cardiac autonomic neuropathy, IL — interleukin, T2DM — type 2 diabetes mellitus, TNF-alpha/IL-10 — tumor necrosis factor-alpha/IL-10 — interleukin 10 ratio.

stage of CAN after 3-months of BFT therapy are given in table 3.

As can be seen from table 3 prescription of BET to patients with T2DM and advanced stage of CAN is accompanied by the statistically significant decrease in the content of IL-6 (Δ=-15,41%±2,03% (p<0,05)), and, at the same time, does not affect on the concentration of IL-8 (p<0,05), IL-10 (p>0,05) and TNF-alpha/IL-10 ratio parameters (p>0,05). In the control group no positive dynamics of the concentration of the studied parameters was found (p>0,05).

Discussion

The protective effect of high-dose thiamine on detrusor contractility and on progression of diabetic cystopathy in streptozotocin-diabetic rats was some of the findings directed to the effect of thiamine on DAN. The deficiency of thiamine in clinical DM may increase the fragility of vascular cells to the adverse effects of hyperglycemia and there by the increase of the risk of developing microvascular complications. A suppression of transketolase (TKT) activity, and subsequent down-regulation of the hexose monophosphate (HMP) shunt, resulting in accumulation of glyceraldehyde 3-phosphate, fructose 6-phosphate, and dihydroxyacetone phosphate may be at least one mechanism in the development of diabetes-induced vascular damage and other comorbidities [7, 8].

Thiamine and its derivatives have been demonstrated to prevent the activation of the biochemical pathways [increased flux through the polyol pathway, formation of AGEs, activation of protein kinase C (PKC), and increased flux through the hexosamine biosynthesis pathway (HBP)] induced by hyperglycemia in DM. TD plays a role in the diabetic endothelial vascular diseases, such as, neuropathy [8, 9]. *In vitro* studies with BFT have shown a reduction in PKC activation in the glomeruli and decreased glomerular AGEs levels. BFT has been shown to prevent increased markers of HBP activity, intracellular AGEs formation, intracellular PKC activity and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) activation seen with *in vitro* hyperglycemic damage. High-dose therapy of thiamine and BFT suppressed AGEs accumulation in the peripheral nerve and reversed diabetic neuropathies (DN's) potentially by reducing the levels of triose phosphates *via* activation of TKT [9].

Cardiac OS is involved in heart failure that is induced by thiamine deprivation in rats. These findings suggest that thiamine modulates OS [9, 10]. Endothelial nitric oxide synthase (eNOS) and nitric oxide (NO) may play an important role in attenuating cardiac remodeling and apoptosis. BFT reduces OS and activates eNOS to enhance the generation and bioavailability of NO, and it subsequently improves the integrity of vascular endothelium to prevent sodium arsenite-induced experimental vascular endothelial dysfunction [10].

The nerve tissues in DM undergo a proinflammatory process that presents symptoms and develops DN. The levels of CRP and TNF-alpha correlate with the incidence of DN's. Production of the initiating inflammatory mediators such as TNF-alpha, transforming growth factor-beta, and NF-κB results from several glucose-induced pathways. Cyclooxygenase-2 (COX-2) is an important enzyme that is upregulated by NF-κB in diabetic peripheral nerves and consecutively generates prostaglandin E2 and ROS that trigger NF-κB. Inducible nitric oxide synthase (iNOS) is an additional inflammatory enzyme which is regulated by NF-κB. Similar to COX-2, iNOS either induces NF-κB or is induced by it. This gives the impression that chronic NF-κB activation is in the center of all the inflammatory elements operating in DN's. The cytokines which are induced by NF-κB in Schwann cells, endothelial cells, and neurons lead to absorption of macrophages in the diabetic nerves. Macrophages promote DN's *via* a variety of mechanisms, including making of cytokines, ROS, and proteases, which all result in cellular oxidative damage and myelin breakdown [10, 11].

BFT can promote neuronal and vascular deficiency correction through participation of NO processes, which

have a significant therapeutic potential for the treatment of CVD. BFT significantly decreased production of pro-inflammatory mediators such as inducible form of iNOS and NO; COX-2, heat-shock protein 70, TNF-alpha, IL-6, whereas it increased anti-inflammatory IL-10 production in lipopolysaccharide (LPS)-stimulated BV-2 microglia. Moreover, BFT suppressed the phosphorylation of extracellular signal-regulated kinases 1/2 (ERK1/2), c-Jun N-terminal kinases (JNK) and a serine/threonine protein kinase (Akt/PKB). Treatment with specific inhibitors revealed that BFT-mediated suppression of NO production was via JNK1/2 and Akt pathway, while the cytokine suppression includes ERK1/2, JNK1/2 and Akt pathways. In murine macrophages, BFT also blocked the expression of COX-2 and its product, prostaglandin E2, by LPS-induces cytotoxicity. In addition, BFT significantly prevented LPS-induced macrophage death and monocyte adhesion to endothelial cells. These anti-inflammatory effects of BFT are mediated through the regulation of the arachidonic acid pathway in macrophages. Therefore, BFT may have therapeutic potential for neurological diseases by inhibiting inflammatory mediators and enhancing anti-inflammatory factor production [7, 12].

The mechanism of BFT influence on diabetic CAN pathogenesis is not well-known. There is moderate evidence from preclinical experimental models that high-dose thiamine and BFT (1) inhibit the HMP, AGEs formation, and diacylglycerol-PKC through the TKT activation; (2) target at various surrogate markers of hyperglycemia-induced pathological processes and (3) can delay the progression of microangiopathic complications [12]. Therefore, the positive influences of BFT is partly confirmed by its neurotropic, cardioprotective, angioprotective and cytoprotective properties [13, 14]; suggests the feasibility of its usage in the complex treatment of patients with T2DM and advanced stage of CAN.

The results obtained in our study indicate that BFT contributed to a decrease in the hs-CRP, TNF-alpha and IL-6 levels. Obtained results could witness, that prescription of BFT may lead to decrease of the proinflammatory immune response.

Conclusion

The obtained data suggest that prescription of BFT is associated with reduction of pro-inflammatory component of the immune response and make it possible to regard BFT as a promising pharmacological agent in a complex therapy of the advanced stage of CAN in T2DM. Thus, further investigations aimed to understand the mechanism of action and confirmation of the beneficial effect of BFT on biochemical parameters, dynamics of independent CARTs, Holter-ECG, arterial wall stiffness parameters among patients with T2DM and CAN, and its associated comorbidities may be needed to validate this clinical findings.

Conflicts of Interest: the research was carried out within the frame of the scientific work of Lviv National Medical University named after Danylo Halytsky (№ 0111U000131).

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