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PECULIAR FEATURES OF GLUCOSE HOMEOSTASIS IN PATIENTS SUFFERING FROM NON-ALCOHOLIC STEATOHEPATITIS WITH COMORBID OBESITY AND OSTEOARTHRITIS ON THE BACKGROUND OF METADOXINE AND GUAR GUM ADMINISTRATION**O.S. Khukhlina, O.D. Liakhovich, V. O. Shuper, L. V. Kanyovska, O.Ye. Hryniuk**

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Key words:*non-alcoholic steatohepatitis, obesity, osteoarthritis, insulin resistance, metadoxine, guar gum.**Bukovinian Medical Herald. 2020. V.24, № 3 (95). P. 143-150.***DOI:***10.24061/2413-0737.
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стеатогепатит, ожиріння,
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метадоксин, смола гуарова.**Буковинський медичний
вісник. 2020. Т.24, № 3 (95),
С. 143-150.***Objective.** *To determine the probable effect of metadoxine and guar gum on glucose homeostasis during the comorbid course of non-alcoholic steatohepatitis (NASH) with obesity and osteoarthritis (OA).***Material and methods.** *60 patients (30 men and 30 women) with the indicated comorbidity were examined and divided into three groups: patients of group 1 - control (C) (n = 20) took Essentiale H 1 capsule 3 times a day, patients in group 2 - main group 1 (M1) (n = 20) - received metadoxine (Liveria IC) at 0.5 g twice daily, in 3 - main group 2 (M2) (n = 20) - in addition to metadoxine patients received guar gum (Guarem) 1 sachet (5 g) 2 times a day. The groups were randomized to age, sex, obesity and cytolytic syndrome activity. The control group consisted of 30 practically healthy individuals of the same age and gender. The average age of patients was (62,3 ± 5,7) years.***Conclusions.** *The conducted analysis showed that the course of treatment with metadoxine and guar gum proved the ability to achieve stable normalization of carbohydrate metabolism over a long period of time, since guar gum together with metadoxine enhance rapid compensation of carbohydrate metabolism with impaired carbohydrate tolerance, ability to resensitize insulin receptors and eliminate insulin resistance syndrome.***ОСОБЛИВОСТІ ГОМЕОСТАЗУ ГЛЮКОЗИ У ХВОРИХ НА НЕАЛКОГОЛЬНИЙ СТЕАТОГЕПАТИТ ЗА КОМОРБІДНОСТІ З ОЖИРІННЯМ ТА ОСТЕОАРТРОЗОМ НА ФОНІ ЗАСТОСУВАННЯ МЕТАДОКСИНУ ТА ГУАРОВОЇ СМОЛИ****О.С. Хухліна, О.Д. Ляхович, В.О. Шупер, Л.В. Каньовська, О.Є. Гринюк****Мета роботи** – з'ясувати ймовірний вплив метадоксину та смоли гуарової на показники гомеостазу глюкози за коморбідного перебігу неалкогольного стеатогепатиту (НАСГ) з ожирінням та остеоартрозом (ОА).**Матеріал і методи.** *Обстежено 60 пацієнтів (30 чоловіків та 30 жінок) із зазначеною коморбідністю, які були розподілені на три групи: пацієнти 1-ї групи - контрольної (К) (n=20) приймали Ессенціале Н по 1 капсулі 3 рази на день, пацієнти 2-ї групи - основна група 1 (О1) (n=20) – отримували Метадоксин (Ліверія ІС) по 0,5 г на прийом двічі на день, у 3-ї - основній групі 2 (О2) (n=20) – пацієнти, окрім метадоксину отримували гуарову смолу (Гуарем) по 1 саше (5 г) 2 рази на день. Групи були рандомізовані за віком, статтю, ступенем ожиріння та активністю цитолітичного*

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синдрому. Контрольну групу склали 30 практично здорових осіб відповідного віку та статі. Середній вік хворих склав $(62,3 \pm 5,7)$ років.

