Clinical outcomes of non-alcoholic fatty liver disease: Polish-case control study

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Abstract

Background. Non-alcoholic fatty liver disease (NAFLD) is becoming the most common cause of chronic liver disease worldwide, affecting up to 30% of population. Non-alcoholic fatty liver disease can lead to non-alcoholic steatohepatitis (NASH), fibrosis, cirrhosis, and hepatocellular carcinoma. Age, obesity, insulin resistance, type 2 diabetes, and dyslipidemia are important risk factors for developing hepatic steatosis. Concomitant diseases, especially cardiovascular, are discussed as important causes of death in NAFLD patients.

Objectives. The objective of this study was to conduct a retrospective comparison of the frequency of concomitant diseases in NAFLD patients and controls, especially metabolic syndrome and cardiovascular disease (CVD).

Material and methods. A total of 1,058 (558 NAFLD patients and 500 controls). Diagnosis of NAFLD was established with ultrasound examination in the absence of other causes of fatty liver. The control group included patients with no history of liver disease, normal liver image in ultrasound examination and normal liver laboratory tests.

Results. Overweight and/or obesity were diagnosed in 80.8% of patients in the study group and 40.8% in the controls ($p < 0.001$). Metabolic syndrome was present in 48.7% patients in the study group compared with 14.4% controls, ($p < 0.001$). In the study group, we found higher prevalence of hypertension (56.1% vs 37%; $p < 0.001$), type 2 diabetes mellitus (24.4% vs 8.6%; $p < 0.001$), decreased concentration of serum HDL (35.1% vs 19.5%; $p < 0.001$), elevated serum triglycerides (36.5% vs 15.4%; $p < 0.001$). Cardiovascular disease was found in 13.6% of individuals in the study group and in 15% controls (NS, $p = 0.32$). The most frequent concomitant gastrointestinal disease present in the study group was gastroesophageal reflux disease (GERD) (31.9% vs 22.8%; $p < 0.001$) followed by colonic diverticulosis (23.7% vs 15.8%; $p < 0.005$).

Conclusions. Metabolic syndrome with its components is more common in NAFLD patients compared to matched controls. Additionally, NAFLD patients are more often affected by GERD and colonic diverticulosis but not by CVD.

Key words: metabolic syndrome, cardiovascular disease, concomitant diseases, non-alcoholic fatty liver disease

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Introduction

Non-alcoholic fatty liver disease (NAFLD) recently has become the predominant cause of chronic liver disease in many parts of the world.¹ The spectrum of the disease ranges from simple liver steatosis through non-alcoholic steatohepatitis (NASH) with possible fibrosis leading to cirrhosis. Furthermore, hepatocellular carcinoma is the complication of liver cirrhosis in patients with NAFLD. In the last decade, NAFLD was revealed to be multisystem disease, affecting also extra-hepatic organs.² Non-alcoholic fatty liver disease is diagnosed in approx. 30–40% of men and 15–20% of women.³ In certain subgroups, like type 2 diabetes mellitus (T2DM) individuals, it occurs even in up to 70% of this group of patients.⁴ Increasing incidence rates of NAFLD are related to the growing prevalence of obesity that is associated with a wide range of complications, including metabolic syndrome (MetS). Non-alcoholic fatty liver disease is strongly connected with metabolic syndrome and its components. Many cross-sectional studies have demonstrated that NAFLD is significantly associated with MetS.^{5–8} Recent data showed that NAFLD increased the overall mortality by 57%, mainly from liver-related and cardiovascular disease (CVD) causes, and the risk of T2DM was increased approx. twofold.⁹ Cardiovascular disease is the most common cause of death globally, with an estimated 17.9 million people dying from CVD in 2016. Emerging evidence shows that NAFLD is also connected to other chronic diseases, such as endocrinopathies (e.g., hypothyroidism, polycystic ovary syndrome, hypogonadism), colorectal cancer, sleep apnea, osteoporosis, and psoriasis.¹⁰ Recent meta-analysis reported that NAFLD was associated with a twofold increased risk of chronic kidney disease.¹¹ As colonic diverticulosis shares the same pathways with NAFLD (obesity, hypertension, dyslipidemia)¹² and its risk is higher in patients with visceral fat accumulation.¹³ The possible connection between NAFLD and colonic diverticulosis is additionally investigated.

