

The Evaluation of the Health-Related Quality of Life and Depressive Disorders in Overweight Patients with Non-Alcoholic Fatty Liver Disease in the Initial Stages of Liver Fibrosis

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Abstract

Introduction: Non-alcoholic fatty liver disease (NAFLD) is considered to be the most common liver disease in the world in recent years. It is closely linked to metabolic disorders and, in the first place, with obesity. This greatly impairs the quality of life of the patients and may also be accompanied by depressive disorders.

Purpose: The study aimed to assess health-related quality of life and depressive disorders in patients with obesity and non-alcoholic fatty liver disease (NAFLD) in the early stages of liver fibrosis.

Materials and Methods: In the present study 45 patients (20 men and 25 women, aged 23 - 78 years, mean BMI 30,47 kg/m²) were examined and divided into 4 groups: 10 obese without fibrosis (age 48,6 ± 18,4, BMI 32,2 ± 2,4 kg/m²), obese with 1 stage of fibrosis (age 55,8 ± 13,6, BMI 32,7 ± 4,7 kg/m²), 11 obese with 2-3 stage of fibrosis (age 63 ± 3,7, BMI 34,8 ± 3,7 kg/m²), and 11 lean without fibrosis (control group) (age 49,6 ± 17,7, BMI 22 ± 2,1 kg/m²). Liver stiffness was measured by shear wave elastography, HRQoL was measured using the Ukrainian version of the SF-36 health survey.

We assessed the depression with the help of the Beck Depression Inventory (BDI).

Results: Main domains of the HRQL score were significantly lower in obese patients with NAFLD in comparison to the lean patients: comparing of three groups of obese patients with different stages of fibrosis with lean patients we found statistically significant difference in physical health: control- F0 (t = 2,6, p = 0,017), in control -F1 (t = 3,6 p = 0,002) and in control - F-2-3 groups (t = 3,53 p = 0,002). Data of mental health in the comparing group control- F0 (t = 2,7, p = 0,013), control- F1 (t = 2,5 p = 0,019). In comparing group with advanced fibrosis no statistically significant difference in mental health control F2-3 (t1,27, p 0,216).

The depression level is higher in the group of obese patients comparing to its stage is the highest in the F2-F3 group.

Conclusion: In obese people, HRQoL is lower than in lean and it decreases with the stage of fibrosis. We suppose that our data show the deterioration of the critical assessment of their condition in patients with advanced fibrosis.

Keywords: NAFLD; Obesity; Depression; SF-36; Steatometry; Elastography; Ultrasound; Hepatology; Psychiatry

Abbreviations

NAFLD: Non-Alcoholic Fatty Liver Disease; BMI: Body Mass Index; HRQoL: Health-Related Quality of Life; BDI: Beck Depression Inventory; WHO: World Health Organization; OSA: Obstructive Sleep Apnea

Introduction

Nonalcoholic fatty liver disease (NAFLD) is becoming one of the most important causes of liver disease throughout the world [1-3].

The global pandemic of Nonalcoholic fatty liver disease (NAFLD) is growing in parallel with the pandemic of obesity. From 1975 to 2016, the number of obese people in the world almost tripled [4].

The World Health Organization (WHO) estimates that, in 2016, more than 1.9 billion adults (39% of the adult population) were overweight, and 650 million (13% of the adult population) were considered obese [5].

The pandemic of obesity continues and grows; the predicted indicator is between 40% and 50% by 2030. The problem of obesity is not just an aesthetic problem. This condition leads to several complications. Recent studies have shown that obesity is associated with more than 195 complications, including obstructive sleep apnea (OSA), dyslipidemia, cardiovascular diseases (hypertension, cardiovascular failure), type 2 diabetes, cancer, osteoarthritis, non-alcoholic fatty liver disease and depression [6].

As these global rates of obesity increase, obesity-related complications are also on the rise and especially NAFLD. NAFLD occupies a leading position among all chronic liver diseases not only among developed countries but also among developing countries. In the United States and Europe, about 40% of the population suffers from NAFLD and approximately 20% have a progressive course leading to fibrosis and cirrhosis, hepatocellular carcinoma (HCC), and liver transplantation [7].

