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NONALCOHOLIC FATTY LIVER DISEASE – CARDIOVASCULAR RISK FACTOR IN PACIENTS WITH TYPE 2 DIABETES MELLITUS

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Abstract
Scopul studiului a fost de a determina relația între doi factori de risc cardiovascular cunoscuți (ateroscleroza subclinică și hipertensiunea arterială) și ficatul gras nonalcoolic (NAFLD - nonalcoholic fatty liver disease) la pacienții cu diabet zaharat de tip 2. Au fost incluși 92 de subiecți cu diabet zaharat de tip 2 tratați cu antidiabetice orale sau doar regim igienodietetic. Ultrasonografia abdominală și ultrasonografia Doppler au fost utilizate pentru a evalua severitatea steatozei hepatice și a aterosclerozei subclinice, prin măsurarea grosimii intimă-medie carotidiană (GIM). Vârsta medie a lotului de studiu a fost de 60,38 ±10,37 ani. Mai mult de 90% dintre subiecți au prezentat diferite stadii de încărcare grasă hepatică. 61% dintre pacienți au avut valori anormale ale GIM. 75% dintre pacienți au prezentat valori crescute ale tensiunii arteriale. S-a demonstrat o relație semnificativă statistic între gradul de steatoză hepatică și GIM (r =0.3636, p =0.0004). De asemenea, s-a constatat o corelație semnificativă între gradul de încărcare grasă hepatică și tensiunea arterială sistolică. Rezultatele susțin ipoteza că NAFLD poate reprezenta un predictor cardiovascular prin relația sa directă cu GIM și tensiunea arterială.
***Cuvinte cheie**: boala ficatului gras nonalcoolic, hipertensiune, steatoză, diabet, risc cardiovascular.*

Abstract
The aim of our study was to determine the relationship between two well known cardiovascular risk factors (subclinical atheroclerosis and hypertension) and nonalcoholic fatty liver disease (NAFLD) in patients with type 2 diabetes mellitus. The study group was represented by 92 patients with type 2 diabetes mellitus who were treated with antidiabetic drugs or diet. Abdominal ultrasonography and Doppler ultrasonography were used to assess the severity of hepatic steatosis and subclinical atherosclerosis, evaluated using intima-media thickness of



the carotid artery (CIMT).The average age of the study group was 60,38 ± 10,37 years. More than 90% of the subjects presented different degrees of hepatic fat load. 61% of the patients had CIMT values above the normal range. 75% of the subjects presented high blood pressure (BP) values. A direct statistically significant correlation between the degree of hepatic steatosis and CIMT (r =0.3636, p =0.0004) was found. Also, we found a positive correlation between the degree of hepatic fat load and the value of systolic blood pressure (SBP). These results sustain the hypothesis that NAFLD can be a predictor of cardiovascular risk due to its direct connection with CIMT and SBP.

Keywords: *nonalcoholic fatty liver disease, hypertension, steatosis, diabetes, cardiovascular risk.*

Introduction

Hepatic steatosis within non-alcoholic fatty liver disease (NAFLD) is a largely encountered condition worldwide. Data show that it affects 20% of world population, but its prevalence increases up to 80% in obese and diabetic subjects[1]. It is considered a major health problem because it represents the most frequent cause of liver disease in developed countries[2], due to its strong relationship with cardiovascular disease and obesity[3].

Only a small percent of the subjects with hepatic steatosis will develop severe forms of hepatic disease (non-alcoholic steatohepatitis, cirrhosis and liver cancer). This aspect is supported by the fact that hepatic steatosis will lead to potentially fatal cardiovascular events and, in rare cases, to the aggravation of the hepatic condition[4]. NAFLD can be seen as the hepatic feature of metabolic syndrome[5]. So, the main risk for the patient with hepatic steatosis is represented by a major cardiovascular event.

Lifestyle changes, especially in highly industrialized countries, led to an epidemic growth of overweight, obesity and type 2 diabetes mellitus during the last decades[6]. A study which included almost 6000 subjects proved that fatty liver is associated with increased cardiovascular risk, independently of traditional risk factors such as sex, age and smoking status[7]. The object of the study was that of underlining any existing correlations between hepatic steatosis level, blood

pressure and subclinical atherosclerosis evaluated by intima-media thickness of the carotid artery (CIMT).

