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Diabetes Mellitus and Non-Alcoholic Fatty Liver Disease: the Facets of Conjugacy

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Abstract: The purpose of the study. To assess the incidence of steatosis (SP) and liver fibrosis (AF) in patients with diabetes mellitus (DM) using non-invasive methods of liver fibroelastometry (FEP) and fibrotest panel (FT); to determine their diagnostic significance and identify factors affecting the development of AF.

Materials and methods. 82 patients with DM were comprehensively examined (mean age 56.7±12.7 years; p=0.033). Statistical evaluation of the data was carried out using ROC analysis, correlation and one-factor analysis of variance, multiple logistic regression.

Results. Among patients with DM, according to FT and FEP, liver cirrhosis was detected in 12 (14.6%) and 15 (18.2%), respectively CPU (F4 on the METAVIR scale). Clinically significant stage of fibrosis (F2—3) was determined in 19 (23.1%) by FT and in 23 (28%) by FEP. SP of varying degrees was present in 79 (96.3%). FEP and FT show comparable results in the detection of cirrhosis of the liver (AUROC: 0.83 and 0.81). The development of AF is influenced by factors such as the level of SP, obesity, the activity of the inflammatory process, the level of alanine aminotransferase, a2 - macroglobulin.

Conclusion. Patients with DM have a high risk of developing NAFLD with the formation of AF and CP. FEP and FT have shown comparably high reliability in the diagnosis of CP in patients with DM and can be used for screening examination. Taking into account the existing risk factors for the development of AF and CP, it is necessary to identify groups of patients with DM for further examination and follow-up. Patients who have been diagnosed with stage F4 should be thoroughly examined to assess competing diseases and perform a liver biopsy.

Keywords: liver fibrosis, type 2 diabetes mellitus, non-alcoholic steatohepatitis.

INTRODUCTION

Over the past few decades, non-alcoholic fatty liver disease (NAFLD) has become the leading etiology of chronic liver diseases (CKD) worldwide in 17-46% of the adult population; differences in this indicator depend on the method of diagnosis, age, gender and ethnicity of patients. The International Diabetes Federation predicts that the number of patients with diabetes mellitus type 2 diabetes (DM-2) will increase from 366 million to 552 million by 2030, i.e. 1 in 10 adults will suffer from DM-2. At the same time, the prevalence of DM will increase simultaneously with the rate of frequency growth the development of obesity and aging of the population. Currently, in patients with DM, the prevalence of NAFLD reaches 40-70%. NAFLD is considered as a polysystemic disease, which is a multifaceted problem "with consequences far beyond the liver". The scale of the problem, the medico-social and economic significance of NAFLD are clearly represented by the PubMed/MEDLINE analysis data from 1989 to 2015, obtained based on the analysis of 86 studies with a sample size of 8,515,431 from 22 countries. So, the prevalence of NAFLD was 25.24%. Metabolic comorbidities associated with NAFLD included obesity (51.34%), DM-2 (22.51%), dyslipidemia (69.16%), arterial hypertension (39.34%), metabolic syndrome (42.54%). The progression of liver fibrosis (AF) and the average

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annual rate of progression in NASH were 40.76% and 0.09, respectively. Incidence of hepatocellular carcinoma (HCC) among patients with NAFLD was 0.44 per 1000 person-years. Mortality associated with liver diseases, as well as general mortality among patients with NAFLD and non-alcoholic steatohepatitis (NASH) reached 0.77 and 11.77 per 1000 person-years and 15.44 and 25.56 per 1000 person-years, respectively.