All these complications significantly affect health, the economy, and are a huge burden for patients, their families and society [8].

The progressive course of this disease necessitates taking active measures at the early stages of the disease. Early diagnosis and active detection of not only signs of steatosis and liver fibrosis, but also the assessment of psychosomatic condition greatly help in choosing a strategy and tactics of the treatment.

Diagnosis of NAFLD

Liver biopsy

The liver biopsy is the gold standard for the diagnosis of NAFLD [9].

This is currently the most reliable approach for identifying the presence of steatohepatitis (SH) and liver fibrosis. However, liver biopsy has disadvantages because it is an invasive procedure and is often associated with a risk of complications such as pain (in 30 to 50% of patients), serious bleeding (0.6%), injury to other organs (0.08%), and in rare cases, death (up to 0.1%) [10].

Also, it is limited by its cost and sampling error. The errors in sampling for histological verification and subjectivity of the pathologist lead to misdiagnosis in a very large number of cases. Even an adequate liver biopsy will show only 0.05 cm³ of the organ, the volume ranging between 800 and 1000 cm³, which corresponds to less than 1: 50,000 in total [11].

Besides, steatosis and liver fibrosis are not evenly distributed in NAFLD [12].

Ultrasound

One of the best tests for the diagnostics of hepatic steatosis remains instrumental. The main non-invasive method for diagnosing the diffuse liver disease is ultrasound. Ultrasound (US) is inexpensive, widely available, and has 60 - 94% sensitivity and 66 - 97% specificity for hepatic steatosis [13].

B-mode which is used makes it possible to detect signs of liver damage by echogenicity, structure, contours and size of the organ, vascular pattern. Also, with the help of B-mode, it is possible to detect signs of steatosis - increased echogenicity, decreased sound conductivity, rounding of contours, often hepatomegaly. But these changes are determined when the lipid saturation of hepatocytes is more than 20 percent of the total mass. Therefore, early detection of steatosis by B-mode is almost impossible. In addition to the inaccuracy in the diagnosis of moderate steatosis, there is also a significant decrease in sensitivity - below 50% and specificity below 75% in morbid obesity. Also, the presence of fibrosis, necrosis, edema, and extrahepatic adipose tissue may adversely affect the assessment of steatosis. Difficulties also arise in differentiating between steatosis and fibrosis. That is why it is so important to have not only qualitative signs but also quantitative indicators for early detection of the initial stages of hepatic steatosis. Although in clinical practice the ultrasound method of diagnosis is the best method to assess steatosis, it does not allow accurate assessment in the early stages. Also considering that the technique is operator dependent and subjective.

Liver steatometry and elastography

Ultrasound steatometry is used as a screening examination for non-alcoholic fatty liver disease and is an indicator of impaired lipid and carbohydrate metabolism. Hepatorenal index, Hamaguchi, US-FLI, and steatometry (CAP, attenuation factor) are used to quantify hepatic steatosis. Determination of the attenuation coefficient is the most convenient method of diagnosing steatosis, which allows for real-time examination with simultaneous B-mode, and to choose of area of interest [14-17].

The attenuation coefficient is measured in dB/cm, the stage of steatosis is correlated to the histological classification (NAS) [18]:

- S0 - No steatosis - The proportion of hepatocytes saturated with lipids up to 5%, up to 2.22 dB/cm.
- S1 - Mild steatosis - The proportion of hepatocytes saturated with lipids up to 33%, 2.22 - 2.33 dB/cm.
- S2 - Moderate degree of steatosis - The proportion of altered hepatocytes - up to 66%, 2.33 - 2.9 dB/cm.
- S3 - Severe steatosis - The number of lipid-saturated hepatocytes above 66%, above 2.9 dB/cm.

The first method used for LS evaluation using ultrasound waves was Transient Elastography (FibroScan®, Echosens® France) [19-22]. Other techniques have been latterly developed, such as Real Time Elastography (by Hitachi) or Acoustic Radiation Force Impulse (ARFI) Elastography [23-28]. They are used more and more, in daily practice. 2D Shear Waves Elastography (2D SWE) has been developed more recently. 2D shear wave (SWE) elastography determines the rigidity of the liver in real time. The method is based on the displacement of the particles of the medium perpendicular to the direction of wave spreading. Using the formula $E = 3\rho C^2$, where E is the Ewing modulus (modulus of elasticity), ρ is the density, C is the shear wave velocity [29-36].