Experimental

The observational study included 92 subjects evaluated for a period of 18 months in the Diabetes, Nutrition and Metabolic Diseases Clinic within the "Sf Spiridon" Emergency Hospital of Iasi. The inclusion criteria were the following: diagnosis of type 2 diabetes mellitus treated with oral anti-diabetics drugs or lifestyle changes. The exclusion criteria were the following: patients with hepatitis B or C, subjects under insulin therapy, subjects with toxic ethylic hepatitis, other rare hepatic conditions (Wilson disease) and persons who refused to sign the informed consent.

The investigations were represented by anamnesis, clinical examination, blood pressure measurement and abdominal ultrasonography for the evaluation of the hepatic fat load. Liver steatosis was divided into four degrees according to five criteria: deep beam attenuation, parenchymal reflectivity, liver-kidney contrast, gallbladder wall appearance and the aspect of the small vessel walls. Subclinical atherosclerosis was assessed by measuring CIMT using a colour Doppler ultrasound LS 128 with linear probe HL9/40/128Z.

The database was created in Microsoft Excel, without including ID data of the subjects. The statistical analysis was made in Statistica, version 7.0. We considered $p < 0.05$ as statistically significant.

Results

The group of 92 subjects was represented by 44 men (47.83%) and 48 women (52.17%). The average age was of 60.38 ± 10.37 years, varying between the ages of 33 and 86. More than 90% of the subjects presented different degrees of hepatic steatosis (Figure 1).

75% of the subjects presented high blood pressure (BP) values. 62% of the subjects presented abnormal values of the CIMT. 9 of the investigated patients were diagnosed with carotid atheromatous plaques. The comparison of average values of the CIMT between different levels of hepatic affection underlined the following significant differences: the first notable aspect refers to the fact that the average value of the CIMT is continuously increasing according to the level of hepatic affection: 0.84 in subjects with normal liver, 0.93 - intermediate steatosis, 1.03 - moderate steatosis, 1.05 - severe steatosis (Figure 2).

Compared to normal liver subjects, the average value of CIMT seemed to be higher in subjects with moderate steatosis (1.03, vs. 0.84, $p = 0.002$) and severe steatosis (1.05, vs. 0.84, $p = 0.01$). Compared to mild steatosis subjects, the average value of CIMT seemed to be higher in moderate steatosis subjects (1.03, vs. 0.93, $p = 0.0098$) and severe steatosis (1.05 ± 0.21 vs 0.93 ± 0.13, $p = 0.03$). The average values in normal liver and mild steatosis subjects showed no statistically significant differences: 0.84 vs. 0.93, $p = 0.10$. Similarly, the average values in subjects with moderate and severe steatosis were statistically not too different: 1.03 vs. 1.05, $p = 0.76$. We compared the average values of the subjects cumulated into two groups: group 1, with normal liver or mild steatosis and group 2, with moderate or severe steatosis. We can see that the significance of the difference between the average value of CIMT in the subjects of the two groups was much higher ($p = 0.0004$). The incidence of normal liver or mild steatosis cases was significantly higher in subjects with

normal CIMT values (54.29%, vs. 25% with values over the normal limit, p =0.003), while the incidence of moderate or severe steatosis cases was significantly higher in subjects with values of the CIMT over the normal limit (75%, vs. 45.71% with normal values, p =0.003) (Figure 3).

The incidence of normal systolic blood pressure (SBP) cases was significantly higher in subjects with normal liver or mild steatosis (50% vs. 29.69% with moderate or severe steatosis, p =0.04), while the cases of moderate and severe steatosis were significantly more frequent in subjects with abnormal SBP values (70.31%, vs. 50% in patients whose SBP values were normal, p =0.0007). The incidence of the normal liver subjects was significantly higher in patients with normal diastolic blood pressure (DBP), in comparison with subjects whose DBP values were over the normal values (19.51%, vs. 2.22%, p =0.005). Also, we found a positive correlation between the degree of hepatic steatosis and the value of SBP (Figure 4). No significant correlations were found between the degree of hepatic steatosis and the value of DBP.

