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ABSTRACT

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METABOLICALLY ASSOCIATED FATTY LIVER DISEASE IN PATIENTS WITH VERY HIGH CARDIOVASCULAR RISK: PREVALENCE, CLINICAL SIGNIFICANCE, GENDER DIFFERENCES

Introduction. Recently, metabolically associated fatty liver disease (MAFLD) had been proposed as a new term. Due to increasing prevalence, significant morbidity and hepatic and cardiovascular mortality, the association of MAFLD with cardiovascular diseases is gaining considerable relevance and needs further study. The aim of our study was to determine the proportion of MAFLD among patients with a very high cardiovascular risk, and to elucidate clinical features and gender differences in this cohort.

Materials and methods. All patients underwent a comprehensive examination to assess both cardiovascular risk and MAFLD. Hepatic steatosis was diagnosed after liver ultrasonography. Participants who met MAFLD criteria were included into the group 1 (n=77; 32 women, 45 men), other patients were assigned to the group 2 (n=39; 19 women, 20 men).

Results. Among patients with very high cardiovascular risk, proportion of MAFLD was 66.7 %. Although mild alanine aminotransferase elevation was much more common among patients with MAFLD (16 women (50.0 %) vs. 2 women (10.5 %) in group 2, P = 0.006; 21 men (46.7 %) vs. 2 men in group 2 (10.0 %), P = 0.005), none of the participants met the criteria for steatohepatitis. Despite, the presence of metabolic disorders in the vast majority of participants, proportion of obesity, metabolic dyslipidaemia, prediabetes and type 2 diabetes were significantly higher in patients with MAFLD. Besides, patients with MAFLD usually met 4 or 5 metabolic syndrome criteria, had higher median values of lipid accumulation product (LAP) and HOMA-IR index, but lower median values of Matsuda index. Significant direct correlations were found between MAFLD and LAP, logarithmic index

(TG/HDL-C), and HOMA-IR; negative correlations were observed between MAFLD and insulin sensitivity indices. Women with MAFLD had significantly higher median values of glycated haemoglobin, post-load glucose, fasting insulin levels; there was direct correlation between MAFLD and non-HDL-C. Among women with MAFLD, a history of menopause before 45 years of age had 15 persons (46.9 %) vs. one person (5.3 %) in group 2 (P < 0.002); the median age when ASCVD was diagnosed was 58.5 [53.0; 64.0] years vs. 68.0 [63.0; 69.0] years in group 2 (P = 0.002); cardiac valve calcinosis was detected in 31 women (96.6 %) vs. 9 women (47.4 %) in group 2 (P = 0.0001); the left ventricular myocardial mass (LVM) index was 77.5 [62.1; 86.9] g/m$^{2.7}$ vs. 64.0 [50.6; 74.0] g/m$^{2.7}$ in women without MAFLD, 67.0 [55.1; 74.0] g/m$^{2.7}$ in men with MAFLD, and 63.9 [50.0; 73.5] g/m$^{2.7}$ in men without MAFLD (Kruskal–Wallis ANOVA P <0.0001; median test P=0.002). The prevalence of smoking and alcohol intake was significantly more common among men (gender differences P <0.0001 and P=0.0001 in group 1; P = 0.0004 and P=0.0023 in group 2 for smoking and alcohol intake, respectively). Men with MAFLD had significantly higher median values of fasting plasma glucose, fasting and post-load insulin levels than men without MAFLD; there was a significant direct correlation between MAFLD and serum TG level. In addition, 11 men with MAFLD (24.4 %) had hypertriglyceridemia >2.3 mmol/l that was not observed among men without MAFLD (P=0.013). The proportion of men with fasting and post-load hyperinsulinemia was much higher in group 1 than in group 2 (28 persons (62.2%) vs. 3 persons (15.0 %), P=0.0005 and 26 persons (57.8%) vs. 2 persons (10.0 %), P = 0.0003, respectively).

Conclusions: among patients with a very high cardiovascular risk, the prevalence of MAFLD was significantly higher than in the general population. Concomitant MAFLD was associated with more severe metabolic disorders (i.e., obesity, metabolic dyslipidaemia, hyperglycaemia, insulin resistance), which usually combined. The LAP index is a simple available tool that may be used in routine clinical practice to determine the need for MAFLD screening. Women with MAFLD frequently had early menopause, cardiac valve calcification, and much higher median value of LVM index; direct correlation was observed between MAFLD and non-HDL-C. Men with MAFLD more often had fasting and/or post-load hyperinsulinemia and moderate hypertriglyceridemia.

Keywords: metabolically associated fatty liver disease, atherosclerotic cardiovascular disease, hepatic steatosis, dyslipidaemia, hyperglycaemia, obesity.

