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The prevalence of metabolic risk factors among outpatients with diagnosed nonalcoholic fatty liver disease in Lithuania

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Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

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Summary

Background: Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver disease; there is growing evidence that it is a hepatic manifestation of a metabolic syndrome. This study aimed to assess the prevalence of metabolic risk factors among patients with NAFLD.

Material/Methods: Outpatients with NAFLD were recruited into the study. Family physicians recorded patients' demographic and anthropometric data, leisure-time physical activity, concomitant diseases, and pharmacological treatment for NAFLD into standardized Case Report Forms.

Results: In total, data on 798 patients were analyzed. Most patients were women and they were older than the men (mean age, 60.2±9.6 *vs.* 54.5±11.4 years; $p<0.05$). Metabolic risk factors (obesity, arterial hypertension, dyslipidemia) were highly prevalent in the study patients, and these factors were more prevalent among women. There were no differences in the mean Body Mass Index (BMI), in the proportion of men or women with BMI >30 kg/m^2 or central obesity in the 2 age groups (≤60 years and >60 years). Hypertension and diabetes were more prevalent among older men and women. Dyslipidemia was more common among older women. The level of leisure-time physical activity was lower in women and in older patients. The most frequently prescribed pharmacological agents were cytoprotective agents, lipid-lowering drugs, and antioxidants.

Conclusions: Metabolic risk factors were highly prevalent among patients with NAFLD. Obesity, hypertension, and dyslipidemia were more prevalent among women. The differences in the prevalence of hypertension seemed to be influenced by older age of women.

key words: **nonalcoholic fatty liver disease (NAFLD) • metabolic syndrome • epidemiology • dyslipidemia • NAFLD • cytoprotective drugs**

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Background

For many years, alcoholic liver disease and viral hepatitis-induced liver disease were considered the main causes of liver disease morbidity and mortality. However, with the dramatic increase in the prevalence of obesity, nonalcoholic fatty liver disease (NAFLD) has become the most common chronic liver disease and is now receiving greater attention globally. NAFLD describes a pathologic condition characterized by significant lipid deposition in the hepatocytes of the liver parenchyma in patients with no history of excessive alcohol consumption [1]. The spectrum of NAFDL includes hepatic steatosis, nonalcoholic steatohepatitis, chronic fibrosis and cirrhosis [2]. The true incidence and prevalence of the disease is difficult to ascertain accurately due to lack of effective screening tests that can be applied to the entire population. Population-based epidemiological studies using ultrasound imaging as a diagnostic modality have detected the presence of fatty liver in 13% to 22% of the population of lean nonalcoholic subjects [3,4]. Estimates in the United States population suggest that up to 30% of adults may have NAFLD. The prevalence estimates from several other countries are quite variable, but depict a highly prevalent condition, with ~20% of the adult population with ultrasound-defined NAFLD [5]. The prevalence of NAFLD increases to 50–55% in type-2 diabetics and patients with hypertriglyceridemia, and to 75% in obese persons [6].

Increasing evidence indicates that NAFLD is the hepatic component of a systemic metabolic syndrome [7] that includes obesity, insulin resistance, hyperlipidemia, and hypertension. Approximately 90% of patients with NAFLD have ≥1 characteristic features of metabolic syndrome and about 33% have the complete diagnosis [8]. In individuals with NAFDL, the prevalence of metabolic syndrome increases with increasing body mass index, from 18% in normal-weight subjects to 67% in obese subjects [9]. Furthermore, with the addition of each of the components of the metabolic syndrome, the risk of steatosis increases exponentially [10].

Considerable controversy surrounds the metabolic syndrome. Criticism has been leveled at the syndrome in part because of varying and incomplete definitions and the lack of a unifying mechanism. In addition, the individual components of the metabolic syndrome themselves are adequate to predict the risk of cardiovascular disease or diabetes. Although the clinical usefulness of metabolic syndrome has been questioned, it is still considered useful as an educational concept [11–14].

There is no published information about prevalence of NAFLD in Lithuania. The metabolic syndrome is estimated to affect about 20% of the Lithuanian middle-aged urban population [15–17]. In this study we aimed to assess the prevalence of the following metabolic risk factors among men and women with NAFLD: obesity, hypertension, dyslipidemia, and diabetes.

