Health Informatics and Biomedical Engineering Applications, Vol. 78, 2023, 66–71
https://doi.org/10.54941/ahfe1003456

Methods of Computer Simulation in the Development of Technology for the Functional Assessment of the State of the Liver in Patients With Metabolic Disorders

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ABSTRACT

Most of the diseases associated with carbohydrate and fat metabolism disorders (type 2 diabetes mellitus, obesity, metabolic syndrome) lead to changes in the structure and function of liver cells, and the formed liver dysfunction negatively affects the further progression of the disease. The process of liver damage develops with varying intensity and does not immediately lead to irreversible consequences; therefore, dysfunction should be detected as early as possible, and the data obtained should be used to assess the current state and predict their reversibility. Using mathematical modeling, the authors developed a formula for calculating the index of functional activity of hepatocytes, which can be used to assess not only the current functional state of the liver but also determine the reversibility of existing functional disorders and the severity of structural changes. The formula included an indicator obtained on the basis of hepatobiliary scintigraphy data – the time to reach the maximum accumulation of radiopharmaceuticals in the liver – Tmax. This method allows assessing the prognosis of the course of the disease and the effectiveness of restorative measures. It is characterized by relative ease of implementation. Only one parameter — T_{max} is required, after which the study can be completed.

Keywords: Functional state of the liver, Dynamic hepatobiliary scintigraphy, Metabolic syndrome

INTRODUCTION

Currently, the most common liver disease is non-alcoholic fatty liver disease (NAFLD), which is pathogenetically associated with metabolic syndrome, visceral obesity, and type 2 diabetes mellitus (Lazebnik, 2021). Early diagnosis of NAFLD is still difficult because at the stage of steatosis, most often

there are no clinical manifestations and changes in the biochemical parameters of the blood. All available methods of laboratory and instrumental diagnostics, including fibrotests, are not methods of early diagnosis, characterize only the current functional state of the liver, do not allow identifying risk groups, assessing the reversibility of liver dysfunctions and drawing up an individual treatment plan. Diagnosis of NAFLD at the stage of steatosis is of great prognostic value because steatosis is an independent risk factor for the development of cardiovascular diseases and their complications (Tishkovsky, 2016; Statsenko, 2019; Lazebnik, 2021; Allahverdieva, 2018).

PURPOSE OF THE STUDY

To create a quantitative evaluation method that allows assessing the current functional state of the liver, the reversibility of existing functional disorders and the severity of structural changes, assessing the prognosis of the course of the disease and the effectiveness of restorative measures.

MATERIALS AND METHODS

A single-stage single-center examination was carried out in 26 overweight patients and 28 people with various degrees of obesity (1 degree of obesity - 13 patients, 2 degree - 11 patients and 3 degree - 4 people). The comparison group consisted of persons with normal body weight (36 people).

The study was approved by the Biomedical Ethics Committee of the Izhevsk State Medical Academy of the Ministry of Health of the Russian Federation, Application No. 468 dated December 22, 2015. The examination was performed on the basis of the informed consent of the patient, in accordance with the order No. 163 (OST9/500.14.001-2002) paragraph P.4.6.1. Ministry of Health of the Russian Federation, provisions of the Bioethics Committee of the FSBEI HE "Izhevsk State Medical Academy of the Ministry of Health of Russia".

Criteria for exclusion from the study: lack of patient consent to participate in the study, renal failure (CKD C 4-5), the presence of viral hepatitis, markers of autoimmune liver diseases and storage diseases, the use of hepatotoxic doses of alcohol. All patients underwent a biochemical blood test: fasting plasma glucose, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, alanine aminotransferase, aspartate aminotransferase. Structural changes in the liver were studied using ultrasound on the MyLabSeven machine (Italy). To assess the degree of hepatic steatosis, the classification of fatty degeneration of the liver by Batskov S.S. was used. (1996). The study of the absorption-excretory function of the liver was carried out using dynamic hepatobiliary scintigraphy using a scintillation gamma camera (Siemens Symbia T16) with subsequent data processing on the SUPER-SEGAMS system (Hungary). Patients were examined on an empty stomach in the supine position, in the anterior projection. A freshly prepared radiopharmaceutical (RP) Bromesida, ^{99m}Tc was administered intravenously at the rate of 1.1 MBq per kg of the patient's body weight in a normal functional state of the liver. The detector of the gamma camera was installed as close as possible to the surface of the body, so that the liver and part of the intestine were included in the field of view of the detector. Registration of information was carried out at

a speed of 1 frame per minute for 60–90 minutes. 30 minutes after the start of the study, the patient was given a standard choleretic breakfast (two raw egg yolks).

A series of obtained scintigrams made it possible to visually assess the passage of the drug through the blood-liver-ducts-intestine system, to characterize the anatomical features and organic changes in the biliary system. Quantitative analysis of the "activity-time" curves obtained from the areas of interest (the right lobe of the liver - 2 zones, the left lobe of the liver, the common bile duct, the intestinal area, the heart area) made it possible to assess the absorption-excretory function of the liver, the patency of the bile ducts, the functional state of the sphincter of Oddi and the presence of duodenogastric reflux (Fig. 1).

