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Nonalcoholic fatty liver disease is associated with low HDL cholesterol and coronary angioplasty in patients with type 2 diabetes

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Background: There is evidence that nonalcoholic fatty liver disease (NAFLD) is associated with increased cardiovascular risk. In this study we examined factors associated with the presence of NAFLD and the prevalence of macroangiopathy in patients with type 2 diabetes.

Material/Methods: Subjects were 101 consecutive patients with type 2 diabetes: 72 with NAFLD and 29 free of NAFLD. NAFLD was diagnosed by ultrasonography. Serum lipids were measured enzymatically and glycated hemoglobin HbA1c was measured by HPLC.

Results: The mean age of patients was 53.1±10.4 in the NAFLD group and 44.9±10.9 years in patients without NAFLD ($p<0.001$). The mean duration of diabetes was 10±6.3 years in patients with NAFLD and 15.1±7.8 years in those without NAFLD ($p<0.001$). Mean values of glycated hemoglobin A1c were similar in both groups. Patients with NAFLD were characterized by a significantly higher prevalence of coronary angioplasty (20.8% *vs.* 0%, $p=0.008$). Overweight and obesity were observed in a higher percentage of patients with NAFLD ($p<0.001$). Patients with NAFLD were characterized by significantly higher values of alanine transaminase ($p=0.033$), and lower serum concentrations of HDL-cholesterol ($p<0.001$) and creatinine ($p=0.034$). Logistic regression analysis ($p<0.001$) revealed that NAFLD was positively associated with waist circumference above normal (women >80 cm, men >94 cm) ($p=0.0083$) and alanine transaminase activity ($p=0.0164$), and negatively with creatinine concentration ($p=0.0226$). In a second logistic regression model ($p<0.001$), waist circumference ($p<0.007$) and total cholesterol ($p<0.008$) were positive predictors, while HDL-C ($p<0.003$) was a negative predictor of NAFLD.

Conclusions: The results of the study suggest that NAFLD is associated with visceral obesity and low HDL-cholesterol in patients with type 2 diabetes.

Key words: fatty liver disease • diabetes type 2 • diabetic macroangiopathy • obesity

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Background

Nonalcoholic fatty liver disease (NAFLD) is very common worldwide. The prevalence of NAFLD in the general population is around 20–30%, whereas among patients with type 2 diabetes it is up to 80% [1,2]. NAFLD is strongly correlated with metabolic syndrome, including visceral obesity, atherogenic dyslipidemia, insulin resistance, impaired glucose metabolism, or type 2 diabetes [1–5]. The pathogenesis of NAFLD is not entirely understood, but there is a great deal of evidence suggesting that NAFLD is actually a hepatic manifestation of metabolic syndrome [1–4]. NAFLD is characterized by steatosis of hepatocytes, which is usually macrovesicular, and can be diagnosed after exclusion of other risk factors for chronic liver diseases such as alcohol abuse, drugs, or chronic viral hepatitis [1].

There is some data indicating that cardiovascular complications are more common among patients with diabetes and NAFLD than in patients without liver disease. NAFLD is associated with increased risk of all-cause mortality and predicts future CVD events independently of other risk factors [6–9]. Targher suggests that NAFLD might be not only a marker, but also an early mediator of cardiovascular diseases [10]. The aim of our study was to determine the factors associated with the presence of NAFLD in patients with type 2 diabetes. We also tried to find an association between NAFLD and diabetic macroangiopathy in patients with type 2 diabetes.

Material and Methods

We examined consecutive patients with type 2 diabetes from a diabetic clinic, 72 of which had nonalcoholic fatty liver disease diagnosed by abdominal ultrasonography. Ultrasonographic measurements were performed by experienced radiologists who were blinded to the clinical presentations and laboratory finding of the subjects. Hepatic steatosis was defined as a diffuse increase in fine echoes in the liver parenchyma, as compared with the parenchyma of the kidney or spleen [11]. All patients were asked about their medical history and alcohol consumption. Individuals that defined themselves as alcohol drinkers or consumed more than 30 g of ethanol daily (or its equivalent) were excluded from the study. Patients with hepatitis B virus antigen or hepatitis C virus antibody, and patients with chronic liver disease were excluded. All participants underwent physical examinations. Laboratory tests were done in the fasting state including serum enzymes activity, serum lipids, glucose and creatinine concentrations, and glycated hemoglobin A1c. Blood lipids were determined by enzymatic methods, using Roche reagents, and HbA1c was assessed by high pressure liquid chromatography. Serum enzymes activity was performed by routine methods.

