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Development of type i diabetes mellitus induced by nonalcoholic fatty liver disease

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НАЖБП в сочетании с сахарным диабетом 1 типа отличается асимптоматическим клиническим течением и отсутствием выраженных клинических признаков поражения печени. НАЖБП существенно влияет на течение СД 1 типа, способствует появлению синдрома неспровоцированных гипогликемий, резким перепадам гликемии, эпизодам кетоацидоза. Значительные перепады гликемии у пациентов с СД 1 типа и НАЖБП вызывают оксидативный стресс, что приводит к нарушению специфической функции печени синтеза и секреции желчных кислот. Для диагностики субклинических форм НАЖБП наиболее информативными биохимическими маркерами являются показатели синтеза первичных желчных кислот и их конъюгирования с таурином и глицином.

Ключевые слова: *сахарный диабет, неалкогольная жировая болезнь печени, углеводный обмен, желчные кислоты.*

Diabetes Mellitus (DM) is one of the most common diseases and poses a global problem, which spreads from year to year. According to statistic, globally 371 million people suffer from this disease, which corresponds to 7% of the total population of the Earth[1, 2]. Prevalence of DM and its consequences such as complications and associated diseases present the biggest challenge to the global healthcare, and according to the International Diabetes Federation (IDF) it is primarily related to the fact that about 46% of the patients are unaware of their illness[3, 4]. The main causes for disablement and mortality of DM patients are the vascular complications of the disease: microangiopathies (retinopathy and nephropathy), macroangiopathies (cerebrovascular accident, myocardial infarction, gangrene of lower extremities) and neuropathies. Metabolic disorders play a key role in the pathogenesis of these complications [5, 6, 7].

According to multiple epidemiological studies, liver damage with the development of diabetic hepatopathy, which includes hepatomegaly and fatty liver infiltration of varying severity, is observed in 25 to 87% of DM patients [8, 9]. Under physiological conditions, insulin, created in the pancreas, is delivered to the liver through the hepatic portal vein system, where 50% of its total amount is bound to hepatocytes and used by them[10, 11]. The liver together with the fat tissue and skeletal muscles are the main consumers of insulin [12] and provide the main processes of gluconeogenesis [13]. The multiplicity of functions of hepatocytes means that in case of their pathology most biochemical processes are disturbed.

The study of functional condition of the liver in DM and treatment of its disorders is of particular interest, because damage to this organ significantly affects the course and level of compensation of DM [14, 15]. Timely detection of hepatic disorders in DM afflicted persons can contribute to adequate treatment of DM [16].

The objective of this study was to determine the influence of Non-Alcoholic Fatty Liver Disease (NAFLD) on the course of type 1 DM (T1DM).

Materials and Methods

At the premises of Endocrinology and Gastroenterology Department of the Municipal Non-Commercial Enterprise of the Kharkiv Regional Council "Regional Clinical Hospital", Kharkiv, we have examined young and middle-aged patients with T1DM (according to the WHO classification), which had no concomitant nephropathies and obesity. In total, 62 patients were examined: of which 38 patients had moderate T1DM and 24 patients had severe T1DM. The control was comprised of 20 apparently healthy people. Verification of pathological conditions and somatic pathology was performed according to ICD-10 classification. The study excluded persons that consumed alcohol and hepatotoxic substances or had signs of viral, autoimmune or toxic liver damage. Examinations were performed according to the international standards regarding ethical issues in conducting research and gathering biosamples. No examined patients had concomitant pathologies of gastrointestinal tract, or diseases of other organs or systems, which could affect the results of the

study. For glycaemic control, all patients received insulin and compensation of carbohydrate metabolism (glycated haemoglobin HbA1c did not exceed 9%). In order to clarify the nature and severity of liver damage, patients with severe NAFLD underwent needle biopsy of the liver followed by morphological examination of biopsy material of 8 patients.

Results and Discussion

No signs of liver damage were detected in 15 patients with T1DM. According to the ultrasonic data, topography and structure of the liver in these patients were normal. Non-alcoholic fatty liver disease was detected in 47 patients. During the clinical examination, meaningful changes were observed in the study groups (Table 1).