Liver biopsy is still a gold standard for the diagnosis of NAFLD and its stage (simple steatosis, steatohepatitis, fibrosis, cirrhosis). It is an invasive procedure, requiring most often hospital admission. Therefore, non-invasive methods were recently implemented, especially to identify the patients with liver fibrosis. Abdominal ultrasound is a simple method to diagnose liver steatosis, but, unfortunately, like computed tomography or magnetic resonance techniques, it is not accurate in defining fibrosis in the liver. Transient elastography estimates liver tissue stiffness in ultrasound method and is a novel imaging technique to evaluate patients with liver fibrosis. Serum cytokeratin-18 is a promising and accurate non-invasive marker of non-alcoholic steatohepatitis (NASH). The staging of liver fibrosis with simple serum marker panels is still a challenge, the most accurate are FIB-4 test and NAFLD fibrosis score.¹⁴ A novel method of fibrosis detection in NAFLD is ¹³C-methacetin breath test.¹⁵

The objective of our study was a retrospective evaluation of patients with NAFLD and a comparison of the frequency of concomitant diseases in NAFLD patients and controls, especially metabolic syndrome with its components and CVD.

Material and methods

Study group

A total of 2,309 consecutive hospital charts of patient hospitalized in the Department and Clinic of Gastroenterology and Hepatology of Wrocław Medical University between 2017–2018 were meticulously searched. Four hundred twenty-two individuals were excluded due to secondary causes of liver injury: viral hepatitis, autoimmune hepatitis, hemochromatosis, Wilson's disease, α -1 antitrypsin deficiency, drug-induced hepatic injury, cholestatic liver disease, and alcohol consumption higher than 30 mg/day for men and 20 mg/day for women.

One thousand eighty-seven patients were left for analysis. The study NAFLD group consisted of 558 consecutive patients with liver steatosis. Five hundred individuals with no history of liver disease, normal liver laboratory tests and normal image of liver on ultrasound examination were matched for age and sex with the study group and served as controls. Flowchart for patient inclusion was shown in Fig. 1.

Diagnosis of type 2 diabetes mellitus (T2DM) was defined as a registered diagnosis in patient charts, a non-fasting glucose value ≥ 180 mg/dL or a fasting glucose value ≥ 126 mg/dL, or having treatment for diabetes. Hypertension was diagnosed when there was a registered diagnosis in the patient's chart, a resting blood pressure $\geq 140/90$ mm Hg or if the patient had any anti-hypertensive drug prescription. Dyslipidemia was defined

Fig. 1. Flowchart for patient inclusion

when the patient had a fasting triglyceride concentration value ≥ 150 mg/dL or HDL-cholesterol value < 40 mg/dL (male), < 50 mg/dL (female). Body mass index (BMI) was calculated as (weight [kg]/height [m]²). The diagnosis of metabolic syndrome was established according to Adult Treatment Panel III criteria.¹⁶ Cardiovascular disease was defined as one of the following: coronary heart disease, cerebrovascular disease, peripheral arterial disease, rheumatic heart disease, congenital heart disease, deep vein thrombosis, or pulmonary embolism. The diagnosis of colonic diverticulosis was based on an endoscopy and/or radiological examination.

Laboratory parameters extracted from patients' charts were blood morphology, AST, ALT, HDL-cholesterol, triglycerides, and glucose. Other parameters were incomplete and not included in the study.

The diagnosis of liver steatosis was defined in ultrasound examination. Patients were examined in the supine and left lateral decubitus position under fasting conditions. A gastroenterologist with over 10 years of abdominal ultrasound experience evaluated the echogenicity of the liver and the right kidney. Increased hepatorenal echogenicity, bright hepatic echoes, and vascular blurring of portal or hepatic vein were classified as exclusive features of NAFLD.

Statistical analysis

Continuous, normally distributed variables were summarized as mean $\pm$ standard deviation (SD). Student's t-test was performed to compare the means in groups with normally distributed data. In groups with non-normal distribution, the Mann–Whitney U-test was used. To compare mean prevalence differences between groups, the χ^2 test (categorical variables) was performed. Statistical analysis was performed using STATISTICA v. 13.3 software (StatSoft Inc., Tulsa, USA).

Ethical considerations

The study protocol was approved by local ethics committee in accordance with the Helsinki Declaration.

Results

Five hundred fifty-eight consecutive patients with liver steatosis and 500 controls were enrolled into the study. According to the absence of other causes of liver steatosis, all the patients in the study group were classified as NAFLD. Twenty-four patients (4.3%) in this group were diagnosed with liver cirrhosis. The mean age of the patients was 58.1 years in NAFLD group and 57.5 years in the controls, respectively. Individuals in the 7th decade of life were most often represented. A total of 50.4% of the patients in the study group were male. The mean age and the sex distribution in both groups did not differ statistically significantly. We tried to estimate the prevalence of NAFLD in all the patients admitted to the gastroenterology department: 558 cases out of 2,309 overall admissions = 24.2%. Selected clinical data of patients in NAFLD patients and controls is shown in Table 1.