Висновки. Проведений нами аналіз показав, що курс лікування метадоксином та гуаровою смолою довів спроможність досягнення стабільної нормалізації показників вуглеводного обміну на тривалий термін часу, оскільки гуарова смола разом із метадоксином сприяє швидкій компенсації вуглеводного обміну при порушеній толерантності до вуглеводів, ресенсибілізації інсулінових рецепторів та усуненню синдрому інсулінорезистентності.

Ключевые слова:

неалкогольный
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ОСОБЕННОСТИ ГОМЕОСТАЗА ГЛЮКОЗЫ У БОЛЬНЫХ НЕАЛКОГОЛЬНЫМ СТЕАТОГЕПАТИТОМ ПРИ КОМОРБИДНОСТИ С ОЖИРЕНИЕМ И ОСТЕОАРТРОЗОМ НА ФОНЕ ПРИМЕНЕНИЯ МЕТАДОКСИНА И ГУАРОВОЙ СМОЛЫ

О.С. Хухлина, О.Д. Ляхович, В.А. Шупер, Л.В. Каневская, О.Е. Гринюк

Цель работы – выяснить возможное влияние метадоксина и смолы гуаровой на показатели гомеостаза глюкозы при коморбидном течении неалкогольного стеатогепатита (НАСГ) с ожирением и остеоартрозом (ОА).

Материал и методы. Обследовано 60 пациентов (24 мужчин и 36 женщин) с указанной коморбидностью, которые были разделены на три группы: пациенты 1-ой группы - контрольной (К) ($n = 20$) принимали Эссенциале Н по 1 капсуле 3 раза в день, пациенты 2-ой группы - основная группа 1 (О1) ($n = 20$) - получали Метадоксин (Ливерия IC) по 0,5 г на прием дважды в день, в 3-ей - основной группе 2 (О2) ($n = 20$) - пациенты, кроме метадоксина получали гуаровую смолу (Гуарем) по 1 саше (5 г) 2 раза в день. Группы были рандомизированы по возрасту, полу, степени ожирения и активности цитолитического синдрома. Контрольную группу составили 30 практически здоровых лиц соответствующего возраста и пола. Средний возраст больных составил $(62,3 \pm 5,7)$ лет.

Выводы. Проведенный нами анализ показал, что курс лечения метадоксином и гуаровой смолой доказал способность достижения стабильной нормализации показателей углеводного обмена на длительный период времени, поскольку гуаровая смола вместе с метадоксином способствует быстрой компенсации углеводного обмена при нарушении толерантности к углеводам, ресенсибилизации инсулиновых рецепторов и устранению синдрома инсулинорезистентности.

Introduction. Many researchers have confirmed that one of the important issues of modern medicine is the study of comorbidity as one of the promising ways to solve personalized treatment, improve overall treatment

outcomes and reduce large-scale social-economic consequences of the population [1, 2].

Today, non-alcoholic fatty liver disease (NAFLD) is one of the most common diseases in hepatology, which

leads to a deterioration in quality and expectancy of life. This is primarily due to the high risk of progression of non-alcoholic steatohepatitis (NASH) with the development of liver failure and hepatocellular carcinoma. The maximum risk of developing NAFLD was observed in the group of obese people with hypertriglyceridemia [3].

As for the etiology of NAFLD, it is quite diverse, although it is closely related to insulin resistance (IR). The liver is the main target of lesions in conditions characterized by IR, which is a risk factor for the progression of hepatic steatosis in NASH, with its inherent risk of advancing to cirrhosis [4].

A number of evidences are involved in the development of NAFLD: insulin resistance, chronic postprandial hyperglycemia, glucose toxicity, glycosylation of structural and transport proteins, hyperlipidemia, dyslipidemia, hepatotoxicity of hypolipidemic agents, etc.) and a number of unknown factors [5–7].

