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Components of metabolic syndrome in Latvian patients with nonalcoholic fatty liver disease

Składowe zespołu metabolicznego u łotewskich pacjentów z niealkoholowym stłuszczeniowym zapaleniem wątroby

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Abstract

Introduction: Nonalcoholic fatty liver disease (NAFLD) has become the most common chronic liver disease and there is growing evidence that it is a hepatic manifestation of a metabolic syndrome.

Aim of the study: The objective of this study was to describe the clinical profile of NAFLD patients with special focus on the prevalence of metabolic syndrome components.

Material and methods: This was a multicenter descriptive epidemiologic study. Outpatients with a diagnosis of NAFLD (aged 18-80 years) were recruited into the study. Family physicians recorded patients' demographic and anthropometric data, medical history, pharmacological treatment for NAFLD, and leisure-time physical activity into standardized Case Report Forms.

Results: In total, data of 476 NAFLD patients were analyzed. There were more women and they were older than men (mean age, 60.8±10.9 vs 51.5±13.9 years; $p<0.05$). The following components of metabolic syndrome (obesity, arterial hypertension, dyslipidemia) were highly prevalent in the study patients. Four hundred and forty patients (92.4%) had more than one of the metabolic syndrome components. Most of these factors were more prevalent among women; however, after stratification by age, only obesity-related components remained more common among women. The level of leisure-time physical activity was also lower in women, despite their age. Lipid lowering drugs and hepatoprotective agents were the most frequently prescribed pharmacological agents for the treatment of NAFLD.

Conclusions: The components of metabolic syndrome were highly prevalent among studied NAFLD patients in Latvia. Obesity, hypertension, and type 2 diabetes were more prevalent in women; however, the higher prevalence of hypertension and diabetes seems to be determined by more advanced age of female patients.

Keywords: nonalcoholic fatty liver disease, obesity, arterial hypertension, dyslipidemia, type 2 diabetes.

Streszczenie

Wprowadzenie: Niealkoholowa choroba stłuszczeniowa wątroby (*nonalcoholic fatty liver disease* – NAFLD) stała się najczęstszą przewlekłą chorobą wątroby, a coraz więcej dowodów wskazuje na to, że stanowi ona wątrobową manifestację zespołu metabolicznego.

Cel pracy: Celem badania była kliniczna charakterystyka pacjentów z NAFLD, ze szczególnym uwzględnieniem występowania składowych zespołu metabolicznego.

Materiał i metody: Przeprowadzono wieloośrodkowe opisowe badanie epidemiologiczne. Do badania włączono pacjentów ambulatoryjnych z rozpoznaną NAFLD (w wieku 18-80 lat). Lekarze rodzinni zgromadzili i odnotowali w postaci wystandaryzowanych kwestionariuszy dane demograficzne i antropometryczne pacjentów, wywiad chorobowy, farmakoterapię NAFLD oraz aktywność fizyczną pacjentów w wolnym czasie.

Wyniki: Łącznie przeanalizowano dane 476 pacjentów z NAFLD. Przeważały kobiety, które były starsze niż badani mężczyźni (średni wiek 60,8 ± 10,9 *vs* 51,5 ± 13,9 lat; $p < 0,05$). U badanych często występowały następujące składowe zespołu metabolicznego: otyłość, nadciśnienie tętnicze i dyslipidemia. U 440 pacjentów (92,4%) stwierdzono więcej niż jedną składową zespołu metabolicznego. Większość tych składowych występowała częściej u kobiet, jednak po uwzględnieniu wieku tylko czynniki zależne od otyłości okazały się częstsze u kobiet. Również stopień aktywności fizycznej w wolnym czasie był mniejszy u kobiet, niezależnie od wieku. W leczeniu NAFLD najczęściej przepisywano leki hipolipemizujące i środki hepatoprotekcyjne.

Wnioski: Składowe zespołu metabolicznego często występowały wśród badanych łotewskich pacjentów z NAFLD. Otyłość, nadciśnienie tętnicze i cukrzyca typu 2 stwierdzano częściej u kobiet, jednak większa częstość występowania nadciśnienia i cukrzycy wydaje się uwarunkowana starszym wiekiem pacjentów płci żeńskiej.

Słowa kluczowe: niealkoholowa choroba stłuszczeniowa wątroby, otyłość, nadciśnienie tętnicze, dyslipidemia, cukrzyca typu 2.

