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HEPATIC FIBROSIS, MEASURED BY FIBROSCAN IN A GROUP OF PATIENTS WITH OBESITY

Raluca Costina Dina [1,✉], ***Maria Moţa*** [1,2], ***Iulia Vladu*** [3], ***Ciprian A Dina*** [4]

[1] Clinic of Diabetes, Nutrition and Metabolic Diseases, Clinical County Emergency Hospital Craiova
[2] University of Medicine and Pharmacy Craiova – Diabetes, Nutrition and Metabolic Diseases Department
[3] Clinic of Nephrology, Clinical Emergency County Hospital Craiova
[4] University of Medicine and Pharmacy Craiova – Discipline of Physiology

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Abstract

Introduction. *Hepatic steatosis is a reversible condition caused by accumulation of triglycerides in liver cells. Non-alcoholic fatty liver disease (NAFLD) can progress to advanced liver disease: fibrosis, cirrhosis, liver failure, cancer, and finally can lead to death; therefore NAFLD contributes significantly to morbidity and mortality of hepatic cause.* ***Materials and methods****: The study was conducted on a group of 88 patients with Body Mass Index (BMI) ≥ 30kg/m², they were excluded patients with known diabetes.* ***Results***, ***Discussion****: The statistical analysis showed that in more than half of subjects elastometry values were higher than those considered normal, obesity is a risk factor for NAFLD that progresses in hepatic fibrosis.* ***Conclusions****: Liver fibrosis is present in high percentage in patients with obesity (52% of subjects) and it was positively correlated with age, arterial stiffness and fasting glucose.*

key words: *steatosis, fibrosis, obesity.*

Introduction

Hepatic steatosis is a reversible condition caused by accumulation of triglycerides in liver cells. Although several causes are known, steatosis is most commonly due to excessive alcohol consumption in obese people, especially those with an abdominal fatty mass distribution. This condition is also associated with other diseases that influence the fat metabolism [1]. NAFLD is a cause of steatosis and is diagnosed by imaging techniques or liver biopsy, in conditions of the exclusion of alcohol >20g/day [2].

The clinicopathological spectrum of NAFLD ranges from simple steatosis to nonalcoholic steatohepatitis (NASH). Simple steatosis has relatively benign clinical evolution, but NASH can progress to cirrhosis and hepatocellular carcinoma. NAFLD affects approximately 30% of the U.S. population, 15% of the Chinese population, 14% of Japan's population [3], 25% of Italian population, 20% of the romanian population

✉ Craiova, Str. Dionisie Eclesiarhul Nr.47, Jud. Dolj, Postal code 200059
corresponding author e-mail: ralucaradulescu2002@yahoo.com

[4], and the incidence appears to be growing with the epidemic of obesity. Currently, the most accurate way to diagnose these diseases is liver biopsy, however, many patients did not perform a liver biopsy and in the absence of more precise imaging technologies and some serum markers, diagnosis is often one of exclusion [5].

Because NAFLD can progress to advanced liver disease including fibrosis, cirrhosis, liver failure, cancer and ultimately can lead to death, it contributes significantly to the morbidity and mortality of the liver. Health systems need to promote public awareness programs on the complications of obesity and to highlight the importance of diet and exercise. NAFLD may be reversible with weight loss and lifestyle changes.

The best data in this sense come from obese patients undergoing bariatric surgery. Even with very severe NAFLD at baseline, some of these patients had a significant improvement or complete healing of liver disease after weight loss, loss of insulin-resistance and, in some cases, even of diabetes [6].

Study objectives: The main objective of our research was to study the structural changes of liver tissue, mainly the liver fibrosis in subjects with obesity, impaired liver tissue, with the study of serum transaminases, knowing that they are important markers of liver injury, the existence of correlations between liver fibrosis and BMI, Waist Circumference (WC), Hip Circumference (HC), age, fasting glucose, glucose 2 hours after oral glucose tolerance test, HbA1c, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, creatinine, gamaGT, C-reactive protein, ferritin, fibrionogen, ESR, creatinine clearance, smoking, arterial stiffness (measured with the Sphygmocor) skin autoflorescence (measured with the AGE Reader) and FINDRISK score.

Materials and methods. The study was conducted in the Clinic of Endocrinology, Jean Verdier Hospital in Paris, on a group of 88 patients, 76 females and 12 males, with ages between 19 and 68 years, with a mean age of 41,36 years. In the study were included patients with BMI $\geq$ 30kg/m² without a history of diabetes. Following data were recorded; demographic: age, sex, anthropometric parameters: height, weight, WC, HC, we calculated BMI; laboratory data: fasting glucose, glucose 2 hours after oral glucose tolerance test, HbA1c, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, creatinine, Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), gamaGT, C-reactive protein, ferritin, fibrionogen, Erythrocyte Sedimentation Rate (ESR), Glomerular filtration rate (GFR) was calculated with MDRD 4 calculator; exploration performed: Transient elastography (FibroScan) - exploring hepatic fibrosis, Sphygmocor - exploring arterial stiffness. FINDRISK score was calculated.