Advantages of SWE elastography:

- Quantitatively and qualitatively determines the degree of fibrosis,
- Has prognostic value,

- Reliable detection of liver cirrhosis,
- Allows controlling treatment in dynamics,
- Determines the indications for liver biopsy,
- Is a low-cost, patient-friendly method that does not require specific training, it takes a relatively short time [37].

Disadvantages of the method are present too. Certain factors affect the results of measurements, respectively, limit the application of the method: cholestasis, process activity (not used with significant process activity, acute hepatitis, with an increase in aminotransferases more than 5 times), severe edema, heart failure, increased pressure in the inferior vena cava, overweight, increase in internal abdominal pressure, narrow intercostal spaces, process activity (incorrect values at high process activity (an increase of aminotransferases more than 5 times), so is operator-dependent [38-43].

The results were evaluated on the METAVIR scale:

- F0 - No fibrosis - Up to 6 kPa
- F1 - Mild fibrosis - 6 - 7 kPa
- F2 - Moderate fibrosis - 7 - 9.5 kPa
- F3 - Severe fibrosis - 9.5 - 12.5 kPa
- F4 - Cirrhosis - 12.5 and more kPa [44].

Materials and Methods

The study included 45 patients aged 23 to 78 years (mean age- (32 ± 2.5) years. The first group included 10 patients (mean age 48.6 ± 18.4 years, BMI 32.2 ± 2.4 kg/m²), with hepatic steatosis without signs of fibrosis (mean liver density on elastography was 2.5 kPa) The second group included 13 patients (mean age 55.8 ± 13.6, BMI 32.7 ± 4.7 kg/m²) with steatosis and liver fibrosis of 1 degree, the third group of 11 patients (mean age 63 ± 3.7, BMI 34.8 ± 3.7 kg/m²) with steatosis and liver fibrosis of 2-3 degrees, the fourth group- comparison group of 11 patients with normal weight without fibroids and steatosis of the liver (mean age 49.6 ± 17.7, BMI 22 ± 2.1 kg/m²). All patients underwent laboratory examination, liver status was assessed using non-invasive ultrasound, steatometry and liver elastography, and each patient completed the SF-36 form. Assessment of psychological status was performed using the Beck Depression Scale. The diagnosis of NAFLD was established using non-invasive research methods. All patients underwent multiparametric ultrasound examination of the liver - B-mode, steatometry and shear wave elastography. We performed 2D shear wave (SWE) elastography, which determines the rigidity of the liver in real time. The examination was performed using the ultrasound diagnostic system Ultrasign Soneus P7, on an empty stomach, when the patient is on his back with his right hand behind his head, in the eighth intercostal space along the anterior or middle axillary line, at a depth of 3 cm from the capsule with ROI to 5 - 8 mm.

Health-related quality of life

One of the most commonly used generic HRQoL instruments; according to a recent review is the Medical Outcomes Study Short Form-36 (SF-36) [45].

“SF-36 Health Status Survey” (SF-36) refers to non-specific questionnaires for assessing the quality of life; it is widely used in the United States and Europe in conducting quality of life research. The SF-36 questionnaire was normalized for the general population of the

United States and representative samples in Australia, France and Italy. In the United States and European countries, studies of individual populations were conducted and the results were obtained according to the norms for the healthy population and groups of patients with various chronic diseases (from the selection of groups by sex and age).

All 36 items of the questionnaire are grouped into eight scales and included in eight individual HRQL domains:

1. Physical functioning (PF) domain reflects how much a patient's physical activities are limited because of their health.
2. Role physical (RP) domain reflects how much the patient's physical health impacts their work and daily activities.
3. Bodily pain (BP) domain evaluates the patient's limitations because of pain.
4. General health (GH) domain measures how a patient sees their personal health and the potential for decline.
5. Vitality (VT) domain reflects how tired/full of energy the patient feels.
6. Social functioning (SF) domain measures how much the patient's physical or emotional problems interfere with their normal social activities.
7. Role emotional (RE) domain assesses the impact of the patient's emotional problems on their work and daily activities.
8. Mental health (MH) domain reflects the patient's state of emotional feeling (e.g. nervous, peaceful, happy).