The role of the liver in maintaining carbohydrate homeostasis determines its key participation in the development of insulin resistance (IR) and provides explanations for the mechanisms of conjugation of the development of NAFLD in diabetes and vice versa: the development of diabetes in NAFLD. Each disease, having a "common ground", can serve as a risk factor for the development of another. Thus, DM interacts with NAFLD through specific pathogenetic links. However , it is unclear the sequence of associative mechanisms, the problem of NAFLD in patients with DM has not been fully studied. It is assumed that the excessive accumulation of free fatty acids (FFA) and triglycerides (TG) in hepatic steatosis (SP) with NAFLD leads to damage to the insulin signaling pathways — the development of IR and, consequently, to a violation of hepatic metabolism, is a direct cause of the development of diabetes and increases the risk of diabetes by 2 times. NAFLD can be a predictor of the development of diabetes regardless of a number of risk factors: obesity, peripheral IR, metabolic syndrome. At the same time peripheral IR triggers the processes of excessive synthesis and accumulation of FFA in hepatocytes and creates conditions for the development of SP, and the "fatty" liver becomes vulnerable to oxidative stress, lipotoxicity, etc., leads to damage to hepatocytes, inflammation and fibrosis. Thus, DM contributes to or aggravates SP and steatohepatitis, causing a vicious circle that closely links the two conditions.

Patients with NASH and DM are more at risk of developing clinically significant stages of fibrosis. AF develops in almost 50% of cases of NASH. Advanced AF often progresses to cirrhosis of the liver (CP) and HCC, and the risk of developing cancer is currently increasing in patients with DM. HCC has partly common, not fully understood mechanisms with obesity, IR and SD. The presence of steatosis and fibrosis in combination with NASG are important prognostic factors prognosis in patients with DM. In the context of population aging and increasing prevalence of DM-2, obesity, NAFLD, more and more data indicate that AF is becoming a prominent public health issue in the near future. It is recommended to conduct a screening examination of all patients with NAFLD for the detection of AF, especially in metabolic syndrome and/or DM-2, in which the risk of developing AF is increased (level of evidence A1). According to the PubMed review (88 references, 14 RCTs, 19 cohort studies, 7 meta-analyses), almost 66% of patients over 50 years old, suffering from diabetes or obesity, have NASG with pronounced AF. Patients with IR and/or metabolic risk factors (obesity, metabolic syndrome) are recommended to be examined to establish the diagnosis of NAFLD, which is based on the detection of excessive fat deposition in the liver (evidence level A1). To establish a diagnosis NASG requires a puncture liver biopsy (PBP). Liver biopsy remains the only method that allows to simultaneously evaluate the histological activity index of NAFLD, the steatosis index and the stage of AF (NAS). Being the "gold standard" in the diagnosis of SP and AF in CKD, liver biopsy is not a 100% reference method. The variability of the sample can be significant. It turned out that the histological changes characteristic of NASH are unevenly distributed throughout the liver parenchyma. When performing PBP during bariatric surgery of both lobes of the liver, there was a discrepancy between the samples in 50% of cases according to the stages of AF. In addition, there are other potential limitations and complications of PBP (invasiveness, high cost, possible errors with an insufficient amount of material, the potential risk of complications; lack of motivation in patients with NAFLD to conduct research, especially in dynamics) make it increasingly necessary to use non-invasive methods for assessing SP and AF.

An example is the assessment of SP and AF using a set of fibrotests (FT), liver fibroelastometry (FEP) and a method for evaluating the controlled parameter of ultrasound attenuation (CPR; controlled attenuation parameter). FEP is based on the physical method and correlates with the true internal physical parameters of the liver parenchyma — determines the elasticity of the liver (EP). Elasticity correlates with the degree of fibrosis in CKD, including NAFLD. The KPZU method, based on the property of ultrasonic signals to fade in tissues containing fat droplets, is a new approach to the

definition of SP. KPZU has proven itself as a fast, simple, non-invasive method that allows to determine the degree of SP in a quantitative value simultaneously with the stage of fibrosis in patients with CKD. In comparative controlled clinical trials compared to liver biopsy The KPZU showed a fairly high accuracy in quantifying the degree of steatosis.

According to the Practical Recommendations of the European Association for the Study of Liver Diseases (EASL, 2015) and the EASL-EASD-EASO clinical guidelines for the diagnosis and treatment of NAFLD, biomarkers and AF assessment scales, as well as ultrasound elastography, are acceptable non-invasive methods for identifying cases with a low risk of severe FP or CP (evidence level A2). Combined the use of determining the level of biomarkers or evaluation scales with ultrasound elastography can provide an increase in diagnostic accuracy and will avoid performing a number of liver biopsies (evidence level B2. Patients with DM should be examined to detect NAFLD regardless of the level of liver enzymes, since patients with DM are characterized by a high risk of disease progression (level of evidence A2).