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ABSTRACT

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МЕТАБОЛІЧНО АСОЦІЙОВАНА ЖИРОВА ХВОРОБА ПЕЧІНКИ У ПАЦІЄНТІВ З ДУЖЕ ВИСОКИМ СЕРЦЕВО-СУДИННИМ РИЗИКОМ: ПОШИРЕНІСТЬ, КЛІНІЧНА ЗНАЧУЩІСТЬ, ГЕНДЕРНІ ОСОБЛИВОСТІ

Вступ. Нещодавно запропоновано новий термін метаболічно асоційована жирова хвороба печінки (МАЖХП). Через зростання поширеності, значну захворюваність та смертність від печінкових та

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серцево-судинних ускладнень зв'язок МАЖХП із серцево-судинними захворюваннями набуває значної актуальності та потребує подальшого вивчення.

Мета нашого дослідження: визначити частку МАЖХП серед пацієнтів із дуже високим серцево-судинним ризиком, з'ясувати клінічні особливості та гендерні відмінності в цій когорті.

Матеріали та методи: усім пацієнтам проведено комплексне обстеження для оцінки серцево-судинного ризику та МАЖХП. Стеатоз печінки встановлювали методом ультразвукового дослідження. Учасники, які відповідали критеріям МАЖХП, були включені до групи 1 (n=77; 32 жінки, 45 чоловіків), інші пацієнти були віднесені до групи 2 (n=39; 19 жінок, 20 чоловіків).

Результати. Серед пацієнтів із дуже високим серцево-судинним ризиком частка МАЖХП становила 66,7 %. Помірне підвищення аланінамінотрансферази переважало у групі з МАЖХП (16 жінок (50.0▫%) проти 2 жінок (10.5 %) у групі 2, P = 0.006; 21 чоловік (46.7 %) проти 2 чоловіків (10.0▫%), P = 0.005); проте, в жодному випадку підвищення не відповідало критеріям стеатогепатиту. Незважаючи на наявність метаболічних розладів у переважної більшості учасників, частки ожиріння, метаболічної дисліпідемії, прediабету та цукрового діабету 2 типу були достовірно вищими у пацієнтів із МАЖХП. Крім того, пацієнти з МАЖХП зазвичай відповідали 4 або 5 критеріям метаболічного синдрому, мали вищі медіани продукту накопичення ліпідів (ПАЛ) та індексу HOMA-IR, але нижчу медіану індексу Matsuda. Виявлено значущі прямі кореляційні зв'язки між МАЖХП та продуктом акумуляції ліпідів (ПАЛ), логарифмічним індексом відношення тригліцеридів до холестерину ліпопротеїнів високої щільності log (ТГ/ХС ЛПВЩ) та індексом HOMA-IR; негативні кореляційні зв'язки виявлено між МАЖХП та індексами чутливості до інсуліну. Жінки з МАЖХП мали значно вищі медіани глікованого гемоглобіну, глікемії через 2 години після навантаження глюкозою та рівні інсуліну в сироватці крові натще; виявлено значущий прямий кореляційний зв'язок між МАЖХП та ХС неЛПВЩ. Серед жінок з МАЖХП анамнез менопаузи у віці до 45 років виявлено у 15 осіб (46,9 %) проти 1 жінки (5,3 %) у групі 2 (P = 0,0019); середній вік, коли було діагностовано атеросклеротичне серцево-судинне захворювання, становив 58,5 [53,0; 64,0] років проти 68,0 [63,0; 69,0] років у групі 2 (P = 0,002); кальциноз аортального та/або мітрального клапанів серця виявлено у 31 жінки (96,6 %) проти 9 осіб (47,4 %) у 2 групі (P = 0,0001); медіана індексу маси міокарда лівого шлуночка (іМЛШ) склала 77,5 [62,1; 86,9] г/м^{2,7} проти 64,0 [50,6; 74,0] г/м^{2,7} у жінок без МАЖХП, 67,0 [55,1; 74,0] г/м^{2,7} у чоловіків із МАЖХП та 63,9 [50,0; 73,5] г/м^{2,7} у чоловіків без МАЖХП (P <0,0001 за тестом Краскела-Уолліса; P=0,002 за медіанним тестом). Поширеність куріння та вживання алкоголю значно переважала серед чоловіків як у групі 1 (P<0,0001 та P=0,0001 відповідно), так і у групі 2 (P = 0,0004 та P = 0,0023 відповідно). Чоловіки з МАЖХП мали значно вищі медіани глікемії натще, рівні інсуліну в сироватці крові натще та через 2 години після навантаження глюкозою, ніж чоловіки без МАЖХП; у чоловіків виявлено значущий прямий кореляційний зв'язок між МАЖХП та ТГ. Серед чоловіків із МАЖХП було 11 випадків гіпертригліцеридемії >2,3 ммоль/л (24,4 %), чого не спостерігалося у чоловіків без МАЖХП (P = 0,013). Частка чоловіків із гіперінсулінемією натще та

через 2 години після навантаження глюкозою була значно вищою в групі 1 у порівнянні з групою 2: 28 осіб (62,2 %) проти 3 осіб (15,0 %), P = 0,0005; 26 осіб (57,8 %) проти 2 осіб (10,0 %), P = 0,0003, відповідно.