The mean BMI was significantly higher in the study group compared to controls (29.2 vs 24.4, $p < 0.001$). Patients with NAFLD had significantly higher serum TG and lower HDL concentration.

The prevalence of metabolic syndrome and its components in NAFLD patients and controls were estimated (Table 2, number of patients in the brackets in cases where the missing data made it impossible to complete the calculation). Not surprisingly, MetS with components (hypertension, T2DM, dyslipidemia) was strongly correlated with NAFLD. The concomitant diseases in NAFLD and controls were evaluated. We managed to estimate the prevalence of consecutive diseases with odd ratios (Table 3). The concomitant diseases connected with NAFLD were: overweight/obesity, gastroesophageal reflux disease (GERD), colonic diverticulosis and cholecystolithiasis. Functional gastrointestinal diseases were less common in NAFLD than in the controls. The prevalence of other diseases was not significantly different in the study group and controls.

We chose FIB-4 scoring system to estimate the possibility of coexisting fibrosis.¹⁷ In 348 patients (62.4%), the FIB-4 score was lower than 1.45, suggesting no advanced fibrosis present. These patients will not require

Table 1. Selected clinical data of NAFLD patients and controls

Clinical data	NAFLD	Controls	p-value
Age [years] ^a	58.1 $\pm$ 14.1	57.5 $\pm$ 16.2	0.73
Sex (female/male)	277/281	252/248	0.81
BMI [kg/m ²] ^a	29.2 $\pm$ 5.5	24.4 $\pm$ 3.9	< 0.001
ALT [U/L] ^a	33.5 $\pm$ 32.5	26.2 $\pm$ 16.5	< 0.001
AST [U/L] ^a	31.8 $\pm$ 24.0	22.5 $\pm$ 16.8	< 0.001
Glucose [mg/dL] ^a	108.5 $\pm$ 30.6	103.6 $\pm$ 32.2	0.35
TG [mg/dL] ^a	147.1 $\pm$ 86.8	108.4 $\pm$ 60.5	< 0.001
HDL (male: > 40 mg/dL, female: > 50 mg/dL) ^a	50.1 $\pm$ 14.4	56.6 $\pm$ 16.7	< 0.001

ALT – alanine transaminase; AST – aspartate transaminase; HDL – high-density lipoprotein; BMI – body mass index; TG – triglycerides; ^a mean, standard deviation (SD).

Table 2. The prevalence of metabolic syndrome and its components in NAFLD patients and controls

Components of metabolic syndrome	NAFLD	[%]	Controls	[%]	p-value
Metabolic syndrome	268 (n = 550)	48.7	72 (n = 487)	14.4	<0.001
Hypertension	313	56.1	185	37	<0.001
Type 2 diabetes mellitus	136	24.4	43	8.6	<0.001
Hyperlipidemia (hypertriglyceridemia)	195 (n = 534)	36.5	75 (n = 487)	15.4	<0.001
Hyperlipidemia (decreased HDL)	183 (n = 522)	35.1	91 (n = 467)	19.5	<0.001

NAFLD – non-alcoholic fatty liver disease; HDL – high-density lipoprotein

Table 3. Concomitant diseases in NAFLD patients and controls

Concomitant diseases	NAFLD (n = 558)	[%]	Controls (n = 500)	[%]	p-value	Odds ratio
Overweight/obesity	451	80.8	204	40.8	<0.0001	6.12
GERD	178	31.9	114	22.8	0.0009	1.59
Colonic diverticulosis	132	23.7	79	15.8	0.0014	1.65
CVD	76	13.6	75	15	0.32	0.89
Cholecystolithiasis	74	13.3	36	7.2	0.0013	1.97
Hypothyroidism	60	10.8	50	10	0.69	1.08
Crohn's disease	60	10.8	38	7.6	0.078	1.46
Ulcerative colitis	53	9.5	54	10.8	0.48	0.87
Cardiac dysrhythmia	43	7.7	30	6.0	0.27	1.31
Pancreatitis	43	7.7	32	6.6	0.41	1.22
Neoplasm	38	6.8	37	7.4	0.71	0.91
Functional GI diseases	20	3.6	47	9.4	0.0001	0.36
Asthma	17	3.0	14	2.8	0.81	1.09
Chronic kidney disease	12	2.1	12	2.4	0.79	0.89
COPD	11	2.0	10	2.0	0.97	0.99

COPD – chronic obstructive pulmonary disease; CVD – cardiovascular disease; GERD – gastroesophageal reflux disease; GI – gastrointestinal.

further diagnostic procedure. Fifteen patients with FIB-4 score above 3.25 are likely to have advanced liver fibrosis. One hundred ninety-one (34.2%) patients with intermediate score 1.45–3.25 require additional diagnostic procedures (Fig. 2). These patients were sent for ambulatory transient elastography.