Patients with NAFLD combined with T1DM had a higher insulin demand, and complications (angiopathies, neuropathies) were more frequent than in patients with T1DM without the liver injury. T1DM control indices were significantly pronounced in patients with NAFLD. Typical for these patients were spontaneous hypoglycaemic episodes, which were not connected to diet violation, inadequate amount of carbohydrates in food or excessive physical activity. In this group, ketoacidosis episodes occurred in 90.9% of cases.

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Table 1. Main clinical characteristics of patients with T1DM

Indicators	1st type Diabetes Mellitus without NAFLD n=15	1st type Diabetes Mellitus+ NAFLD n=47
Insulin demand (U/kg)	0,46±0,07	0,68±0,17
1st type Diabetes Mellitus duration (years)	3,7±0,7	10,2±2,3
Neuropathies	4	42
Angiopathies	1	42
Pain in the right hypochondrium	-	5
Heaviness in the right hypochondrium	-	9
Enlarged liver	-	42
Bitter taste	2	8
Meteorism	3	15
Asthenia	2	25
Spontaneous hypoglycaemic episodes	2	41
Ketoacidosis episodes	5	39
Moderate 1st type Diabetes Mellitus	16	30
Severe 1st type Diabetes Mellitus	4	18

In most patients with NAFLD, liver was enlarged on palpation, surface of the liver was smooth, edge was sharp or rounded, painless on palpation. The overwhelming majority of patients with NAFLD (92%) showed subclinical, painless development of liver damage. There were symptoms specific to the involvement of hepatobiliary system – bitter taste, meteorism, asthenia. Deficiency in subjective signs of NAFLD is probably caused by the damage to sensory receptors and autonomic liver innervation disorder. The painless development of NAFLD creates certain problems, where patients incorrectly evaluate their condition; the patient is not interested in deeper examination of the liver and is not aware of the necessity of additional therapeutic intervention.

Increased activity of AST and ALT in the blood serum demonstrates the development of cytolysis syndrome in the examined patients. The tendency to increase of bilirubin, excretory enzyme - LPH, evidences the development of cholestasis syndrome with bile-excreting liver dysfunction and biliary micella disorder and small biliary duct damage. Increased biochemical markers of liver tissue damage in the background of RI evidence the structural-functional changes in hepatocyte with development of cytolysis and cholestasis syndrome in the patients suffering from NAFLD and comorbide pathology.

Table 2. Biochemical blood indicators in T1DM patients

Indicators	Control n=18	1st type Diabetes Mellitus without NAFLD n=15	1st type Diabetes Mellitus+ NAFLD n=47
Glycemic excursion amplitude (mmol/l)	1,46±0,32	2,64±0,97	6,34±1,2*,**
Hb A_{1c} (%).	4,72±0,04	5,01±0,23	9,81±0,74*,**
Cholesterol (mmol/l)	4,91±0,30	5,02±0,26	6,33±0,45*,**
□-lipoprotein (U)	45,20±3,84	55,13±2,64 *	68,33±0,45*,**
Albumins (%)	56,1±0,68	46,6±0,32*	41,1±2,53*,**
Indicators	Control n=18	1st type Diabetes Mellitus without NAFLD n=15	1st type Diabetes Mellitus+ NAFLD n=47
Taurocholic bile acid (umol/l)	4,68±0,39	5,23±0,64	15,23±0,94*,**
Glycocholic bile acid (umol/l)	5,04±0,32	6,54±0,37	9,34±0,57*,**
Cholic bile acid (umol/l)	3,01±0,23	4,33±0,41 *	12,33±0,52*,**
Desoxycholic bile acid (umol/l)	6,48±0,39	9,27±0,50 *	19,27±0,61*,**
PTI (%)	89,4±0,3	91,0±0,2	102,4±0,5 *, **
Fibrinogen (g/l)	3,7±0,9	3,6±0,6	4,45±0,8 *, **
Glycemic excursion amplitude (mmol/l)	1,46±0,32	2,64±0,97	6,34±1,2*,**