Changes in liver microstructure are reflected by an increase in liver tissue stiffness, which can be quantified due to radiological progress which allow the assessment of the degree of liver stiffness by methods/techniques such as FibroScan or Magnetic Resonance (MRI). Hepatic fibrosis was measured using FibroScan; FibroScan is a technology based on ultrasound used for quantitative assessment of liver stiffness, this method was introduced in the recent years in Europe and in other parts of the world. FibroScan measures the stiffness (or elasticity)

of the liver parenchyma using ultrasound between 5MHz and 50Hz. As the fibrous tissue is stiffer than healthy liver tissue, the measurement provides a quantitative assessment of "the degree of rigidity" [7, 8]. Should be mentioned technical limitations of the device in patients with obesity: if perihepatic fat is excessive (≥ 3cm) we can not register any measurements even with XL probe (recommended for obese patients), because of that 17 of the subjects could not be examined using FibroScan. Measurements were performed at the right lobe of the liver between the intercostal spaces, with the patient supine with the right arm in maximum abduction. Ten valid measurements were performed for each patient. Liver stiffness was expressed in kilopascals (kPa). Determination of liver parenchyma elasticity is at a depth of 2 cm and it has a diameter of 1 cm, representing an area 500 times greater than liver biopsy. Hepatic fibrosis is staged by the FibroScan values as follows: F0 ≤ 5.60 (kPa), F1 = 5.7 - 6.65 (kPa), F2 = 6.66 - 8.00 (kPa), F3 = 8.1 - 17 (kPa), F4 ≥ 17.1 (kPa) [9].

One of the main advantages of elastography is that it is not invasive, is performed in less than five minutes, so it can be repeated, allowing longitudinal monitoring of the disease and a comparative assessment. Tracking the dynamics is difficult to achieve when the main means of diagnosis is liver biopsy [10, 11]. Arterial stiffness was measured using the Sphygmocor.

Statistical analysis. All calculations were performed using Statistical Package for Social Sciences software (SPSS) version 17.

Results. Following the statistical analysis more than half of subjects had values above those considered normal of elestometry, so the distribution of the fibrosis stages (Figure 1) in our study group is as follows: F0=48%, F1=27%, F2=21% , F3=4%, F4=0%.

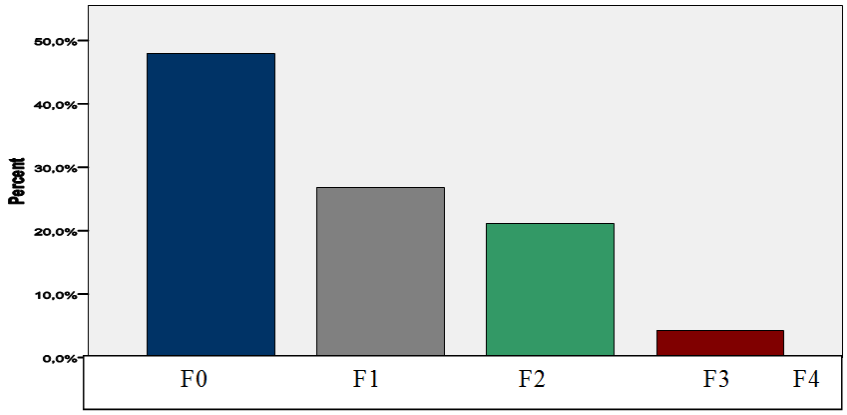

Figure 1. Distribution by stage of liver fibrosis in our study group.

45% of subjects (Figure 2, 3) had transaminase values, important markers of steatosis, above the limit considered normal (≥ 30IU). AST and ALT values were not correlated with the degree of obesity (BMI) and also were not correlated degree of hepatic fibrosis.

Following statistical analysis the hepatic fibrosis did not correlate directly with the degree of obesity (BMI) (p=0.104) (Figure 4) or with the WC (p=0.852) (Figure 5).

Hepatic fibrosis was correlated with age (p=0.027) (Figure 6), arterial stiffness (p=0.010) (Figure 7) and fasting glucose (p=0.018) (Figure 8).