Material and Methods

The protocol of the study was reviewed and approved by the Lithuanian Bioethics Committee. The study was conducted in accordance with the recommendations laid down by the 18th World Medical Assembly (Helsinki, 1964) and all applicable amendments.

This was an epidemiologic study. In order to ensure that the data reflect the health status of patients living in urban as well as rural areas, randomly selected family physicians throughout Lithuania were asked to participate in the study. Fifty-six family physicians agreed to take part in the study. The regions covered included Anykščiai, Elektrėnai, Jonava, Jurbarkas, Kaunas, Kėdainiai, Klaipėda, Kretinga, Marijampolė, Mažeikiai, Palanga, Panevėžys, Plungė, Prienai, Radviliškis, Raseiniai, Šiauliai, Šilalė, Tauragė, Utena, and Vilnius. Every physician had to include at least 10 patients. Every patient fulfilling the inclusion criteria who visited the physician on a working day for any reason was asked to take part in the study.

A total of 798 patients were recruited between September 2008 and April 2009. Patients included in the study had to be outpatients with NAFLD, aged 18–80 years old. The diagnosis of NAFLD had to be confirmed during previous consultations by means of ultrasonography, liver biopsy, computed tomography or magnetic resonance imaging [18,19] and documented in the patient's record. The majority of NAFLD cases were diagnosed using ultrasonography. All patients provided written informed consent. The following exclusion criteria were applied: pregnancy, alcoholic liver disease (established diagnosis of alcoholic liver disease or confirmed alcohol intake in daily doses ≥40 g for men and ≥20 g for women), known or evidenced virus hepatitis, autoimmune hepatitis, toxic liver damage, gene pathology, and confirmed absence of liver pathology.

The following data were collected during a single patient visit: weight, height, waist circumference, body mass index (BMI), age, sex, leisure-time physical activity, concomitant diseases, and use of antioxidants, cytoprotective agents, insulin secretagogues, and lipid-lowering agents. No laboratory evaluations were performed specifically for the purposes of the study. Demographic and medical data were retrieved from patients' cards, while anthropometric parameters (height, weight, BMI and waist circumference) were measured during the study visit. Height (cm) and weight (kg) were measured with indoor clothing and without shoes. The waist circumference (cm) was measured at the level of the umbilicus, with the participant standing and breathing normally. The participants also answered questions about their leisure-time physical activity. All data were recorded anonymously into standardized Case Report Forms.

Hypertension was defined as elevated blood pressure at or above 140/90 mm Hg (130⁄80 mm Hg for diabetics) or a history of hypertension and use of antihypertensive medication.

Dyslipidemia was defined as abnormal fasting lipid profile (total cholesterol >5.0 mmol/l or low-density lipoprotein (LDL) cholesterol >3.0 mmol/l or high-density lipoprotein (HDL) cholesterol <1.0 mmol/l in men and <1.2 mmol/l in women or triglyceride >1.7 mmol/l).

Leisure-time physical activity was classified into 3 categories: (1) low (almost completely inactive, e.g., reading, watching television, housework, etc.), (2) moderate (some physical activity for >4 hours per week (eg, walking, cycling, light exercising, light gardening, etc.), and (3) high (vigorous physical activity for >3 hours per week, e.g., running, jogging, swimming, heavy gardening, or regular exercise or competitive sports several times per week).

Table 1. The prevalence of metabolic syndrome components among men and women with NAFDL, N (%).

Components of metabolic syndrome	Men (N=298)	Women (N=500)
Mean BMI* (± SD), kg/m^2	31.4±5.5	34.1±6.5**
BMI >30 kg/m^2	181 (60.7%)	377 (75.4%)**
Abdominal obesity	186 (62.4%)	446 (89.2%)**
Arterial hypertension	231 (77.5%)	420 (84.0%)**
Dyslipidemia	195 (65.4%)	362 (72.4%)**
Diabetes mellitus	60 (20.1%)	115 (23.0%)

* BMI – Body Mass Index; **p<0.05.

BMI was calculated by dividing the individual's body weight by the square of his/her height: BMI = weight (kg)/height^2 (m^2).

Abdominal obesity was defined as waist circumference >102 cm in men and >88 cm in women.