IR is more pronounced in patients with abdominal obesity. These differences are due to genetically different expression of adipocyte genes in abdominal and subcutaneous fat [8]. Hyperglycemia and hyperinsulinemia are important prognostic factors in patients with NAFLD. Impaired carbohydrate tolerance and type 2 diabetes mellitus (DM) have been shown to stimulate lipogenesis [9]. The increase in overweight (OW) and obesity (OB) is one of the most important health problems in all countries today, due to a huge number of diseases associated with overweight [10].

Because the development of NAFLD is associated with metabolic disorders, the purpose of treatment is to eliminate them or significantly reduce the negative effects [11]. Drugs used in a comprehensive therapy of NASH should have not only anti-inflammatory, antioxidant, hypolipidemic, hypoglycemic, hepatoprotective effect, but also have antifibrotic activity [12-13].

Certain studies suggest that detoxification drugs should be used to correct the established disorders of NASH comorbidity with obesity and osteoarthritis (OA) in order to eliminate the potent pathogenetically significant effects of endotoxemia, postprandial hyperglycemia, IR, which use drugs from the group of enterosorbents, and neutralize their effects in the systemic circulation by restoring metabolic processes and liver function with hepatotropic cytoprotectors. In the practice of internal medicine and endocrinology in type 2 diabetes mellitus and obesity a drug of sorption, hypoglycemic, hypolipidemic action - guar gum is used. In a comprehensive treatment of alcoholic fatty liver disease and withdrawal syndrome hepatotropic drug with powerful antioxidant, membrane-stabilizing, detoxifying properties - metadoxine is widely used [14-15].

The effect of these drugs on the clinical course of NASH in comorbidities with obesity and OA, the effect

on the course of comorbid diseases is unknown today.

Objective. To determine the probable effect of metadoxine and guar gum on glucose homeostasis during the comorbid course of NASH with obesity and OA.

Material and methods. The study was carried out on the basis of Higher State Educational Establishment of Ukraine "Bukovinian State Medical University" and is a fragment of the research work conducted at the Department of Internal Medicine, Clinical Pharmacology and Occupational Diseases "Features of Comorbidity of Diseases of Internal Organs: Risk Factors, Mechanisms of Development and Interaction, Pharmacotherapy" (State registration number: 0114U002475).

To determine the effectiveness of treatment, 60 patients (24 men and 36 women) with NASH, obesity and OA were examined, and were divided into three groups, randomized to age, sex, degree of obesity, and cytolytic syndrome activity. Control group (C) (20 patients (8 men and 12 women, mean age (62.5 ± 5.4) years) with NASH received a low-calorie diet, Essentiale H - a preparation of essential phospholipids (EFL) as a hepatoprotective and hypolipidemic drug (1 capsule 3 times a day), rosuvastatin 10 mg 1 time per day, NSAIDs (meloxicam) at a dose of 7.5 mg - 1 time per day, chondroprotectors (Teraflex) 1 capsule 3 times a day for 90 days. Main group 1 (M1) (20 patients (8 men and 12 women, mean age (63.1 ± 5.3) years)), which received metadoxine (Liveria IC) instead of Essentiale H (manufacturer of TDV "Interchem", Odessa) at a daily dose of 1.0 g (0.5 g twice daily) for 90 days. Main group 2 (M2) (20 people (8 men and 12 women, mean age) (62.9 ± 5.2) years), in addition to diet, Metadoxine 0.5 g 2 times a day instead of rosuvastatin received guar gum (Guarem) (manufacturer "Orion Corporation", Finland) 1 sachet (5 g) 2 times a day. The recommended dose of gum was dissolved in a homogeneous suspension in 250 ml of neutral mineral or chilled boiled water for 90 days. No cases of adverse drug reactions were identified during the study.

Control examinations were performed in the group of practically healthy individuals (PHI) ($n = 30$), including 14 men and 16 women. At the time of the examination they had no exacerbations of chronic diseases of the respiratory system, gastrointestinal tract, cardiovascular system, as well as those who did not have acute diseases, including respiratory, for the last 3 months. Individuals in the control group were comparable to patients in other age and sex groups.