The purpose of the study: to assess the frequency of the development of SP and

AF in patients with DM using non-invasive methods FEP and a set of FT; to determine their diagnostic significance and to identify factors affecting the development of AF.

MATERIALS AND METHODS

A study on the screening assessment of AF in patients with DM with an analysis of possible risk factors leading to its progression with the development of clinically significant stages FP (≥ F2), was conducted in SamMU. 82 patients were comprehensively examined in 2021-2022 (35% men and 65% women) aged 30 to 82 years (average age 56.7± 12.7 years). 12 patients were examined in the CKD department, the remaining 67 were treated in the endocrinology department with a diagnosis of DM-2. The study does not include included patients who had positive markers of hepatitis B and C (HBsAg and a-HCV), excluded patients who consumed hepatotoxic doses of alcohol (Esh test set FibroMac (FM), questionnaires CAGE-2b and AUDIT-C-0b), having markers of autoimmune liver diseases and accumulation disease. In addition to the generally accepted studies, all patients were screened for AF using an indirect ultrasound FEP on a FibroScan device (XL sensor), and serum markers were examined using a FT set of FM ("BioPredictive", France). Patients from the CKD department were evaluated for the degree of steatosis (S), fibrosis stage (F) on the device FibroScan with CAP function, using a set of FM PBP; these patients have agreed to conduct PBP.

The stages of fibrosis on the FibroScan apparatus were determined in accordance with the manufacturer's recommendations: with an elasticity of 7.3 kPa, according to the FEP data, the 2nd stage of AF was determined on the METAVIR scale (F2), and at 12.5 kPa and above - the 4th stage (CP).

The FM set includes 5 calculation algorithms: FibroTest (determination of the stage of AF), ActiTest (determination of the activity of the necroinflammatory process), SteatoTest (determination of the degree of SP), National test (determination of NASH in patients with overweight, insulin resistance, hyperlipidemia, SD) and ESHTEST (alcoholic steatohepatitis in alcohol abusers). The algorithms of the FM panel are based on the determination of blood serum parameters: aspartate aminotransferase (AsAT), alanine aminotransferase (AlAT), γ-glutamyltranspeptidase (GGTP), glucose, TG, total cholesterol (OHC), total bilirubin, a2 - macroglobulin (a2 -MG), apolipoprotein A1, haptoglobin, as well as information about gender, age, mass index body (BMI). Biochemical parameters were determined on the Olympus AU 400 analyzer using Achitect c8000 reagents

(Abbott, USA). The sensitivity and specificity of FT and FEP to determine the stage of fibrosis. A correlation analysis using multiple logistic regression, a one-factor analysis of variance of the influence of various factors on the prognosis of the development of AF was carried out. The presence of F0—1 was regarded as the absence of fibrosis; F2—4 — as clinically significant (expanded) fibrosis; with F4 stated the CPU.

Statistical analysis was carried out using modules for mathematical calculations and data analysis SciPy: Open Source Scientific Tools for Python (0.16.1), Scikit-learn: Machine Learning in Python (0.17.0).

RESULTS

The general characteristics of patients depending on gender, age, BMI, levels of AlAT, AsAT, glucose and other biochemical parameters, the stage of fibrosis are. Patients with DM older than 50 years were 73,2% (n=60). Only 6 had normal body weight (7.3%) people; 56 (68.3%) had obesity, while 32 (39%) were diagnosed with grade I obesity, 15 (18.3%) had grade II obesity, and 9 (11%) had grade III obesity. Interestingly, as the AF stage increases, higher AlAT levels are observed (37.04±24.10 and 78.04±51.76 at F0—1 and F4 respectively), GGTP (51.39±57.58 and 131.11±72.31 at F0—1 and F4, respectively).

Assessment of SP and NASH in patients with DM. SP (S — according to the SteatoTest of the FM panel) of varying degrees was detected in 79 (96.3%) patients and only 3 (3.7%) was not determined (S0). When determining the effect of the degree of S on the reliability of AF according to FT and FEP data (with the calculation of the correlation coefficient r and the value p), it turned out that steatosis does not correlate with fibrosis according to FT data and weakly correlates according to the results of FEP (direct dependence).