Sample size was calculated based on the following assumptions: anticipated prevalence of NAFDL is 20% (P=0.2), its absolute precision is 3% (d=0.03), and confidence level is 95%. For sample size calculation the following equation was used:

$$n = \frac{z^2_{1-\alpha/2} \times P \times (1-P)}{d^2},$$

Based on the above assumptions, the minimum sample size for this study was calculated to be 780 patients.

The descriptive statistics and statistical tests for group comparisons were applied for data analysis. The χ^2 test was used to assess the difference between categorical data. Parametric Student's t-test test or non-parametric Wilcoxon test was applied to test the difference between continuous data. Statistical tests were interpreted at the 5% significance level (two-tailed). Statistical software SAS 9.1.2 was used for statistical data analysis.

Results

In total, 804 patients were recruited in the study and of these 798 were included in the analysis (6 patients were protocol violations). There were 298 (37.3%) men and 500 (62.7%) women among the study participants. The mean (± standard deviation [SD]) age of patients was 58.1 (±10.7) years; range, 23 to 80 years. Women were slightly older than men (mean age, 60.2±9.6 *vs.* 54.5±11.4 years; p<0.05).

The prevalence of obesity (BMI >30 kg/m^2) was 69.9% among study patients and it was significantly higher among women compared to men (75.4% *vs.* 60.7%, p<0.05); 62.4% of the men and 89.2% of the women (p<0.05) had abdominal obesity. Hypertension and dyslipidemia were also highly prevalent in this group of NAFDL patients, and metabolic risk factors were more prevalent among women (Table 1). The prevalence of diabetes was similar in both men and women; 21.9% of patients had diabetes; all except 1 were cases of Type 2 diabetes mellitus.

The prevalence of metabolic risk factors was compared in different age groups (≤60 years and >60 years) separately in men and in women. There were no differences in the mean BMI in the proportion of men or women with BMI >30 kg/m^2 or central obesity in the 2 age groups (Table 2). The prevalence of arterial hypertension was higher among older men and women. The proportion of patients with diabetes was also significantly higher among elderly men and was numerically higher among elderly women. Dyslipidemia was more common among women aged >60 years, while no such age-related differences were observed in men.

Very few NAFDL patients (3.1%) reported high leisure-time physical activity (regular vigorous exercise, competitive sports or similar physical activity for at least 3 hours per week). Among women, the proportion of subjects reporting low leisure-time physical activity was higher than that among men (45.8 *vs.* 29.2%; p<0.05). Consequently, there were more men than women with moderate physical activity (66.1 *vs.* 52.0%; p<0.05). In both sexes, the level of leisure-time physical activity was lower in older patients (Table 3).

Table 2. The prevalence of metabolic syndrome components among men and women in different age groups, N (%).

Components of metabolic syndrome	Men		Women	
	≤60 years (N=210)	>60 years (N=88)	≤60 years (N=253)	>60 years (N=247)
Mean BMI* (± SD), kg/m^2	31.5±5.6	31.4±5.5	33.2±6.6	32.9±5.7
BMI >30 kg/m^2	126 (60.0%)	55 (62.5%)	192 (75.9%)	185 (74.9%)
Abdominal obesity	128 (60.9%)	58 (65.9%)	221 (87.4%)	225 (91.1%)
Arterial hypertension	155 (73.8%)	76 (86.4%)**	196 (77.5%)	224 (90.7%)**
Dyslipidemia	137 (65.24%)	58 (65.9%)	173 (68.4%)	189 (76.5%)**
Diabetes mellitus	33 (15.7%)	27 (30.7%)**	49 (19.4%)	66 (26.7%)

* BMI – Body Mass Index; **p<0.05.

Table 3. The level of leisure-time physical activity among men and women in different age groups, N (%).

Leisure-time physical activity	Men		Women	
	≤60 years (N=210)	>60 years (N=88)	≤60 years (N=253)	>60 years (N=247)
Low	53 (25.2%)	34 (38.6%)*	98 (38.7%)	131 (53.0%)*
Moderate	147 (70.0%)	50 (56.8%)*	147 (58.1%)	113 (45.8%)*
High	10 (4.8%)	4 (4.6%)	8 (3.2%)	3 (0.6%)

* $p<0.05$.