*Note: * – the differences are significant ($p<0.05$) in comparison with the control; ** – the differences are significant ($p<0.05$) in comparison with T1DM group without NAFLD and T1DM + NAFLD group.*

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Changes in proteometabolism were observed in the patients suffering from NAFLD and type 2 DM, and were more expressed in combination of NAFLD and type 2 DM, can be warning about development of protein and energy syndrome with the impaired metabolic processes flowing with synthesis inhibition and protein ability. Monitoring these kinds of metabolism is of prognostic value for liver diagnostics in the patients with NAFLD, type 1 DM and their combination

In the patients with type 1 diabetes mellitus and NAFLD, the indicators of carbohydrate and lipid metabolism were reliably high than in the patients with type 1 DM and intact liver. These patients had the signs of coagulopathy - increased prothrombin index and plasmic fibrinogen (Table 2).

These patients had the signs of coagulopathy - increased prothrombin index and plasmic fibrinogen.

Therefore, the NAFLD significantly affects the development of type 1 diabetes mellitus. Failure of hepatic buffer and liver starch deficiency increase the likelihood of hypoglycemia that leads to retinal hemorrhages [17, 18], as well as represent one of the most important pathogenetic mechanisms of the nervous system damage in type 1 DM [19, 20]. Frequent hypoglycemias induce lipidemia and atherosclerosis [21].

Conclusions:

NAFLD is distinguished by asymptomatic clinical progression.

NAFLD significantly affects the development of type 1 DM, induces the forced hypoglycemia syndromes, sudden drop of glycemia, ketoacidosis episodes. The patients with NAFLD suffer from specific liver dysfunction of bile acid synthesis and secretion. For NAFLD subclinical form diagnostics, the most informative biochemical markers are indicators of primary bile acid synthesis and conjugation with taurin and glycin.

References:

1. American Diabetes Association (2018) Comprehensive Medical Evaluation and Assessment of Comorbidities: Standards of Medical Care in Diabetes-2018. Diabetes Care, Jan., 41(Suppl. 1): S28–S37.

2. EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. Diabetologia. 2016; 59: 1121-40.

3. Диабет. Информационный бюллетень, октябрь 2018 г. // Всемирная организация здравоохранения [Diabetes. Information Letter, October 2018 // World Health Organization (in Russ.)]

4. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 26:S5-S20, 2003

5. Кляритская И.Л. Коморбидность сахарного диабета и заболеваний печени / Кляритская И.Л., Максимова Е.В. // Крымский терапевтический журнал. – 2012. – № 2(19). – с. 109-115. [Klyaritskaya I.L. Comorbidity of Diabetes Mellitus and Liver Diseases / Klyaritskaya I.L., Maksimova Y.V. // Krymskiy Therapeutic Journal. - 2012. – No. 2(19). – P. 109-115. (in Russ.)]

6. Селивёрстов П.В. Неалкогольная жировая болезнь печени: от теории к практике // Архивъ внутренней медицины. – 2015. – № 1(21). – с. 19-26. [Seliverstov P.V. Nonalcoholic Fatty Liver Disease: from Theory to Practice // Archive of Internal Medicine. – 2015. – No. 1(21). – P. 19-26. (in Russ.)]

7. Castera L. Noninvasive evaluation of nonalcoholic fatty liver disease. Semin Liver Dis. 2015;35:291-303. DOI: 10.1055/s-0035-1562948.

8. Forlani G, Giorda C, Manti R. The burden of NAFLD and its characteristics in a nationwide population with type 2 diabetes. J Diabetes Res. 2016; 2016. DOI: 10.1155/2016/2931985.

9. Lin SC, Heba E, Wolfson T. Noninvasive diagnosis of nonalcoholic fatty liver disease and quantification of liver fat using a new quantitative ultrasound technique. Clin. Gastroenterol. Hepatol. 2015;13:1337-45. DOI: 10.1016/j.cgh.2014.11.027.

10. Lomonaco R, Bril F, Portillo-Sanchez P. Metabolic impact of nonalcoholic steatohepatitis in obese patients with type 2 diabetes. Diabetes Care. 2016; 39: 632-8. DOI: 10.2337/dc15-1876.