Introduction

Nonalcoholic fatty liver disease (NAFLD) is an acquired metabolic stress-induced liver disease associated with insulin resistance and genetic susceptibility, sharing histological similarities with alcoholic liver disease in the absence of substantial alcohol consumption or other causes of liver diseases [1]. It comprises a disease spectrum which includes variable degrees of simple steatosis (non-alcoholic fatty liver), nonalcoholic steatohepatitis and cirrhosis [2, 3].

Patients with a diagnosis of NAFLD have worse outcome when compared with an age and gender-matched general population. The excess mortality in this group is attributable to both cardiovascular and liver-related causes [2]. Although in most of the cases fatty liver does not progress to more severe liver diseases, approximately 20% to 30% of patients have histologic signs of fibrosis and necroinflammation, indicating the presence of non-alcoholic steatohepatitis. These patients are at higher risk of developing cirrhosis, terminal liver failure, and hepatocellular carcinoma [4].

During the last two decades, NAFLD has been increasingly recognized as the most common liver disease in Western countries and is expected to increase in the future as a result of an ageing population, the improving control of other major causes of chronic liver disease and the epidemics of obesity and diabetes [5]. A NAFLD prevalence of 10–25% has been reported in the general population [6]. This prevalence increases to 50–55% in type 2 diabetics in patients with hypertriglyceridemia and to 75% in obese persons [7]. Abdominal obesity is also considered a risk factor for NAFLD. In the absence of obesity and diabetes, hyperinsulinemia and insulin resistance are associated with NAFLD. The presence of hyperinsulinemia or insulin resistance and the association with some of the features of the metabolic syndrome suggest that NAFLD might be the liver component of the metabolic syndrome [2, 3, 7, 8].

Approximately 90% of patients with NAFLD have ≥ 1 characteristic feature of metabolic syndrome and about 33% have the complete diagnosis [9]. In individuals with NAFLD, the prevalence of metabolic syndrome increases with the increasing body mass index, from 18% in normal-weight subjects to 67% in obese subjects [4]. Furthermore, with the addition of each of the components of the metabolic syndrome, the risk of steatosis increases exponentially [10].

Aim of the study

There is no published information about the prevalence of NAFLD and clinical characteristics of NAFLD patients in Latvia. In this study we aimed to describe the clinical profile of Latvian NAFLD patients with special focus on the prevalence of metabolic syndrome components.

Material and methods

This was a multicenter descriptive epidemiologic study. A similar study was previously conducted under the same protocol in another Baltic country, Lithuania. The protocol of the study was reviewed and approved by the Independent Ethics Committee for the Investigation of Drugs and Pharmaceutical Products (Latvia). The study was conducted in accordance with the recommendations laid down by the 18th World Medical Assembly (Helsinki, 1964) and all applicable amendments.

Randomly selected family physicians throughout Latvia were asked to participate in the study. Thirty-five family physicians agreed to take part in the study. 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 492 patients were recruited between June 2011 and December 2011. 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 [1, 5] and documented in the patient's card. 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 and gene pathology.

During a single patient's visit, physicians collected the following data: weight, height, waist circumference, body mass index (BMI), age, gender, leisure-time physical activity, concomitant diseases, the use of antioxidants, hepatoprotective agents, insulin secretagogues, and lipid lowering agents. No laboratory evaluations specifically for the purposes of the study were performed. Demographic and medical data were retrieved from patients' cards, while anthropometric parameters (height, weight, and waist circumference) were measured during the study visit. The 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, respectively, for diabetics) or a history of hypertension and use of antihypertensive medication [11].

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) [11].

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, e.g., 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, regular exercise or competitive sports several times per week).

BMI was calculated by dividing the individual's body weight by the square of his/her height: BMI = weight (kg)/height^2 (m^2). The classification of overweight and obesity by BMI established by the World Health Organization (WHO) was used.

Abdominal obesity was defined as waist circumference ≥94 cm in men and ≥80 cm in women (according the European Group for the Study of Insulin Resistance, 1999).