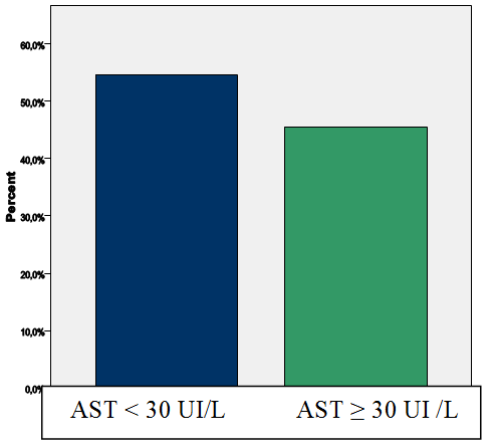

Figure 2. Normal and pathological values of AST in our study group

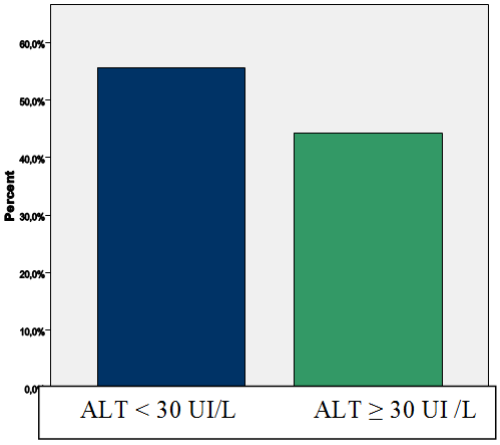

Figure 3. Normal and pathological values of ALT in our study group

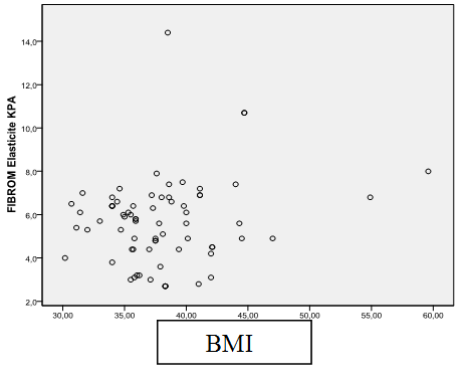

Figure 4. Correlation between liver fibrosis and BMI (p = 0,104)

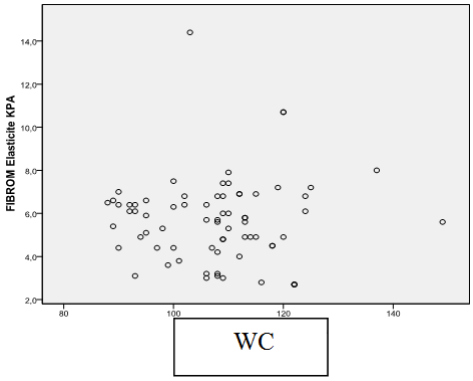

Figure 5. Correlation between liver fibrosis and WC (p = 0,852)

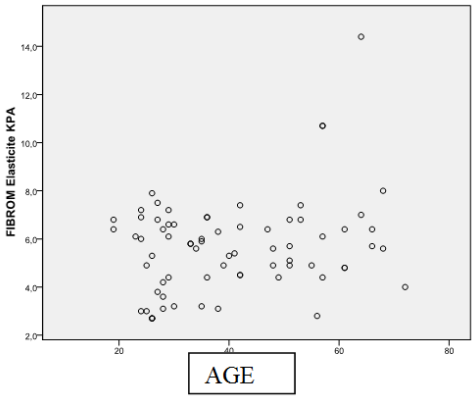

Figure 6. Correlation between liver fibrosis and age (p = 0,027)

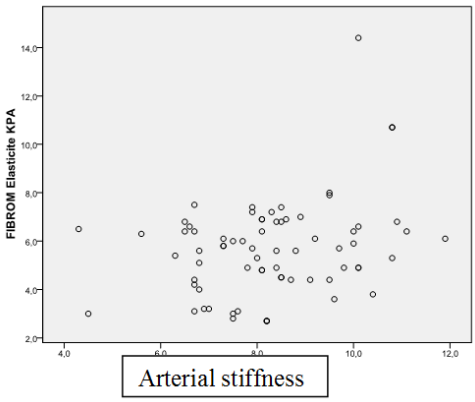

Figure 7. Correlation between liver fibrosis and arterial stiffness (p = 0,010)

Fibrosis did not correlate with HC (p=0,113), blood glucose 2 hours after oral glucose tolerance test (p=0,192), HbA1c (p=0,119), total cholesterol (p=0,203), LDL cholesterol (p=0,992), HDL cholesterol (p=0,066), serum triglycerides (p=0,420), serum creatinine (p=0,528), gamaGT (p=0,125), C-reactive protein (p=0,080), ferritin (p=0,561), fibrionogen (p=0,829), ESR (p=0,876), GFR (p=0,299), smoking (p=0,928), skin autoflorescence (p=0,331) (measured with the AGE reader) and FINDRISK score (p=0.899).

