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Relationship between NAFLD and hypertension in patients with type 2 diabetes mellitus

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Abstract

Nonalcoholic fatty liver disease (NAFLD) represents one of the most frequent cause of liver disease and it has a high prevalence, especially among pacients with type 2 diabetes mellitus. The aim of our study was to evaluate the connection between the degrees of hepatic load fat and cardiovascular risk factors – hypertension, obesity and atherogenic dyslipidemia. The observational study included 92 subjects with type 2 diabetes mellitus. More than 90% of the subjects presented different hepatic fat load. We found a direct correlation between tryglicerides and the degree of hepatic steatosis and a negative correlation between the amount of fat load and HDLc. 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 cases with normal liver was significantly higher in subjects 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. The results sustain the hypothesis that NAFLD can be a predictor of cardiovascular risk through its direct connection with SBP.

Keywords: NAFLD, hypertension, cardiovascular risk, atherogenic dyslipidemia

Introduction

Nonalcoholic fatty liver disease (NAFLD) is the most common cause of liver disease in many developed countries [1] and is closely associated with obesity and cardiovascular disease [2]. Also, it is estimated that NAFLD will become a major problem due to the increased prevalence of obesity and aging [3]. Epidemiological data show that NAFLD affects almost 20% of world population. Prevalence increases among subjects who associate other risk factors, such as morbid obesity, in which case it can be up to 80% [4]. The prevalence is even higher (96%) among pacients who undergo bariatric surgery [5].

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A study which included 5671 subjects showed that the presence of fatty liver is associated with an increased cardiovascular risk, independently of traditional risk factors such as smoking, age, sex, essential hypertension and C – reactive protein (CRP). Cardiovascular risk was determined by measuring the carotid intima-media thickness (CIMT), which is a valid predictor of miocardial infarction and stroke [6].

Increased liver fat load is correlated with all components of metabolic syndrome, which increases cardiovascular risk. The prevalence of metabolic syndrome is increasing, even among children, adolescents and women with gestational diabetes [7]. The components of the metabolic syndrome, such as obesity, hyperglycemia, dyslipidemia, and hypertension are commonly found in NAFLD [8]. The aim of our study was to evaluate the connection between the degrees of hepatic load fat and well known cardiovascular risk factors – blood pressure and atherogenic dyslipidemia.

Material and methods

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 group was represented by patients hospitalized within the Diabetes In-Patient Unit for a period of 60 days. The inclusion criteria were the following: subjects hospitalized within the Diabetes In-Patient Unit during the above-mentioned period, diagnosis of type 2 diabetes mellitus treated with oral anti-diabetics or hygiene-dietetic regime. The exclusion criteria were the following: subjects suffering from hepatitis B or C, subjects under insulin therapy, subjects with toxic-ethylic hepatitis, persons who refused to participate in the study or those who did not sign the informed consent, patients suffering from other hepatic conditions (e.g. Wilson's disease – declarative).

We solicited and obtained the authorization of the Research Ethics Commission of the "Grigore T. Popa" University of Medicine and Pharmacy of Iaşi.

Our investigations included: clinical examination, anamnesis and anthropometrical evaluations, lipid profile – triglycerides, total cholesterol, high density lipoprotein cholesterol (HDLc), low density lipoprotein cholesterol (LDLc) and evaluation of the hepatic fat loading by ultrasound. The degree of fatty load of the liver was evaluated by ultrasound with a probe of 3.5 MHz. Liver steatosis was divided into 4 degrees according to 5 criteria: parenchymal reflectivity, the contrast between the liver and kidney, deep beam attenuation, viewing the small vessel walls of the liver and gallbladder wall appearance. 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

From the group of 92 subjects, 44 were male (47.83%) and 48 women (52.17%). According to the provenance environment, 68 subjects belong to the urban environment (73.91%) and 24 to the rural environment (26.09%). The average age was of 60.38 ± 10.37 years, varying between the ages of 33 and 86. 9.89% of the cases were those of normal liver, while the incidence of the cases according to the level of hepatic steatosis represented 26.37% of mild steatosis, 36.26% of moderate steatosis and 27.47% of severe steatosis.

Most of the subjects presented values over the normal limit of the body mass index (BMI). Most of the patients were obese and overweight, only 5 having a normal weight. Only 9 subjects presented normal values of the abdominal circumference (AC).

75% of the subjects presented high blood pressure (BP) values. As regards the atherogenic dyslipidemia markers, over half of the subjects presented high values of total cholesterol, 65% presented HDLc values under the regular limits and 50% presented hypertriglyceridemia. The metabolic syndrome criteria were met in most cases (81%).