11. Kumar R, Mohan S. Non-alcoholic fatty liver disease in lean subjects: characteristics andimplications. J Clin Transl Hepatol.2017; 5(3): 216–23.

12. Mechanick JI. Global dimensions of diabetes: information and synthesis. Ann. Glob. Health.2015; 1:6:733–4. DOI:http://dx.doi.org/10.1016/j.aogh.2015.12.015.

13. Rinella ME. Nonalcoholic fatty liver disease: a systematic review. JAMA. 2015; 313:2263-73. doi: 10.1001/jama.2015.5370.

14. Standards of Medical Care in Diabetes. American Diabetes Association (ADA). Diabetes Care.2017; 40(1): P. 75-98.

15. Никитин И.Г. Скрининговая программа по выявлению распространенности неалкогольной жировой болезни печени и определению факторов риска развития заболевания // Российские медицинские вести. 2010. № 15(1). С. 41–46. [Nikitin I.G. Screening program for identifying the prevalence rate of nonalcoholic fatty liver disease and determining the risk factors for disease development // Russian Medical News. 2010. No. 15(1). P. 41–46. (in Russ.)]

16. Дедов И.И. Осложнения сахарного диабета: лечение и профилактика / Дедов И.И., Шестакова В.М. // Медицинское информационное агентство. – 2017. [Dedov I.I. Diabetes Mellitus Complications: Treatment and Prophylaxis / Dedov I.I., Shestakova V.M. // Medical Information Agency. – 2017. (in Russ.)]

17. Смирнова О.М. Сахарный диабет и неалкогольная болезнь печени // медицинский совет № 2004. – 2014. – с. 57-61 [Smirnova O.M. Diabetes Mellitus and Nonalcoholic Liver Disease // Medical Council No. 2004. – 2014. – P. 57-61(in Russ.)]

18. Стаценко М.Е. Неалкогольная жировая болезнь печени как мультисистемное заболевание / Стаценко М.Е., Туркина С.В., Косивцова М.А., Тыщенко И.А. // Вестник ВолгГМУ. – 2016. - №2(58). – с. 8-14. [Statsenko M.Ye. Nonalcoholic Fatty Liver Disease as Multisystem Disease / Statsenko M.Ye., Turkina S.V., Kosivtsova S.V., Tyshchenko I.A. // VolgGMU Newsletter. – 2016. - No. 2(58). – P. 8-14(in Russ.)]

19. Бородина В.Д. Осложнения сахарного диабета / Бородина В.Д., Баграмян Д.В. //Международный студенческий научный вестник. – 2016. – № 4-1. [Borodina V.D. Diabetes Mellitus Complications / Borodina V.D., Bagramyan D.V. // International Student's Scientific Bulletin. – 2016. – No. 4-1(in Russ.)]

20. Высотин С.А. Современные подходы к лабораторной диагностике стеатоза печени / Высотин С.А., Сайфитова А.Т., Невзорова М.С. // Международный студенческий научный вестник. – 2017. – № 6.; [Vysotin S.A. Modern approaches to laboratory diagnostics of hepatic steatosis / Vysotin S.A., Saifitova A.T., Nevzorova M.S. // International Student's Scientific Bulletin. – 2017. – No. 6; (in Russ.)] [Vysotin S.A. Modern approaches to laboratory diagnostics of hepatic steatosis / Vysotin S.A., Saifitova A.T., Nevzorova M.S. // International Student's Scientific Bulletin. – 2017. – No. 6; (in Russ.)]

21. Шевчук В.В. Подходы к рациональному питанию у больных неалкогольной жировой болезнью печени / Шевчук В.В., Кашкина Н.В., Высотин С.А., Сайфитова А.Т. // Международный студенческий научный вестник. – 2018. – № 5. [Shevchuk V.V. Approaches to sensible nutrition in patients with nonalcoholic fatty liver disease / Shevchuk V.V., Kashkiba N.V., Vysotin S.A., Saifitova A.T. // International Student's Scientific Bulletin. – 2018. – No. 5. (in Russ.)]