Висновки: серед пацієнтів із АССС3 поширеність МАЖХП значно вища, ніж у загальній популяції. Супутня МАЖХП асоціювалася з більш вираженими метаболічними порушеннями (ожиріння, метаболічна дисліпідемія, гіперглікемія, низька чутливість до інсуліну), які зазвичай поєднувалися. Індекс ПАЛ є простим і доступним інструментом для визначення потреби скринінгу МАЖХП. У жінок з МАЖХП часто виявляли ранню менопаузу в анамнезі, кальциноз клапанів серця та значно вищі показники іМЛШ; спостерігалася пряма кореляція між МАЖХП та ХС неЛПВЩ. У чоловіків з МАЖХП частіше виявляли помірну гіпертригліцеридемію та гіперінсулінемію натще та/або після навантаження.

Ключові слова: метаболічно асоційована жирова хвороба печінки, атеросклеротична серцево-судинна хвороба, стеатоз печінки, дисліпідемія, гіперглікемія, ожиріння.

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Abbreviations

ALT – alanine aminotransferase
ASCVD – atherosclerotic cardiovascular disease
AST – aspartate aminotransferase
BMI – body mass index
ECG – electrocardiography
ELISA – enzyme-linked immunosorbent assay
GGT – gamma glutamyl transferase
HbA1c – glycated haemoglobin
HDL-C – high-density lipoprotein cholesterol
HOMA-IR – Homeostasis Model Assessment of Insulin Resistance
hsCRP – high-sensitivity C-reactive protein
KDIGO – Kidney Disease Improving Global Outcomes
LAP – lipid accumulation product
LDL-C – low-density lipoprotein cholesterol
LVM – left ventricular mass
MAFLD – metabolically associated fatty liver disease
NAFLD – non-alcoholic fatty liver disease
Non-HDL-C – non-high-density lipoprotein cholesterol
OGTT – oral glucose tolerance test
PCSK9 – proprotein convertase subtilisin/kexin type 9
TC – total cholesterol
TG – triglycerides
WC – waist circumference

INTRODUCTION / ВСТУП

Metabolic disorders (i.e., overweigh, glucose dysregulation, and dyslipidaemia) are recognized modifiable risk factors for cardiovascular diseases. In combination with arterial hypertension, these disorders significantly increase cardiovascular risk [1]. On the other hand, metabolic disorders are closely related to fatty liver, the main morphological feature of non-alcoholic fatty liver disease (NAFLD), affecting a quarter of world population [2]. Hepatic steatosis is an asymptomatic initial condition in the continuum of chronic liver damage, followed by steatohepatitis, liver fibrosis, cirrhosis, hepatocellular carcinoma, and death [3]. All-cause mortality among people with NAFLD is higher than in the general population; the most common causes of death are cardiovascular diseases, extrahepatic malignancies, and liver complications [4, 5]. The results of a meta-analysis indicated that NAFLD moderately increases the risk of fatal and non-fatal cardiovascular complications [6].

Recently, international experts proposed a new term – metabolically associated fatty liver disease (MAFLD). The diagnosis of MAFLD requires combination of hepatic steatosis with any of the following three criteria: 1) overweight or obesity; 2) type 2 diabetes; 3) presence of any two of the following metabolic disorders: waist circumference (WC) ≥102 cm for men, ≥88 cm for women; blood pressure ≥130/85 mm Hg or antihypertensive therapy; hyperglycaemia below diabetic range or glycated haemoglobin (HbA1c) from 5.7 % to

6.4 %; serum triglyceride (TG) level ≥1.7 mmol/L or high-density lipoprotein cholesterol (HDL-C) level <1.0 mmol/L for men, <1.3 mmol/L for women or lipid-lowering therapy; Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) index ≥2.5; serum high-sensitivity C-reactive protein (hsCRP) levels >2 mg/L [7]. Unhealthy lifestyle, high prevalence of obesity and type 2 diabetes might double mortality due to hepatic complications in the next decade [8]. In the next two decades, MAFLD might cause 1.27 million person-years of decompensated liver cirrhosis, 29 % of liver transplants, 812,000 deaths due to liver disease, and 1.37 million deaths due to cardiovascular diseases [9]. Thus, the problem of MAFLD, especially in combination with cardiovascular diseases, is an important medical and social problem, requiring further investigations. The purpose of our study was to determine the proportion of MAFLD among patients with very high cardiovascular risk (i.e., established atherosclerotic cardiovascular disease) and to clarify clinical features and gender differences in this cohort.