Anthropometric measurements included weight, height, and blood pressure. Body mass index (BMI) was calculated by dividing the weight in kilograms by the height in meters squared. Blood pressure was measured twice, with the subjects in a sitting position, using an automated device; the mean of 2 measurements was calculated.

Coronary heart disease (CHD) was defined as the presence of stable angina, past AMI, past revascularization procedure, or PTCA.

Statistical analyses were conducted with STATISTICA 10. Means and standard deviations were calculated for continuous data. For group comparisons of continuous variables, the Mann-Whitney test was used. The chi-square test of independence I was used for comparison of categorical variables. The Pearson correlation was used to examine the relationship. Serum lipids were standardized for age and glycated hemoglobin levels. The logistic regression model was used to estimate the importance of examined variables association with fatty liver disease. A significance level of 0.05 was used throughout.

Consent was obtained from the Bioethics Committee of the Jagiellonian University.

Results

Characteristics of the studied group are presented in Tables 1 and 2. We examined 101 patients with type 2 diabetes (64 men and 37 women). Patients with NAFLD were older than patients without NAFLD (mean age 53.1±10.4 yrs *vs.* 44.9±10.9 yrs, respectively ($p<0.001$). However, mean duration of diabetes was shorter: 10.0±6.3 years in patients with and 15±7.8 years in those without NAFLD ($p<0.001$). Insulin treatment had been received by 72% of NAFLD patients, and insulin dosage was significantly higher in patients with NAFLD than without NAFLD (69.9±30 units of insulin /24 h *vs.* 51.7±31.4 units/24 h, $p=0.016$); the mean insulin dosage per kilogram of body weight was 0.71±0.3 *vs.* 0.65±0.3 (p=ns.)

Patients with NAFLD were characterized by significantly higher prevalence of coronary angioplasty (20.8% *vs.* 0%, $p=0.008$), but the incidences of coronary heart disease and by-pass surgery were not different between groups.

Overweight and obesity were observed in a higher percentage of NAFLD patients ($p<0.001$). NAFLD patients were characterized, as expected, by significantly higher values of alanine transaminase ($p=0.033$) and lower concentrations of serum of HDL-cholesterol ($p<0.001$) and creatinine ($p=0.034$). After standardization by age and glycated hemoglobin, only HDL-cholesterol and triglyceride concentrations were significantly

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Table 1. Characteristic of the studied groups.

Parameter	Group with NAFLD n=72		Group without NAFLD n=29		p
	x	SD	x	SD	
Age, yrs	53.1	10.4	44.9	10.9	0.001
Duration of diabetes, yrs	10.0	6.3	15.0	7.8	0.001
BMI, kg/m^2	33.9	6.4	28.1	4.9	0.001
Waist circumference, cm	108.9	14.4	97.4	16.0	0.001
WHR	0.98	0.08	0.97	0.07	n.s.
SBP, mmHg	128.1	16.0	127.1	16.0	n.s.
DBP, mmHg	79.0	10.4	77.0	10.5	n.s.
HbA1c,% (mmol/mol)	9.1 (76)	1.9 (-3)	8.4 (68)	2.0 (–2)	n.s
ALAT, U/L	42.7	39.5	26.0	14.53	0.033
AST, U/L	34.2	34.5	24.3	9.97	n.s.
GGTP, U/L	60.6	75.4	44.2	89.61	n.s.
FA,U/L	107.5	61.4	100.5	46.2	n.s.
Cholesterol, mmol/l	4.9	1.7	4.4	1.5	n.s
Triglycerides, mmol/l	3.0	5.1	1.8	2.26	n.s
HDL-C, mmol/l	1.0	0.26	1.3	0.41	<0.001
LDL-C, mmol/l	2.8	1.24	2.5	0.96	n.s
Creatinine, µmol/l	76.3	22.8	92.6	54.6	0.037
GFR, ml/min/1.73 m^2	90.7	24.5	84.8	33.3	n.s
ACR, mg/mmol	5.5	7.1	3.9	7.2	n.s.