After comparing the incidence of the levels of hepatic steatosis (normal liver, mild, moderate and severe steatosis) to the BMI classification categories we can notice the following aspects: mild steatosis is significantly more frequent in subjects with class I obesity (44.44%) in comparison with overweight (17.65%, $p = 0.01$) and class III obesity (9.09%, $p = 0.02$). Also, moderate steatosis is significantly more frequent in overweight subjects (47.06%) in compar-

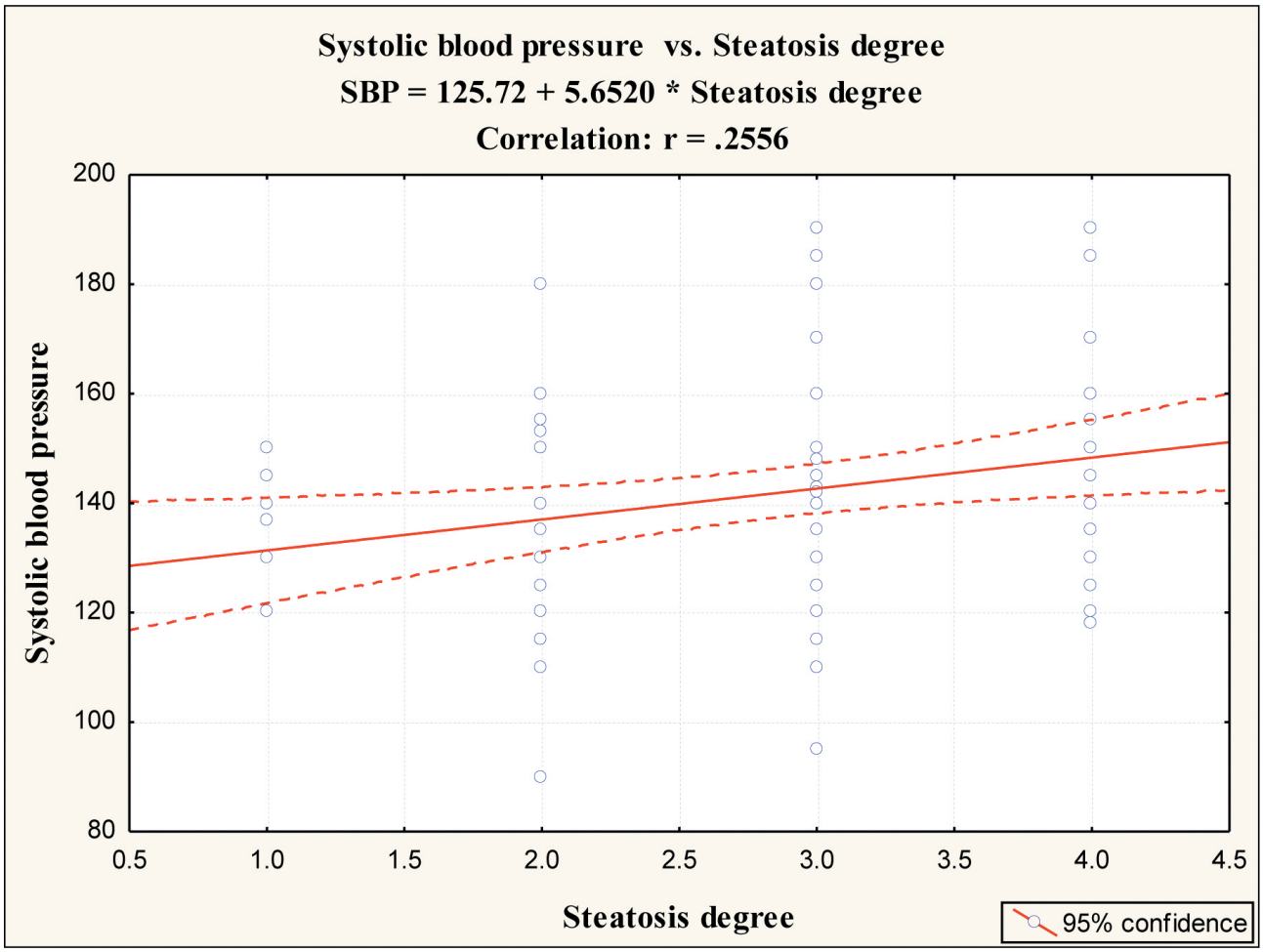

Figure 1. Hepatic steatosis and systolic blood pressure (SBP) – regression analysis.

ison with class I obesity (25.93%, p = 0.048) and (9.09%, p = 0.02).