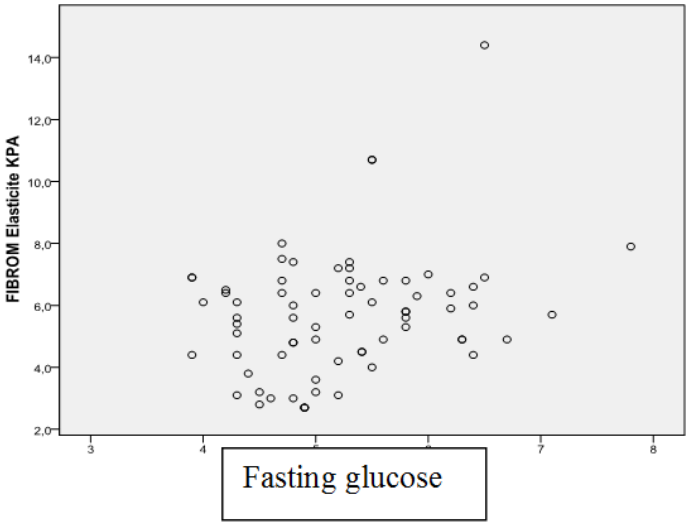

Figure 8. Correlation between liver fibrosis and fasting glucose (p = 0,018).

Discussions

NAFLD can progress to fibrosis, which is defined as the formation of excessive extracellular matrix (ECM) in liver parenchyma. Fibrosis is also a normal healing response to various types of injuries. In the liver, this healing process normally imply the recruitment of immune cells and/or inflammation at lesion/injury, secretion of ECM, proteins ECM reorganization and regeneration of liver tissue. In the case of cronic damage of liver tissue, excess fibrous connective tissue accumulates over time, this process distorts the normal structure and function affecting liver parenchyma. The pathogenesis of NASH-related liver fibrosis is not fully known. Evidence from numerous studies show the interdependence between obesity, insulin resistance and fibrosis. For example, adipokines are produced in proportion with the visceral fat mass. Leptin promotes fibrogenesis by promoting phagocytic activity and also cytokine secretion by Kupffer cells and macrophages, stimulates the proliferative activity in endothelial cells. Other adipokines such as resistin exercise the pro-inflammatory actions by increasing the expression of monocyte chemoattractant protein-1 (MCP-1) and interleukin-8 (IL-8), and activation of transcription factors such as Nuclear factor NFkB. The initial stages of liver fibrosis associated with NAFLD pathogenesis depend mainly of soluble factors produced by the excess visceral adipose tissue [12].

Liver biopsy in the past 50 years, was considered as the gold standard for staging liver fibrosis. This technique not only allows diagnosis of fibrosis, but also of many liver

processes such as inflammation, necrosis, steatosis, hepatic iron deposits or copper. Clinical studies showed that the risk of hospitalization after liver biopsy is 1-5%, risk of severe complications is 0.57%, and mortality rates vary from 0.009% to 0.12% [13, 14].

Most studies in literature have as research theme obesity and NALFD and less themes addresses fibrosis in people with obesity. The results of a prospective study conducted on a population of Chinese and French people are concordance with those obtained by us, they did not found a direct correlation between liver fibrosis and degree of obesity [15], but the fact that obese people develop hepatic steatosis and then develop liver fibrosis is cited by most studies of the literature. Another similar study conducted in the Department of Hepato-Gastroenterology Haut-Leveque Hospital in the town of Pessac, France, by Lédinghen V. et al., had among the results also correlation of liver fibrosis with fasting glucose, our results were in accordance with this study [16].

Many studies associated hepatic fibrosis in obese patients with advanced age [17, 18], also in our study liver fibrosis was correlated with patient age.

Conclusions

The fact that obesity is a cause of hepatosteatosis and therefore it progresses to liver fibrosis is demonstrated conclusively by studies after bariatric surgery, where weight loss is associated with the disappearance of these pathological processes [19]. In more than half of the subjects elastometry values were higher than those considered normal, these data are in concordance with the literature, we found no direct correlation between liver fibrosis and BMI or WC, this fact suggesting that fibrosis did not increase in proportion to their obesity. Serum transaminase levels are an important marker of liver tissue damage, in our study 45% of subjects had liver transaminase values above 30 UI/L. Among subjects that participated in the study 15% could not be evaluated with the FibroScan because of the excessive perihepatic fat (≥ 3cm), for them other methods of assessment of liver fibrosis are necessary [20]. Hepatic fibrosis was correlated with age, arterial stiffness and fasting glucose.

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