The sample size was calculated based on the following assumptions: the anticipated prevalence of NAFLD is 20% (P = 0.2),

its absolute precision 3% (d=0.3), and confidence level 95%. For the sample size calculation the following equation was used:

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. The parametric Student t-test ~~test~~ or the 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, 492 NAFLD patients were recruited in the study and 476 of them were included in the analysis (16 patients were protocol violations). There were 170 (35.7%) men and 306 (64.3%) women among study participants. The mean (± standard deviation [SD]) age of patients was 57.5 (±12.9) years, range – 20 to 80 years. Women were considerably older than men (mean age, 60.8±10.9 vs 51.5±13.9 years; p<0.05).

Three hundred and sixty-two (76.1%) patients had dyslipidemia. There were 328 (68.9%) hypertensive patients and 109 (22.9%) patients with type 2 diabetes. Most of study patients were obese (64.9%) and/or had abdominal obesity (88.9%) (Table I). Only 14 (2.9%) patients had none of these conditions, considered in this study as the components of metabolic syndrome. As a single metabolic syndrome component, abdominal obesity was found in 20 (4.2%) patients, dyslipidemia – in 10 (2.1%) patients, and hypertension – in 5 (1.1%) patients. Four hundred and forty patients (92.4%) had more than one of the metabolic syndrome components.

All analyzed components of metabolic syndrome except dyslipidemia were more prevalent among women (Table II).

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

Components of metabolic syndrome	Men (N=170)	Women (N=306)
Mean BMI* (± SD), kg/m^2	30.8±4.9	32.8±5.7†
BMI ≥30 kg/m^2	103 (60.6%)	223 (72.9%)†
Abdominal obesity	136 (80.0%)	287 (93.8%)†
Arterial hypertension	97 (57.1%)	231 (75.5%)†
Dyslipidemia	123 (72.4%)	239 (78.1%)
Type 2 diabetes mellitus	29 (17.1%)	80 (26.1%)†

* BMI – Body Mass Index; †p<0,05

Table I. Clinical and laboratory characteristics of the subjects

Characteristic	
Mean age (± SD), years	57.5 (±12.9)
Mean weight (± SD), kg	89.7 (±17.4)
Mean height (± SD), cm	167.7 (±9.5)
Mean waist circumference (± SD), cm	102.0 (±13.7)
Abdominal obesity	423 (88.9)
Mean BMI* (± SD), kg/m^2	32.09 (±5.5)
BMI range, kg/m^2 18.5-24.9 (normal) 25.0-29.9 (overweight) 30.0-34.9 (Class I obesity) 35.0-39.9 (Class II obesity) ≥40.0 (Class III obesity)	 25 (5.3%) 125 (26.3%) 171 (35.9%) 90 (18.9%) 48 (10.1%)
HDL-C** <1.0 mmol/l in men or <1.2 mmol/l in women	71 (14.92%)
LDL-C*** >3.0 mmol/l	287 (60.29%)
Total cholesterol >5.0 mmol/l	333 (69.96%)
Triglycerides >1.7 mmol/l	159 (33.40%)

* BMI – Body Mass Index; **HDL -C- high-density lipoprotein cholesterol; LDL-C - low-density lipoprotein cholesterol

The stratification by age showed that components related to obesity remained more common among women, whereas prevalence of arterial hypertension and type 2 diabetes seemed to be determined by more advanced age (Table III).

Very few NAFLD patients (3.2%) 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 (60.4 vs 34.1%; p<0.05). Consequently, there were more men than women with moderate physical activity (57.1 vs 39.6%; p<0.05). After stratification by age, gender-related differences in physical activity remained (Table IV).

Two thirds of patients (63.9%) received continuous pharmacological treatment for NAFLD. The most common medicines were lipid lowering drugs (47.9%) and hepatoprotective agents ursodeoxycholic acid, pentoxifylline, betaine or phospholipid preparations (26.9%). The rest of patients took antioxidants (vitamin E, N-acetylcysteine, selenium, or beta-carotene), 19.1% or insulin secretagogues (metformin, pioglitazone or rosiglitazone), 15.1%.