The incidence of mild steatosis was significantly higher in subjects with abnormal abdominal circumference (p = 0.03). The incidence of normal liver cases was significantly higher in subjects with normal waist to hip ratio (23.53% vs. 5.63%, p = 0.001).

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 cases with normal liver was significantly higher in subjects 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 1). No significant correlations were found between the degree of hepatic steatosis and the value of DBP.

The incidence of mild steatosis was significantly higher in normal cholesterol subjects (35.9% vs. 19.23% of those with cholesterol over the normal limits, p = 0.04), while the incidence of moderate steatosis cases was significantly higher in subjects with cholesterol values over the normal limits (44.23% vs. 25.64% of those with normal cholesterol values, p = 0.03). We did not notice significant incidence differences per level of hepatic steatosis determined by the LDLc values (Table 1). The incidence of normal liver or mild steatosis cases was significantly higher in subjects with HDLc

Table 1. Pearson R correlation coefficient with the degree of hepatic steatosis. HDLc – high density lipoprotein cholesterol; LDLc – low density lipoprotein cholesterol; TG – triglycerides.

Parameters	r coefficient	p value
Total cholesterol	0.1289	0.27
HDLc	-0.5654	<0.0001
LDLc	0.0136	0.91
TG	0.3716	0.001
Glycemia	0.0335	0.78

values within the normal limits, while the incidence of moderate and severe steatosis cases was significantly higher in subjects with HDLc values under the normal limits.

Among the subjects with normal values of the HDLc there were significantly more cases of normal liver or mild steatosis (70.97% vs. 18.33% of those with values under the normal limits, $p < 0.00001$), while among subjects with values under the normal limit, we encountered significantly more cases of moderate or severe steatosis (81.67% vs. 29.03% of those with normal values, $p < 0.00001$). Seen that the value of $\chi^2=24.5$ is very significant ($p < 0.00001$), we can say that we confirmed the hypothesis of a relation between HDLc and hepatic steatosis (Figure 2).

Discussion

The incidence of various degrees of hepatic steatosis in our study group exceeded 90%, values comparable to the research literature [9]. It is reported to be even higher (up to 95%) in obese subjects [10]. A Japanese study has shown that the prevalence of NAFLD was 43% higher in subjects with impaired glucose tolerance and 62% higher in patients with type 2 diabetes compared to the control group [11]. The high prevalence of steatosis obtained in our research might be explained by the particular eating habits in our country (diet rich in saturated fats of animal origin) compounded by a sedentary lifestyle (mainly for the urban majority in our study).

In our study, we were interested in the severity of steatosis as additional factor that can predict the severity of dyslipidemia in subjects with type 2 diabetes.

It is known that hepatic steatosis is a predictor of insulin resistance and hypertriglyceridemia in diabetic patients and also in nondiabetic subjects [12]. Our patients had cardiovascular risk factors, high triglycerides and low HDLc results which are similar to other studies [13, 14].

This type of atherogenic dyslipidemia is associated with cardiovascular events [15].

A study that included a total of 70 subjects showed that the degree of fatty liver was significantly associated with increased levels of total cholesterol, LDLc, VLDLc and inversely correlated with HDLc [16].

The relationship between hypertension and NAFLD was also investigated. There was found a higher prevalence of NAFLD among obese hypertensive subjects with normal liver enzymes compared to normotensive subjects. A study which included 55 subjects with normal body weight, non-diabetic and normal liver enzymes showed that hypertensive patients have shown a significantly increased prevalence of NAFLD, increased insulinresistence and BMI compared to the control group. Insulinresistance could be predicted by ALT, presence of hypertension and BMI [17]. In our study there were significant correlations only between SBP and the degree of fatty liver, even if there were only included subjects with type 2 diabetes and we did not use a control group.

A study conducted on 22 090 subjects followed the link between the degree of steatosis and hypertension. They concluded that NAFLD is an independent risk factor for hypertension, with higher incidence of hypertension according to the degree of fatty liver (normal liver 14.4%, 21.8% mild steatosis, moderate and severe steatosis 30, 1%, $p <0.001$) [18]. This study evaluated the incidence of hypertension but over a period of five years, while in our study were taken into account