For calculation of all these domains, patients' responses (all on Likert scales of various sizes, from 2 to 6) were averaged and then transformed to range from 0 to 100 with higher scores representing better health. Then, these domain scores were used for the calculation of the two summary scores:

- Physical Component (Summary) Score (PCS) summarises the physical health-related items of SF-36: PF, RP, BP and GH.
- Mental Component (Summary) Score (MCS) summarises the MH-related items of SF-36: VT, SF, RE, and MH. The summary scores were calculated from the normalised domain scores using weights reported from factor analysis of the SF-36 items and with adjustment for interitem correlations [46].

Assessment of depression

Diagnosis of a mental disorder following the Law of Ukraine "On Mental Care" is the exclusive competence of a psychiatrist or a commission of psychiatrists. Doctors of other specialties have the competence to suspect the presence of a mental disorder, to establish a syndromic diagnosis or a diagnosis of a syndromic disorder. For this purpose, screening scales for depressive disorder are used, which also allow assessing its severity. To detect depression in patients with CKD, both objective scales completed by a clinician experienced in mental health assessment (Hamilton's scale for assessing depression) and subjective self-questionnaires completed by the patient can be used (most common: Beck Depression Scale, Zung Depression Self-Assessment Scale, Depression Scale, Anxiety, Stress DASS-21).

In our work, the Beck Depression Inventory scale proposed by A.T. Beck, developed based on clinical observations, which revealed a limited set of the most relevant and significant symptoms of depression and the most frequent complaints [47]. With the help of subscales (cognitive-affective and subscale of somatic manifestations of depression) the severity of 21 symptoms of depression is gradually assessed. This scale is simple and quick to use.

Results

The study found a significant reduction in generalized physical and mental health in patients with NAFLD and obesity compared with normal weight patients. Comparison of three groups of obese patients with different degrees of liver fibrosis with a group of overweight patients showed a statistically significant difference in physical health: control group - F0 ($t = 2.6, p = 0.017$), control group - F1 ($t = 3.6, p = 0.002$), control group - F2-3 ($t = 3.53, p = 0.002$). There is also a decrease in the physical component of health as liver fibrosis increases. The highest level of the average physical component of health is observed in the group with hepatic steatosis without fibrosis, the lowest in the group with fibrosis of 2 - 3 degrees.

The following results were obtained from the evaluation of the mental component of health. a statistically significant difference in the indicators of the mental component of health was observed in the comparison groups control group - F0 ($t = 2.7, p = 0.013$), control group - F1 ($t = 2.5, p = 0.019$). In the control group - control group - F2-3 ($t = 1.27, p = 0.216$) there was no statistically significant difference in the indicators of the mental component of health.

The level of depression was higher in the group of obese patients compared to overweight patients and, accordingly, the highest level of depression was in the F2-3 group with fibrosis of 2 - 3 degrees. According to the Beck Depression Scale, only one person in the control group had symptoms of mild depression, while among patients with obesity and fibrosis, depression was found in 50% of those surveyed.

Discussion and Conclusion

Patients with obesity and NAFLD have a significantly reduced rate of BPH, namely the generalized indicators of the physical and mental component of health, compared with patients with normal body weight. These rates decrease as fibrosis progresses. The study also found a significant decrease in the physical component of health in obese patients and NAFLD with increasing liver fibrosis. The results obtained in the assessment of the mental component in patients of the third comparison group (control group - F2-3) - no statistically significant difference in the mental component of health may indicate a non-critical assessment of their condition in patients with severe liver fibrosis and need further study.

It was found that patients with obesity and NAFLD also have depressive disorders that occur in the early stages of liver fibrosis and that the level of depression increases as liver fibrosis progresses. High levels of depression in patients with obesity and liver fibrosis increase the risk of complications and reduce compliance.

Thus, obese patients and NAFLD require a comprehensive approach to diagnosis, including assessment of psychological status. But already in the initial stages of liver fibrosis, it is necessary to carry out treatment, including modification of lifestyle and diet, which should include psychological correction.

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