It can be assumed that a high level of steatosis in the liver may affect the reliability of the diagnosis of AF during FEP.

Among 79 patients with DM with steatosis, 9 (11.4%) had NAFLD at the stage of steatosis, 70 (85.4%) had NASH (N) — according to the national test of the FM panel. The correlation between NASH and AF is weak, which indicates a statistical relationship: r=0.337 (p=0.002) and r=0.228 (p=0.039) for FE; at the same time, a high degree of NASH does not affect the reliability of determiningAF. It should be noted that among patients with F4 AF, 22.6% had NASH of pronounced activity (N2). Additionally, we calculated the correlation coefficient for the possible effect of the level of AlAT and the activity of the inflammatory process in the liver (A according to the actitest of the FM panel) on the determination of AF. The correlation coefficient for AlAT was r=0.232 (p=0.036) and r=0.305 (p=0.005) for FT and FE, respectively, i.e. there is a weak positive correlation. An average positive correlation was obtained between A and the degree of AF: r=0.607 (p<0.00000001) for FT and r=0.528 (p<0.000001).

Conclusion: almost all patients with DM (96.3%) have SP of varying degrees, most of them (85.4%) have NAFLD was at the stage of NASG. Among patients with AF in the F4 stage, there are more patients with NASH of pronounced activity.

Evaluation of AF in patients with DM-2. In patients with DM-2 according to each noninvasive method — FT and FEP— CP was detected in 14.6 and 18.2% of cases, respectively. AF at the clinically significant stage of fibrosis (F2—3) was determined in 19 (23.1%) people according to FT data and in 23 (28%) according to the results of FEP.

Evaluation of the frequency of AF in patients with DM depending on age showed that after 50 years, the number of patients with clinically significant stage of fibrosis F2—3 increases (13.7% before 50 years and 26.7% after 50 years of FT or 22.7 and 30%, respectively, for FEP) and CP (4.5 and 18% for FT and 13.7 and 20% for FEP) according to both methods. The average age of patients without fibrosis (F0—1) was 55.7± 13.7 years, and for F4 — 62.5±10.3 years (p=0,033). Age in real terms does not correlate with fibrosis according to FT and FEP data. However , it was detected weak correlation of age in binary calculus (younger than 50 years and older) with the stage of fibrosis according to the results of FT: r=0.236 (p=0.033), i.e. direct dependence on FE: r=0.093 (p=0.405) — there is no correlation. The frequency of detection of AF in patients with DM, depending on BMI. According to both methods, there were more patients with diabetes with obesity and advanced stage of fibrosis than without obesity. It should be noted that in patients without obesity (BMI less than 30 kg/m^2), 100% matches were obtained for the detection of CP (F4) in FT and FEP. In obese patients, the proportion of

coincidences in the detection of CP was 54.5% for FEP and 75% for FT (6 matches). When calculating the correlation coefficients of the dependence of the AF stage on BMI, it turned out that when determined on the FibroScan device, there is a weak correlation indicating a statistical relationship between the effect of obesity on the AF stage (correlation coefficient 0.311 (p=0,056). There is no correlation with the stage of fibrosis by FT: r=0,072 (p=0,052).

The frequency of detection of AF depending on gender.

Despite the fact that more women participated in the study, the percentage of men with F2—3 and CP it turned out to be more: 27% versus 17% of women on FEP and 22% vs. 11% of women on FT). When determining the possible influence of gender on the accuracy of determining the stage AF according to FT and FEP, a very low positive correlation with the stage of AF was obtained, determined using a set of FM: r=0.202 (p=0.352) and on the FibroScan apparatus: r=0.297 (p=0.068). There is no statistically significant effect.