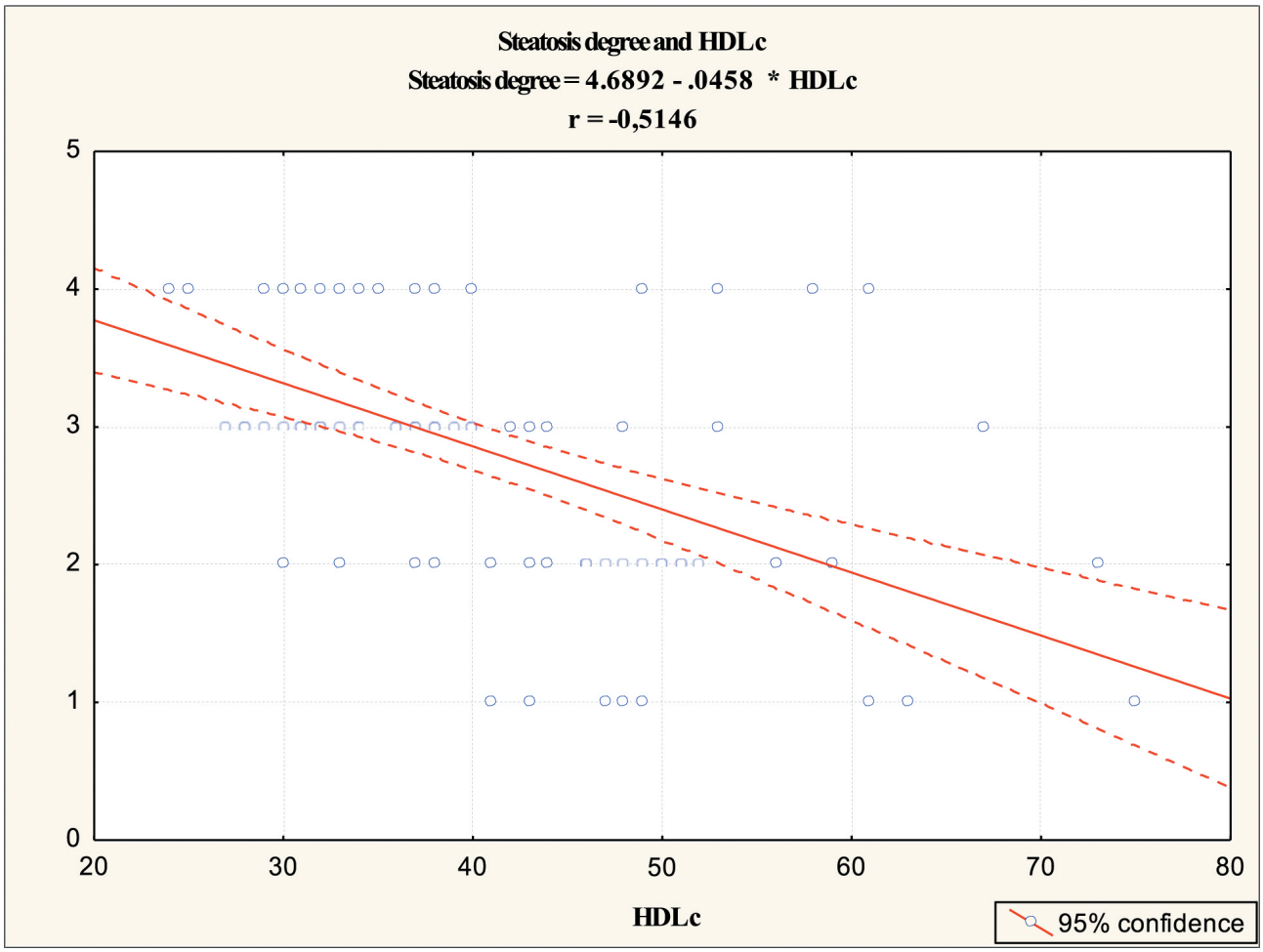

Figure 2. HDLc and hepatic steatosis – regression analysis. HDLc = high density lipoprotein cholesterol.

only the blood pressure values measured on the day of the clinical examination.

There are common situations when clinicians encounter patients with NAFLD without hypertension and guidelines for behavior therapy are not yet listed in guidebooks. If clinical association between NAFLD and hypertension will be clarified, it will be useful in preventing cardiovascular disease in patients with NAFLD.

Conclusions

We conclude that subjects with type 2 diabetes have an increased incidence of NAFLD, with different degrees of fat loading, which cause an increased cardiovascular risk. We found a positive correlation between the degree of steatosis and atherogenic dyslipidemia (increase in tryglicerides and decrease in HDLc). At the same time, the degree of hepatic steatosis has proved to be a predictor of cardiovascular risk through its direct connection with SBP.

Conflict of interest

The authors confirm that there are no conflict of interest.

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