The diagnosis of NASH was made on the ground of anamnestic, clinical, laboratory data, determination of serological markers for hepatitis B and C viruses, the results of USG according to the unified clinical protocol, approved by the Order of the Ministry of Health of Ukraine № 826 from 06.11.2014, in the presence of criteria for the exclusion of chronic diffuse liver disease of the viral, hereditary, autoimmune or medicinal genesis as causes of cholestatic or cytolytic syndromes, taking

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into account the 10th revision of ICE. The OA diagnosis was made on the basis of the EULAR recommendations (2010) and the Order of the Ministry of Health of Ukraine № 676 dated October 12, 2006, "Clinical Protocol for the Provision of Medical Aid to Patients with Osteoarthritis" in accordance with section 13 "Rheumatology" and the Protocol of the Ministry of Health of Ukraine № 263 from section "Rheumatology" April 11, 2014. The presence of abdominal obesity in patients was determined on the basis of the Order of the Ministry of Health of Ukraine № 16 dated January 14, 2013 "Methodical Recommendations for General Practitioners - Family Medicine on Counseling Patients on the Basic Principles of Healthy Eating".

Analysis of clinical manifestations, laboratory indicators of glucose metabolism was performed according to conventional methods, which were studied in the dynamics after 30, 90 days of treatment, as well as three months after treatment.

The degree of carbohydrate metabolism compensation was determined by fasting glycemia and two hours after glucose loading (glucose tolerance test) by glucose oxidase method, fasting insulin content (DRG System) - ELISA method, blood glycosylated hemoglobin (HbA1c) using standard sets of reagents "Danush Ltd" (Lviv). The degree of IR was determined by the value of BMI, the ratio: WC/HC; Caro index; HOMA-IR (D. R. Matthews), which was calculated using the HOMA Calculator Version 2.2 Diabetes Trials Unit University of Oxford (UK).

The protocol for the examination of patients was approved at the Biomedical Ethics Committee meeting at HSEE of Ukraine „Bukovinian State Medical University“. The document has been compiled in accordance with the requirements regulated by the 6th chapter of the manual CH GPC (1996) and created on the basis of its national guide "Guidelines for Clinical Research. Medicines. Approved Clinical Practice ", approved by the Order of the MOH of Ukraine No. 373 dated July 22, 2005. In drawing up the protocol the basic principles of the Helsinki Declaration on Biomedical Research (1974), adapted to the 41st International Assembly in Hong Kong (September 1989), in which a person acts as their object, as well as "Ethical Principles for Medical Research Involving of Human Subjects", adopted by the 52nd Assembly of the World Medical Association (2000) were followed. The Committee on Biomedical Ethics of the HSEE of Ukraine „Bukovinian State Medical University“ has not revealed any violations of moral and legal standards during the scientific research.

The results of the study were statistically processed on a personal computer with the help of the standard applications Microsoft Excellence and SPSS Statistics 20 Multilingual. The mean values (M), the arithmetic mean (t), and the validity of the differences p according to Student's t-distribution were evaluated. The difference in indices for various periods of the study was considered

probable at $p < 0.05$. To determine the relationship between the indices, Kendall's tau-b correlation coefficient was used.

Results and their discussion. It should be noted that in patients with NASH against the ground of obesity and OA, the most pronounced syndrome of IR was found, which is probably primary (hereditary predisposition), and may be secondary to liver damage against the ground of NASH. According to the above data, surveyed all the groups, according to the "Diagnostic criteria for diabetes and other disorders of carbohydrate metabolism, WHO" were diagnosed with impaired glucose tolerance. The most significant metabolic prerequisites for the development of NASH against the ground of OB and OA are probable postprandial hyperglycemia, hyperinsulinemia, peripheral tissue IR (increase in HOMA-IR, decrease in S), increase in glycosylated hemoglobin.