Fig. 2. FIB-4 score in patients with NAFLD

Discussion

Non-alcoholic fatty liver disease, a chronic condition of the liver related to hepatic steatosis, was recently recognized as the most common chronic liver disease. Increasing prevalence rates of the risk factors for NAFLD are the following: obesity, diabetes and metabolic syndrome will most probably result into further increasing incidence rates of NAFLD all over the world.

The mean age of the patients in the study group was 58.1. Non-alcoholic fatty liver disease was found slightly more often in men than in women (not statistically significant difference in our study group). This is consistent with the results of the epidemiological studies performed in the USA. The frequency of hepatic steatosis varies significantly with ethnicity (45% in Hispanics; 33% in Whites; 24% in Blacks).³ Our study group was monoethnic – 100% individuals were White. We can only estimate the prevalence of hepatic steatosis in all the patients admitted to the gastroenterology department as approx. 25% (558 out of 2,309).

Non-alcoholic fatty liver disease afflicts overweight and obese people and presents the coexistence with

the MetS-associated disorders, like T2DM, hypertension and dyslipidemia.¹⁸ These comorbidities have a negative impact on the natural course of NAFLD.¹⁹ In fact, progression to fibrosis in NAFLD is highly influenced by the presence of T2DM and obesity.^{20,21} In a very recent review, authors have mapped shared gene/protein interaction networks and performed gene-disease analysis.¹⁸ Shared mechanisms among NAFLD and the MetS diseases were revealed and provided evidence that NAFLD and especially NASH, requires taking multi-target approaches, rather than focusing on single mechanisms of disease. Indeed, in our study we have confirmed strong connections between either MetS itself or its components and NAFLD. The prevalence of MetS was 48.7%, overweight/obesity was 80.8%, atrial hypertension 56.1%, T2DM 24.4%, hypertriglyceridemia 36.5%, and decreased HDL 35.1%, respectively. The difference in all the cases was significantly different from the corresponding rates in the control group.

Unexpectedly, the frequency of CVD was almost the same in the study group compared to controls (13.6% vs 15%). As patients with NAFLD have features of MetS, they also have important clinical implications for the development of future CVD. Many studies have addressed this issue before, finding the prevalence of CVD significantly higher in NAFLD patients.²² Recently, a vast European study has been performed in Sweden²³ and its authors claim that it is the largest ever study of biopsy-proven NAFLD. Over 600 patients were followed up during a mean of 20 years. The authors found that death rates due to cardiovascular reasons did not differ statistically in NAFLD group compared to controls. The most common gastrointestinal disease in NAFLD group was GERD. It was statistically more common compared to controls. Large cohort study (over 34,000 participants) showed that NAFLD is not independently associated with the risk of the development of reflux esophagitis after adjusting for BMI and other metabolic factors.²⁴ The authors suggest that reflux esophagitis is primarily the consequence of increased BMI commonly associated with NAFLD. Probably for the same reason, cholecystolithiasis appeared more often in NAFLD patients, as both diseases share the same main risk factor: overweight and obesity. Moreover, this association is more strongly seen in females than in males.²⁵

In the literature there is lacking evidence on connection between NAFLD and colonic diverticulosis. Only 1 case-control study claimed that diverticulosis in the elderly (>65 years) was a negative predictor of liver steatosis.²⁶ Our findings in the younger group were different. In NAFLD patients, the prevalence of diverticulosis was much higher compared to controls.

We have evaluated the FIB-4 score that is simple and easy to calculate and to estimate the risk of fibrosis in the liver. In our study group, most cases were classified as not having fibrosis, whereas only 1/3 of patients required additional examinations (for instance transient elastography).

Conclusions

Overweight and obesity as well as metabolic syndrome with its components: hypertension, type 2 diabetes mellitus, and dyslipidemia are more common in NAFLD patients compared to matched controls. No significant difference between the study group and controls was found in the frequency of CVD. Additionally, NAFLD patients are more often affected by GERD, colonic diverticulosis and cholecystolithiasis.

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