Conclusion: DM patients with F4 fibrosis were older than in the F0—1 stage. There were more men than women with AF in the F4 stage. There were more obese patients with advanced stage fibrosis than without obesity. Assessment of the reliability of FEP and FT using ROCanalysis. Using the construction of characteristic curves (ROC analysis), the diagnostic significance of FT and FEP was evaluated and the reliability of the relationship was determined by AUROC. When assessing the quality of the FEP, AUROC was generally 0.8, i.e. the reliability of the method is high, the accuracy of the FEP is 0.719512195122, sensitivity is 0.741935483871, specificity is 0.705882352941. The AUROC values for F0—1, F2—F3 and F4 were 0.52, 0.67 and 4 -0.83, respectively, which indicates a very high reliability of the FEP for the CPU stage (F4), to satisfactory — for F2—3 and unsatisfactory for F0—1. When assessing the quality of FT, AUROC as a whole was 0.73, i.e. this method also has high reliability. The accuracy of FT is similar to that of FEP — 0.719512195122, the sensitivity is slightly lower (0.605263157895), and the specificity is higher (0.818181818182). AUROC values for F0—1, F2—3 and F4 are equal to 0.51, 0.59 and 0.81 respectively. Based on this, it can be concluded that the reliability of FT is very high for stage F4, but unsatisfactory for stages F0—1 and F2—3.

We determined the proportion of coincidences of fibrosis stages by FT and FEP. The proportion of coincidences in determining the minimum stages of fibrosis (F0—1) was 0.71 for FT and 0.81 for FEP. In the case of more advanced stages of fibrosis F2—3 has the lowest percentage of coincidences: 0.47 — FT and 0.39 — FEP. When determining the CPU, the percentage of matches for FT was 0.83, and for FEP — 0.67.

Conclusion: noninvasive methods of diagnosis of AF — FT and FEP have high reliability and accuracy in determining CP (F4 on the METAVIR scale) in patients with DM. With the help of multiple logistic regression analysis, the factors that can influence on the development of AF when it is evaluated by the methods of the FM panel and FEP. It was found that such characteristics as BMI (regression coefficient y=0.783220), steatosis (y=0.927253), a2 -MG (y=2.570192), affect the development of AF. To check whether the indicators are really related, a one-factor analysis of variance was additionally performed, which demonstrated that the progression of AF is influenced by age (y=2.235792), steatosis (y=2.099240), AlAT activity (y=2.265505) and AsAT (y=2.949355), as well as NASG (y=2.904732). The level of a2 has a pronounced effect-MG (y=28.413505), activity of the necroinflammatory process in liver tissue according to ACTITEST (y=13.437218), concentration of apolipoprotein A1 (y=2.789638).

Conclusion: a correlation analysis of some of the study data demonstrated that the reliability of determining AF using FEP can be affected by obesity and cytolysis syndrome; FT can be affected by cytolysis syndrome and the activity of the inflammatory process.

Analysis of variance and multiple logistic regression revealed that in patients with DM, the development/progression of AF can be influenced by factors such as age, steatosis (S), NASH (N), its activity (A), BMI (namely obesity), as well as indicators such as AlAT, AsAT, a2-MG, apolipoprotein A1.

Further examinations. Among the identified 16 patients with AF indicators in the F4 stage according to the FEP data 12 people were examined in the department of CKD and 2 of them had signs of portal hypertension and hepatodepression; the diagnosis of CP class A (6 points) according to Child—Pugh was established. 10 patients agreed to the PBP. 7 received confirmation F4 on a scale METAVIR without signs of portal hypertension and hepatodepression.

Conclusions: patients with DM-2 have a high risk of developing NAFLD with the formation of AF and CP. Noninvasive tests can be used to screen clinically significant AF in patients with DM. FEP and FT demonstrate comparable results when detecting CP (AUROC 0.83 and 0.81). Taking into account the available FR of clinically significant AF development (age over 50 years, pronounced steatosis, high AlAT level, obesity), it is necessary to identify groups of patients with DM for further examination and follow-up. Patients who have been diagnosed with stage F4 should be carefully examined to evaluate competing diseases and conduct PBP.

CONCLUSION

The presence of SP in NAFLD is still perceived as a benign condition. Also, NAFLD is considered as a non-dangerous manifestation of excess weight body or obesity, as a complication of diabetes without clinical significance. Most practicing endocrinologists have not and still do not track how often their patients with DM develop CP. It is important that therapists, endocrinologists and other specialists are aware of the scale and long-term consequences DM and NAFLD, and understood that early detection of patients with DM, existing FR of the development of AF, can help improve patient treatment outcomes.

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