A number of 9 subjects (9.89% of the cases) were diagnosed with atheroma of the carotid arteries, 8 of the 9 cases (88.89%) showing a moderate or severe steatosis level. The comparison of the incidence of these cases for the two subgroups showed that the incidence of atheroma cases was significantly higher in the group of subjects with moderate or severe steatosis (13.79% vs. 3.03% in those with normal liver or mild steatosis, p =0.049).

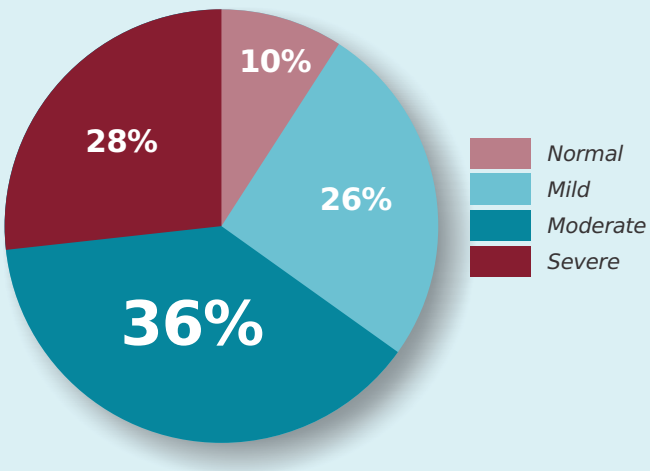


***Figure 1**. Degrees of hepatic steatosis*

Discussion

The prevalence of steatosis in the studied group was more than 90%, data which is also shown in other studies, where the prevalence of the hepatic condition is mentioned between 70 and 90% among patients with type 2 diabetes mellitus[8,9]. The prevalence is even higher in obese subjects[10].

The high prevalence of steatosis obtained in our research might be explained by the particular eating habits in our country (high saturated fats diet) combined with a sedentary lifestyle. As regards the studied