Known methods for diagnostic liver diseases (ultrasound, fibroscanning, ect.) describe the *structure* of the organ and changes after they have already occurred and are irreversible. The method of hepatobiliary scintigraphy allows to evaluate the *function* of the liver (absorption-excretory), therefore, it was chosen as the base for the development of a method for the early diagnosis of NAFLD.

Statistical processing of the obtained data was carried out using the STATISTICA 10.0 software package and MedCalc 12.5.0.0 software. The normality of the distribution of actual data was verified with the Shapiro-Wilk test. Values that do not follow the normal type of distribution were presented as median, lower and upper quartiles; relative - in the form of the frequency of occurrence of the trait and 95% confidence interval calculated by the Wilson method. The significance of differences between independent groups of quantitative variables that do not obey the normal type of distribution was calculated by a nonparametric method using the Mann-Whitney U test, qualitative variables - by Pearson's Chi-Square ($\chi 2$) method with Yate's

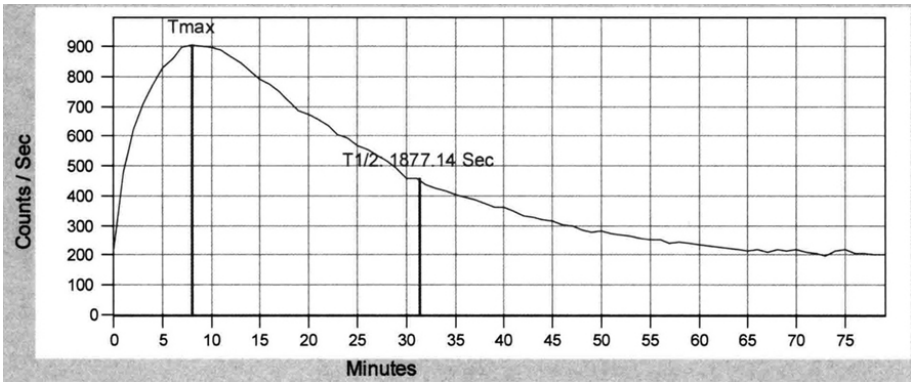

Figure 1: Hepatobiliary scintigram characterizing the absorption-excretory function of the liver depending on time. Note: T_{max} - the time to reach the maximum accumulation of radiopharmaceuticals in the liver; $T_{1/2}$ - an indicator that reflects the rate of removal of the radiopharmaceutical from the liver parenchyma by 50% relative to the maximum.

correction. To determine the magnitude of the relationship between phenomena, mathematical modeling was used by constructing 3D graphs. ROC analysis was used to determine the predictive significance of the indicators. Quantitative interpretation of the results was carried out according to ROC curves with an assessment of the AUC. The level of statistical significance was taken as $p<0.05$.

RESULTS

Ultrasound examination revealed signs of liver steatosis in all patients with 2 and 3 degrees of obesity. In patients with 1 degree of obesity, ultrasound signs of fatty liver infiltration were detected in 69.2% of cases out of 13 patients, with overweight - in 30.8% of cases out of 26 patients, with normal body weight - in 13.9% of cases out of 36 patients.

According to dynamic hepatobiliary scintigraphy in overweight patients, a statistically significant slowdown in the time to reach the maximum accumulation of radiopharmaceuticals in the liver (T_{max} 16.0 (14.04-18.02) min, $p = 0.003$) and the rate of radiopharmaceutical excretion from the liver parenchyma ($T_{1/2}$ 31.24 (21.7-66.0) min, $p = 0.013$) compared with subjects with normal body weight (T_{max} 12.53 min, and $T_{1/2}$ 23.8 min respectively). In patients with the first degree of obesity, similar data were obtained (T_{max} 16.02 min and $T_{1/2}$ 29.9 min respectively). In patients with the second and third degree of obesity, a tendency to slow down the absorption-excretory function of the liver was revealed in Table 1.

Analysis of the data of a radioisotope study of liver function in patients with a normal ultrasound picture of the liver revealed a statistically significant slowdown in the absorptive function of the liver in overweight patients compared with patients with normal body weight (T_{max} 16.0 (13.25-17.87) min and T_{max} 12.5 (11.1-15.2) min, $p = 0.024$). The data obtained confirm the possibility of early diagnosis of liver damage in overweight and obese patients using dynamic hepatobiliary scintigraphy.

Table 1. Indicators of dynamic hepatobiliary scintigraphy in persons depending on body weight with a normal ultrasound picture of the liver, Me [Q1;Q3].