Table III. The prevalence of metabolic syndrome components among younger and older men and women with NAFLD

Components of metabolic syndrome	≤60 years		>60 years	
	Men (N=119)	Women (N=137)	Men (N=48)	Women (N=169)
Mean BMI* (± SD), kg/m^2	31.1±5.3	32.9±5.9†	29.9±3.8	32.9±5.6†
BMI ≥30 kg/m^2	75 (61.5%)	101 (73.7%)†	28 (58.3%)	122 (72.2%)
Abdominal obesity	39 (81.3%)	160 (94.7%)†	97 (79.5%)	127 (92.7%)†
Arterial hypertension	59 (48.4%)	80 (58.4%)	38 (79.2%)	151 (89.3%)
Dyslipidemia	84 (68.9%)	96 (70.1%)	39 (81.3%)	143 (84.6%)
Type 2 diabetes mellitus	16 (13.1%)	25 (18.2%)	13 (27.1%)	55 (32.5%)

* BMI – Body Mass Index; †p<0,05

Table IV. The level of leisure-time physical activity in younger and older men and women with NAFLD

Leisure-time physical activity	≤60 years		>60 years	
	Men (N=119)	Women (N=137)	Men (N=46)	Women (N=169)
Low	37 (30.3%)	65 (47.8%)†	21 (43.8%)	118 (70.7%)†
Moderate	70 (57.4%)	71 (52.2%)	27 (56.3%)	49 (29.3%)†
High	15 (12.3%)	0	0	0

†p<0.05

Discussion

In this study we found that the components of metabolic syndrome were highly prevalent in Latvian patients with NAFLD. More than two thirds of patients were obese, similar proportion of patients had hypertension or dyslipidemia. More than 90% of patients had >1 metabolic syndrome components. Such results are consistent with published data from other countries [9, 12, 13].

Data on gender 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 [14-16], while others stated that the risk of this disease is greater among women [17]. We did not evaluate the prevalence of NAFLD; however, the number of female patients in our study was almost two-fold higher than the number of males. Besides, most of metabolic syndrome components (obesity, hypertension, type 2 diabetes), which are also generally considered as NAFLD risk factors, were more prevalent among women in comparison with men.

The risk of NAFLD increases with increasing age [18]. Since women in this study population were significantly older than men, we performed stratified analysis which revealed that components related to obesity and low physical activity remained more common among women. The high prevalence of hypertension and diabetes seems to be determined by more advanced age of female patients.

The study conducted under the same protocol in Lithuania also reported the high prevalence of metabolic risk factors among patients with NAFLD. The prevalence of obesity, hypertension, and dyslipidemia was higher among women [13].

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 [9, 17, 19]. In our study, two thirds of patients received continuous pharmacological treatment for NAFLD, the most common medicines being lipid lowering drugs (47.9%), followed by hepatoprotective agents (26.9%). In the Lithuanian study, the practice of pharmacological NAFLD treatment was different: the most common medicines were hepatoprotective agents (24.9%), lipid lowering drugs (21.3%) and antioxidants (19.1%) [10].

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 population 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 [20]. We had no information on weight management efforts if any taken by study participants. However, available information on leisure-time physical activity implied that lifestyle-related therapeutic modalities were not fully utilized in this group, especially among women.

Currently, several different definitions of metabolic syndrome exist: World Health Organization criteria (1998), European Group for the Study of Insulin Resistance criteria (1999), National Cholesterol Education Program Adult Treatment Panel III (NCEP:ATPIII) criteria (2001), American Association of Clinical Endocrinology criteria (2003), International Diabetes Federation (IDF) criteria (2005), American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI) criteria (2004), and the Consensus definition incorporating IDF and AHA/NHLBI definitions (2009). Since this study was based mainly on the review of existing medical records, available data were restricted to diagnostic criteria and laboratory measurements cut-off values defined in relevant local guidelines (e.g., Latvian guidelines on hypertension management [11]). Although we were unable to strictly follow any of the existing definitions, the components of metabolic syndrome analyzed in our study can be considered as close approximates of criteria used in the diagnosis of metabolic syndrome.

There are several other limitations to the present study. This study lacked a control group. Nevertheless, it provided initial data which at least partially fill the gap in knowledge of the epidemiology of NAFLD in Latvia. Further studies are required to estimate the prevalence and incidence of NAFLD in Latvian population and the relative contribution of each component of the metabolic syndrome to the risk of NAFLD. The physicians who participated in the study constituted only about 2% of the family physicians in Latvia. Although efforts were made to invite physicians working in urban as well as rural areas, the possibility that study population was not representative of the general population remains.

Conclusions

The components of metabolic syndrome were highly prevalent among studied NAFLD patients in Latvia. Obesity, hypertension, and type 2 diabetes were more prevalent in women; however, the higher prevalence of hypertension and diabetes seems to be determined by more advanced age of female patients.

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