Table 2. Prevalence of macroangiopathy and mode of treatment.

Parameter	Group with NAFLD n=72		Group without NAFLD n=29		p
	n	%	n	%	
Men, %	64		37		
Insulin treatment	52	72.2	25	86.2	n.s
Insulin, units/24 h/1 kg m.c.	0.71	0.3	0.65	0.29	n.s.
Metformin treatment, %	61	84.7	11	37.9	0.001
Hypotensive treatment, %	70	97.2	27	93.1	n.s
Hypolipidemic treatment, %	66	91.7	21	72.4	0.011
Coronary heart disease, %	36	48.6	19	65.5	n.s.
Coronary angioplasty, %	15	20.8	0	0	0.008
Coronary bypass surgery, %	6	8.3	3	10.3	n.s.

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Table 3A. Logistic regression for NAFLD with waist circumference, HbA1c, alanine transaminase (ALAT) and creatinine as independent variables.

Parameter	B coefficient	Odds Ratio	95% CI	p
Constant	–2.873764			
Waist circumf.	2.373005	10.729588	1.844174 to 62.42582	0.0803
HbA1c	0.161049	1.174742	0.907537 to 1.52062	0.2213
ALAT	0.070164	1.072684	1.012926 to 1.135968	0.0164
Creatinine	–0.02026	0.979944	0.963032 to 0.997153	0.0226

Table 3B. Logistic regression for NAFLD with waist circumference, Hb A1c and serum lipids concentrations as independent variables.

Parameter	B coefficient	Odds Ratio	95% CI	p
Constant	–2.598566			
Waist circumf.	2.708466	15.006238	2.096109 to 107.431061	0.007
HbA1c	0.080584	1.08392	0.774619 to 1.516724	0.6383
cholesterol	1.865242	6.457495	1.63119 to 25.56369	0.0079
LDL-C	–0.91476	0.400613	0.145157 to 1.105633	0.0774
HDL-C	–4.550695	0.01056	0.000513 to 0.217473	0.0032
Triglyceride	–0.063693	0.938293	0.412967 to 2.131873	0.8791

different between groups. Multiple logistic regression analysis with NAFLD as a dependent variable was examined in 2 models (Table 3A and 3B) – both models were significant ($p<0.001$). In the first model, which included waist circumference above normal (women >80 cm, men >94 cm), HbA1c, ALAT, and creatinine concentration, only waist circumference and alanine transaminase were associated positively, while creatinine was negatively associated with the presence of fatty liver. In the second model (which included serum lipids), waist circumference above normal ($p=0.007$) and total cholesterol ($p=0.0079$) were positive predictors of NAFLD, and HDL-C ($p=0.0032$) was a negative predictor of NAFLD. Another measure of obesity, body mass index was also a significant predictor of NAFLD, while waist to hip ratio did not have significant influence. LDL-cholesterol and triglycerides were not significant in this analysis. We did not find an association between presence of NAFLD and glycemic control as measured by HbA1c.

Interestingly, glycemic control was associated with liver enzymes in patients with type 2 diabetes and NAFLD. In patients with NAFLD, there were significant positive correlations between glycated hemoglobin and waist circumference ($r=0.3188$, $p=0.010$), LDL-C ($r=0.2479$, $p=0.048$), GGTP ($r=0.3275$, $p=0.032$), and FA ($r=0.5882$, $p<0.01$) and negative correlations with HDL-C ($r=–0.2602$, $p=0.038$) were observed. In patients without NAFLD, the only significant correlation was observed between HBA1c and triglyceride level ($r=0.5122$, $p=0.009$).