Indicators	Normal Body Weight (n = 36)	Overweight (n = 26)	1 Degree of Obesity (n = 13)	2 Degree of Obesity (n = 11)	3 Degree of Obesity (n = 4)
T_{max}, min	12,53 [10,75;15,03]	16,01 [14,04;18,02]	16,02 [14,51;19,50]	10,0	—
P	-	(p=0,003)	(p=0,003)	-	-
$T_{1/2}$, min	23,8 [19,45; 29,45]	31,24 [21,72; 66,00]	29,9 [26,77; 37,20]	16,7	—
P		(p=0,013)	(p=0,011)		

Note: P – statistical significance of differences in values compared with data from patients with normal body weight.

Mathematical modeling with the construction of a 3D graph established a relationship between the degree of fatty infiltration of the liver (according to Batskov S.S., 1996) with BMI and the absorptive function of the liver. With an increase in the patient's body weight and a slowdown in the absorption function, the degree of fatty infiltration steadily increases (Fig. 2).

The obtained results of the study made it possible to calculate the formula for the diagnosis of functional disorders of the liver:

$$IFAH = (-1{,}1564 + 0{,}0653 \times BMI - 0{,}0144 \times T_{max}) \times 100,$$

where:

IFAH – index of functional activity of hepatocytes; BMI – body mass index (kg/m^2); T_{max} - indicator of the absorption function of the liver (min).

According to the index value obtained, the conclusion about the functional activity of hepatocytes was substantiated: from 0 to 9.9 - normal functional activity of hepatocytes; from 10 to 19.9 - the risk of developing functional disorders; from 20 to 29.9 - reversible dysfunction of hepatocytes (steatosis); more than 30 - irreversible (organic) liver dysfunction (Kurnikova et al., 2016).

Subsequently, IFAH was calculated for all examined patients with a normal ultrasound picture of the liver, which revealed a risk of developing functional disorders in 32.3% of patients with normal body weight, and reversible functional disorders in 19.3% of patients. In overweight patients, reversible functional disorders were detected in 20% (95% CI: 7,05–45,19) of cases,

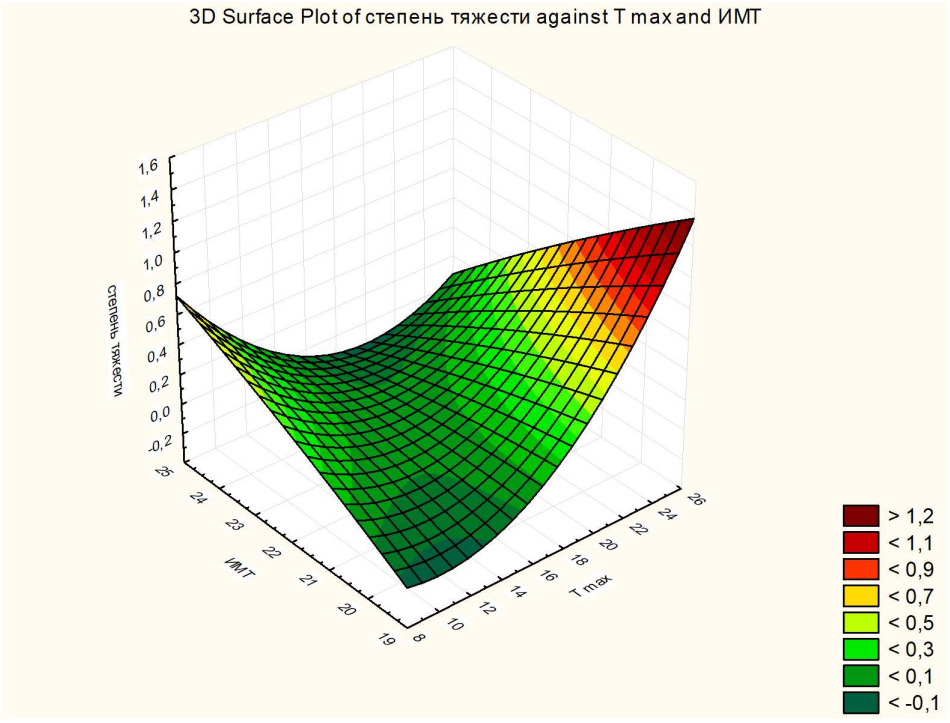

Figure 2: Correlations between the severity of liver damage, BMI and T_{max}.

and irreversible in 80%(95% CI: 54,81– 92,95). All obese patients had irreversible functional impairments according to IFAH calculation. In patients with 1 degree of obesity, irreversible functional disorders of the liver were detected in 100% of cases in the absence of morphological and laboratory changes. All patients with III degree of obesity showed changes in the ultrasound picture of the liver and biochemical parameters of the blood. These results confirm that ultrasound diagnostics cannot be a method of early diagnosis of liver damage.

CONCLUSION

The method for diagnosing fatty hepatosis developed using mathematical modeling allows diagnosing liver damage before the appearance of ultrasound changes characteristic of fatty liver infiltration and predicting the course of the process. Using the calculation of IFAH, it is possible to identify a group of patients at risk of developing functional disorders of the liver, which will allow timely start of preventive measures. To calculate IFAH, it is required to calculate only one indicator during dynamic hepatobiliary scintigraphy (T_{max}), which will reduce radiation exposure and examination time.

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