Analysis of the effect of metadoxine and the combination of metadoxine with guar gum in the course of prescribing to patients with NASH against the ground of OB and OA on the course of the disease in comparison with the control group revealed the following results. A significant effect of the suggested therapy in patients of main group was determined concerning the correction of blood glycemie profile and IR (Table). In patients of the M1 group on the 30th day of treatment, fasting blood glucose 1.3 times decreased ($p < 0.05$), while in patients of the M2 group, the glucose content 1.4 times decreased ($p < 0.05$), with normalization of the indicator, which indicates a more significant level of reduction under the influence of Guarem ($p < 0.05$), with the presence of a probable intergroup difference ($p < 0.05$). Changes in group C were unlikely. On the 90th day of treatment, fasting glycemia in patients of M1 and M2 groups was within the norm ($p < 0.05$).

Glucose content 2 h after glucose loading in patients of M1 group on the 30th day of treatment 1.3 times decreased, M2 group - by 1.4 times, C group - by 1.2 times ($p < 0.05$). After treatment - on day 90, the level of basal and postprandial glycemia in patients of M1, M2 groups was normalized, but in group C the glycemie level significantly exceeded that in PHI ($p < 0.05$). (Table). At the same time, when observed 1 month after the end of treatment in patients with NASH of the main group (M1, M2), the level of postprandial glucose was probably lower than in group C ($p < 0.05$). The content of HbA1c in the blood on the 30th day of treatment probably decreased only in M1 and M2 comparison groups (by 7.9% and 11.5% ($p < 0.05$), respectively) and essentially normalized, in C group the indicator only had downward trend ($p > 0.05$). A probable decrease in HbA1c content in patients of C group was not observed until the end of the observation period ($p < 0.05$). 1 month after the end of treatment in patients with NASH M1 and M2 groups, the content of HbA1c in the blood continued to decrease ($p < 0.05$), remaining within normal limits ($p > 0.05$).

Table

Indicators of glucose homeostasis and the degree of insulin resistance in patients with nonalcoholic steatohepatitis, osteoarthritis and obesity in the dynamics of treatment, (M ± m)

	Indicators	Patients with NASH, obesity, OA		
		Group C (n=20)	Group M1 (n=20)	Group M2 (n=20)
PHI	Fasting glucose	4,06±0,04		
	Glucose in 2 hours	7,48±0,12		
	Insulin, mcU / ml	9,57±0,04		
	HbA1c, %	5,07±0,15		
	HOMA IR	1,17±0,01		
Before treatment	Fasting glucose	5,86±0,04 *	5,91±0,07 *	5,85±0,05 *
	Glucose in 2 hours	10,32±0,12 *	10,35±0,15 *	10,34±0,12 *
	Insulin, mcU / ml	26,89±0,17 *	26,87±0,16 *	26,89±0,21 *
	HbA1c, %	5,93±0,11 *	5,90±0,15 *	5,94±0,12 *
	HOMA IR	3,45±0,02 *	3,50±0,03 *	3,47±0,05 *
In 30 days	Fasting glucose	5,48±0,13 *	4,43±0,11 °	4,13±0,13 °
	Glucose in 2 hours	8,42±0,12 */°	7,72±0,153 °	7,45±0,11 °/#
	Insulin, mcU / ml	24,24±0,62 *	15,54±0,42 °/#	13,01±0,22 °/#
	HbA1c, %	5,98±0,28 *	5,48±0,12 °/#	5,33±0,13 °/#
	HOMA IR	3,12±0,06 *	1,93±0,03 */°/#	1,59±0,02 °/#
In 90 days	Fasting glucose	5,36±0,12 °	4,30±0,10 °	4,05±0,05 °
	Glucose in 2 hours	7,89±0,12 */°	7,52±0,13 °	7,25±0,11 °/#
	Insulin, mcU / ml	20,58±0,41 *	11,03±0,25 °/#	9,51±0,17 °/#
	HbA1c, %	5,65±0,20 *	5,24±0,09 °/#	5,09±0,05 °/#
	HOMA IR	2,66±0,17 */°	1,37±0,11 °/#	1,16±0,09 °/#
1 month after treatment	Fasting glucose	5,30±0,11 °	4,22±0,09 °	4,01±0,03 °/#
	Glucose in 2 hours	7,65±0,10 */°	7,42±0,13 °	7,16±0,11 °/#
	Insulin, mcU / ml	19,84±0,38 *	10,25±0,17 °/#	9,33±0,12 °/#
	HbA1c, %	5,68±0,23 *	5,07±0,05 °/#	5,02±0,04 °/#
	HOMA IR	2,56±0,27 *	1,26±0,09 °/#	1,14±0,05 °/#