Discussion

This study characterized the clinical and biochemical features of patients with type 2 diabetes and NAFLD. We also confirmed the important role of central obesity in the development of NAFLD, observed by others, in patients with diabetes. In our study, presence of ultrasonographically documented NAFLD was associated with 2 features of metabolic syndrome: central obesity and low HDL cholesterol concentrations. Visceral obesity seems to be the key associate of NAFLD in patients with as well as without diabetes [12–14].

Low serum concentration of HDL-C and higher concentrations of triglycerides, the key features of insulin resistance dyslipidemia, were significantly different between patients with and without NAFLD, after standardization by age and HbA1c. However, only low concentration of HDL-C and high levels of total cholesterol remained highly significant predictors of NAFLD in multiple logistic analysis. In The Multi-Ethnic Study of Atherosclerosis, a prospective population-based study, NAFLD was associated with lower fasting HDL-C, as in our group of patients. In the above study, higher fasting triglyceride levels and LDL particle concentrations were also significant associates of NAFLD [15]. Our findings suggest that serum triglyceride, a marker of insulin resistance, is less associated with NAFLD than HDL-C. According to data in the literature, it is well established that HDL lipoproteins are small, dense, and dysfunctional in patients

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with type 2 diabetes, so it seems that our results warrant further investigation of HDL function [16]. Statins are currently the first-line drug and LDL-C is the goal of treatment of diabetic dyslipidemia. However, it seems important, from the present study and literature data, to obtain desirable HDL cholesterol, not only because of cardiovascular disease prevention, but also to prevent of fatty liver disease. At the present time we do not have efficacious treatment of low HDL cholesterol, apart from life-style modification, fibrates, and statins. Effects of statins and fibrates on HDL-C in patients with type 2 diabetes are modest, while niacin does not seem to bring improvement in clinical trials on cardiovascular events, despite increase of HDL-C concentrations [16,17].

In patients with fatty liver, the duration of diabetes was shorter than among people without NAFLD. It is surprising, as literature data indicates, that the presence of NAFLD enhances insulin resistance and cytokine release from fat-loaded liver cells and thereby enhances development of diabetes type 2 [18]. The same results were found in studies by Japanese researchers [7]. We also noted that NAFLD patients with type 2 diabetes are older than those without fatty liver.

Several studies showed an association between NAFLD and higher prevalence of coronary heart disease and other diabetes complications [18–21]. In our study, we did not confirm these observations; however, in our group of patients, a higher number of those with NAFLD required PTCA than patients without fatty liver. This phenomenon might be related to higher procoagulant activity or worse endothelial function associated with low HDL cholesterol concentrations, as observed in our patients with NAFLD [22].

The group of patients with NAFLD had lower levels of creatinine as compared to the group without NAFLD. Serum creatinine concentration is dependent on age, sex, muscle mass, volume status, and renal hemodynamics. Thus, lower creatinine levels in NAFLD patients could be the result of lower body muscle mass among people with NAFLD, because creatinine level is strongly correlated with total body muscle mass.

In our study, glycemic control was negatively associated with FA and GGTP activity, the markers of NAFLD in patients with metabolic syndrome [23]. We did not observe any association between ALAT and HbA1c levels. ALAT is elevated in up to 80% of patients with NAFLD and is mainly a marker of hepatocellular damage. Recently, Iwasaki et al reported that NAFLD is associated with adverse therapeutic effect of sitagliptin in patients with type 2 diabetes. This could be the result of high serum DDP-4 activity observed in patients with NAFLD [24]. Taken together, the presence of NAFLD could be an indicator suggesting requirements for higher doses of DPP-4 inhibitor.

This study has some limitations. The diagnosis of NAFLD was based on ultrasonographic examination, performed by 2 experienced technicians, which is a generally accepted method of fatty liver diagnosis; however, we did not use reference and invasive biopsy diagnosis.

The diagnoses of cardiovascular events were based only on medical history, so some patients with coronary heart disease could have been under-detected.

Conclusions

The results of this study indicate that central obesity and dyslipidemia, with low HDL cholesterol, are important associates of NAFLD in patients with type 2 diabetes. In our patients with type 2 diabetes, glycemic control was associated with abnormal liver function tests and with unfavorable lipid profile, as well as with central obesity.

Statement

Conflict of interest: no

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