Two-thirds of patients (68.7%) received continuous pharmacological treatment for NAFDL. The most common medicines were cytoprotective agents, ursodeoxycholic acid, pentoxifylline, betaine or phospholipid preparations (24.9%), lipid-lowering drugs (21.3%), and antioxidants – vitamin E, N-acetylcysteine, selenium, or beta-carotene (19.1%). Insulin secretagogues (metformin, pioglitazone or rosiglitazone) were used by 11.7% of patients. Almost 30% of patients received combined treatment and the most frequent combination was a lipid-lowering drug and a cytoprotective agent (10.6%).

Discussion

In this study we found that metabolic risk factors were highly prevalent in patients with NAFLD. More than two-thirds of patients were obese, and similar proportions of patients had hypertension or dyslipidemia. Such results are consistent with published data from other countries [20]. An Italian study showed that NAFLD was associated with most of the features of the metabolic syndrome – obesity, hyperglycemia, hyperinsulinemia, hypertriglyceridemia, and systolic hypertension [4].

Data on sex differences in the prevalence of NAFLD are conflicting. Several studies reported that NAFLD is 3 to 5 times more common in men than in women [21–23], while others stated that the risk of this disease is greater among women [24]. We did not evaluate the prevalence of NAFLD; however, the number of female patients in our study was approximately 1.5-fold higher than the number of males. Besides, most of metabolic risk factors, which are also generally considered as NAFDL risk factors (obesity, hypertension, dyslipidemia), were more prevalent among women compared to men. Only diabetes was equally common in both men and women.

Since the women in this study population were significantly older than the men, we conducted a further analysis to determine if these differences could have been caused by age rather than sex. The distribution of obesity parameters (mean BMI, proportion of patients with BMI >30 kg/m^2 or central obesity) was similar in the 2 age groups, thus the difference observed in men and women was most likely determined by sex. Contrarily, the differences in the prevalence of arterial hypertension and diabetes seemed to be related to advanced age, as the prevalence of these diseases was higher among older men and women.

Published data on the prevalence of metabolic syndrome among Lithuanian men and women are inconsistent. A study that used the definition of International Diabetes Federation, reported that the prevalence of metabolic syndrome was almost two-fold higher among men compared to women (28.1% *vs.* 16.6%) (15). Other studies, which employed World Health Organization or National Cholesterol Education Program – Adult Treatment Panel III criteria, reported opposite results, showing higher prevalence among women. Prevalence of metabolic syndrome among men and women increased with age [16,17]. One Lithuanian study also reported some sex-related differences in the prevalence of metabolic syndrome components in patients with acute ischemic syndromes [25]. In this study women were significantly older than men; however, the potential confounding effect of age was not analyzed.

There is no specific therapy for NAFLD that has clearly been proven effective; however several pharmacological options, including antioxidants, lipid lowering agents, hepatoprotective agents, and insulin secretagogues, have been tried with some successes [8,26,27]. In our study, two-thirds of patients received continuous pharmacological treatment for NAFDL – the most common medicines being cytoprotective agents, followed by lipid-lowering drugs and antioxidants. It is recommended to initiate pharmacological treatment only when there is no change in the course of disease after adequate lifestyle changes have been undertaken. The published results of several studies in NAFLD populations have reported that short-term moderate weight loss with regular physical activity leads to improvement in liver biochemical tests and to resolution of hepatic steatosis [28]. We had no information on weight management efforts if any taken by study participants. However, available information on leisure-time physical activity suggests that lifestyle-related therapeutic modalities were not fully utilized in this group, especially among women.

There are several limitations to the present study. The physicians who participated in the study constituted only about 3% of the family physicians in Lithuania. Although almost half of Lithuanian administrative regions were covered and efforts were made to invite physicians working in urban as well as rural areas, it is possible that the study population was not representative of the general population. Second, the enrollment of a greater proportion of women into the study, and the fact that they were older than men, may have biased the results. The effect of this potential bias was reduced by applying stratification by sex and age. The study did not include a control group. Further studies involving a control group are needed for a better understanding of true prevalence of metabolic risk factors in the population of patients with NAFDL in Lithuania.

CONCLUSIONS

Metabolic risk factors were highly prevalent among studied patients with NAFLD. Obesity, arterial hypertension, and dyslipidemia were more prevalent among women compared to men; however, the differences in the prevalence of hypertension seemed to be determined by advanced age.

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