1. Group C (control), n = 20 - patients with NASH who received Essentiale H, rosuvastatin; Group M1 (main), n = 20 - patients with NASH who received metadoxine, rosuvastatin. Group M2, n = 20 - patients with NASH who received metadoxine, guar gum.

2. * - the difference is probable in comparison with the indicator in PHI (p <0,05);

° - the difference is probable in comparison with the indicator before treatment (p <0,05);

- the difference is probable in comparison with the indicator after treatment in patients of group M1 (p <0,05).

Оригінальні дослідження

Fasting insulin content after 30 days of treatment probably decreased only in patients of the main observation groups M1 and M2 - 1.7 and 2.1 times ($p < 0.05$) with the actual normalization of the indicator. At the same time, after 3 months of treatment, the content of insulin in the blood of patients in groups M1 and M2 2.4 and 2.8 times decreased ($p < 0.05$) against 1.3 times in group C ($p > 0.05$), indicating a significant contribution of metadoxine and guar gum in overcoming hyperinsulinemia and IR in general (Table).

This is evidenced by the dynamics of changes in IR index - HOMA IR, which in patients with NASH of the main group on the 30th day of treatment in groups M1 and M2 - 1.8 and 2.1 times decreased, respectively ($p < 0.05$). After a course of treatment HOMA IR was normalized only in the M1 and M2 observation groups, in particular, in the M1 group 2.6 times decreased, M2 group - 2.9 times against 1.3 times decreased in the C group ($p < 0.05$) with the actual normalization of the indicator in M1 and M2 groups ($p > 0.05$). Thus, a 90-day course of treatment with metadoxine and guar gum proved the ability to achieve stable normalization of carbohydrate metabolism over the long term, as guar gum together with metadoxine helps to quickly compensate carbohydrate metabolism in disturbance of glucose tolerance, insulin receptor resensitization and elimination of IR syndrome.

This is, in our opinion, due to the known detoxifying effects of guar gum. When it is ingested in the gastrointestinal tract (GI tract), as an enterosorbent, it promotes the absorption on the substrate surface of simple and complex carbohydrates, intestinal bacterial toxins, which reduces the exposure time in the GI tract and their absorption into the systemic circulation. It was due to enterosorption by guar gum that stable normoglycemia was achieved in contrast to EFL, which also contributed to the normalization of the glycemic profile, but did not lead to the normalization of IR indices.

Conclusion. Preparations of metadoxine and guar gum in a comprehensive treatment of patients with NASH and OA with concomitant obesity contributed to a rapid compensation of carbohydrate metabolism with impaired carbohydrate tolerance, resensitization of insulin receptors and elimination of peripheral IR tissue syndrome, (guar gum - reducing the absorption of carbohydrates, fermentation products in the intestine, toxins of intestinal bacteria with increased excretion, reducing the degree of endogenous intoxication, oxidative stress, metadoxine - due to the ability to adjust metabolism, reduce oxidative modification of receptors, restore the sensitivity of insulin receptors in the liver to the action of insulin - therefore reduce the incidence of insulin glycogen as an energy substance).

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