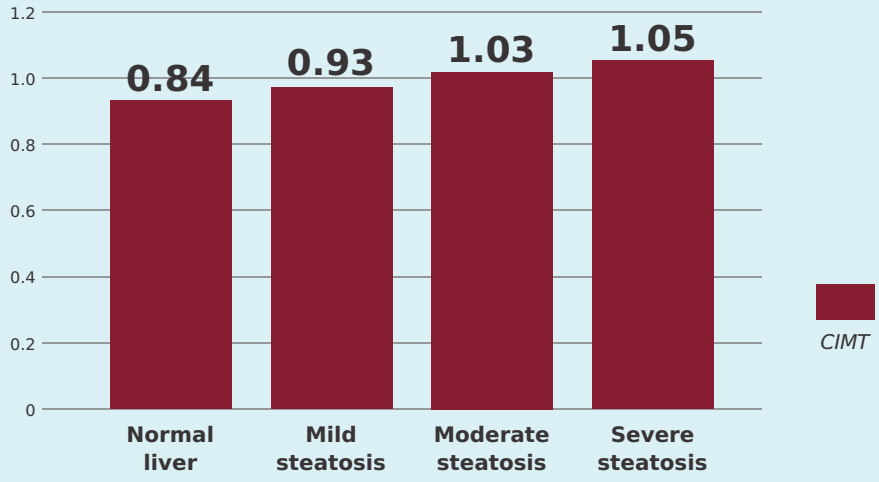


***Figure 2**. Degrees of hepatic steatosis and subclinical atherosclerosis*

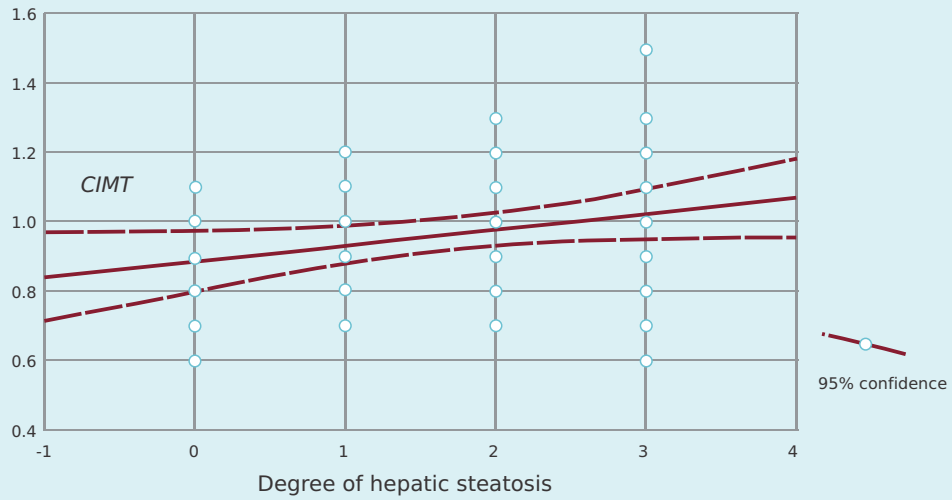


***Figure 3**. The degree of hepatic steatosis vs. CIMT*

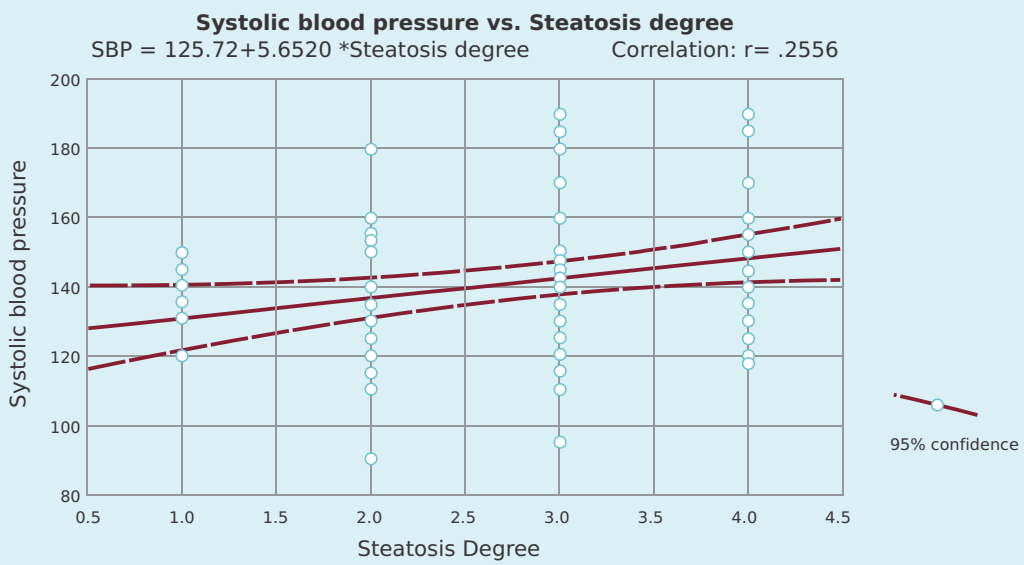


***Figure 4**. Systolic blood pressure vs. steatosis degree*



group, we noticed no statistically significant correlations according to the sex relative to the incidence of normal liver and hepatic steatosis cases, although other researchers claim that the males present a higher risk for hepatic steatosis[11].

In our study, we noticed both a statistically significant correlation between the levels of hepatic steatosis and CIMT, as well as to the presence of carotid plaques. Another research showed that subjects with NAFLD present a high incidence of cerebrovascular disease (20% vs. 133%, p <0.001)[12]. Other authors, however, mention the fact that hepatic steatosis does not represent a direct mediator of cardiovascular disease[13].

We also investigated the relationship between NAFLD and hypertension. A study which included 22090 subjects over a period of five years showed that NAFLD is an independent risk factor for hypertension according to the degree of fatty liver[14]. In our study there was a significant correlation between the SBP and the severity of hepatic steatosis, even if the blood pressure values were measured only on the day of the clinical examination.

Conclusions

The vast majority of type 2 diabetes mellitus subjects presented different degrees of hepatic fat load.

We established a direct correlation between subclinical atherosclerosis and the level of hepatic fat loading. Thus, it was proved that the average values of CIMT are continuously increasing, according to the level of hepatic affection. In addition to this, the incidence of carotid atheroma plaques was significantly higher in subjects with severe forms of hepatic steatosis. Hepatic steatosis was also associated with SBP.

NAFLD has proved to be a predictor of cardiovascular risk through its direct connection with subclinical atherosclerosis and other major cardiovascular risk factors.

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