Table 1 – Characteristics of conditions associated with very high risk in study participants

	Gender	Group 1 (n=77) MAFLD +	Group 2 (n=39) MAFLD-	P
Characteristic of arterial hypertension				
Duration of hypertension, years	women	10.0 [7.0; 15.0]	10.0 [7.5; 20.0]	0.802
	men	6.0 [3.0; 16.0]	8.5 [5.0; 16.5]	0.506
Systolic blood pressure, mm Hg	women	137 [125; 160]	150 [130; 160]	0.505
	men	140 [125; 160]	147 [120; 150]	0.740
Diastolic blood pressure, mm Hg	women	88 [77; 98]	80 [80; 90]	0.555
	men	85 [80; 95]	85 [75; 98]	0.838
Coronary artery disease, n (%)				
Stable angina CCS class II-IV	women	10 (31.3 %)	6 (31.6 %)	1.00
	men	15 (33.3 %)	5 (25.0 %)	0.572
Recent acute coronary syndrome	women	18 (56.3 %)	12 (63.1 %)	0.771
	men	25 (55.6 %)	12 (60.0 %)	0.792
Recent acute myocardial infarction or revascularization	women	4 (12.5 %)	1 (5.3 %)	0.639
	men	5 (11.1 %)	3 (15.0 %)	0.418
Prior myocardial infarction	women	5 (15.6 %)	7 (36.8 %)	0.101
	men	24 (53.3 %)	9 (45.0 %)	0.507
Heart failure, n (%)				
Preserved ejection fraction	women	19 (59.4 %)	9 (47.4 %)	0.561
	men	22 (48,9 %)	9 (45.0 %)	0.795
Mildly reduced ejection fraction	women	10 (31.3 %)	9 (47.4 %)	0.370
	men	21 (46.7 %)	8 (40.0 %)	0.788
Reduced ejection fraction	women	3 (9.4 %)	1 (5.2 %)	1.00
	men	2 (4.4 %)	3 (15.0 %)	0.165
Other conditions associated with very high risk				
Peripheral artery disease, n (%)	women	9 (28.1 %)	5 (26.3 %)	1.00
	men	13 (28.9 %)	6 (30.0 %)	1.00
Prior transient ischaemic attack or stroke, n (%)	women	7 (21.9 %)	5 (26.3 %)	0.743
	men	8 (17.8 %)	3 (15.8 %)	1.00
Glomerular filtration rate, ml/min/1.73m^2	women	68 [59; 77]	66 [63; 78]	0.961
	men	97 [91; 111]	90 [79; 103]	0.098
Atrial fibrillation, n (%)	women	7 (21.9 %)	2 (10.5 %)	0.455
	men	6 (13.3 %)	4 (20.0 %)	0.482

Notes: [1]CCS - The Canadian Cardiovascular Society classification

Materials and Methods. Study design: cross-sectional cohort study was conducted at the clinical base of the Department of Internal Medicine No 2. The study complies with the Declaration of Helsinki and was performed according to ethics committee approval of Danylo Halytsky Lviv National Medical University (protocol No 2 dated February 21, 2022). All participants provided written informed consent prior to enrolment.

Totally 116 patients (51 women, 65 men) aged 38 to 84 years (median age 63 years) with a very high cardiovascular risk were included. Verification of atherosclerotic cardiovascular disease (ASCVD) was performed according to the National standards for diagnosis and treatment of cardiovascular diseases [10]. All study participants had a long-term history of arterial hypertension, and were on permanent triple antihypertensive therapy (angiotensin-converting enzyme inhibitor or angiotensin receptor blocker in combination with a thiazide or thiazide-like diuretic or a calcium channel blocker, and a beta-blocker). At the time of enrolment, all patients had established stable coronary artery disease; some patients had ASCVDs of another location or other conditions associated with a very high risk, but not stage 4 chronic kidney disease (Table 1). Known viral hepatitis B or C, previously diagnosed diabetes mellitus or other chronic diseases in the acute stage were exclusion criteria. After liver ultrasonography and necessary laboratory tests for MAFLD diagnosis, 77 patients who met criteria for MAFLD were included into group 1 (66.4 % of all participants; 32 women and 45 men). Other 39 participants (19 women and 20 men) were assigned to group 2. The were no significant differences in the prevalence of various ASCVD or conditions associated with very high risk between the groups (Table 1).

Evaluation of ASCVD and other conditions associated with very high risk. The diagnosis of stable angina was based on the results of electrocardiography (ECG), exercise tests and ambulatory ECG monitoring. The diagnosis of recent unstable angina was based on the results of ECG, troponin test and echocardiography performed during hospitalization within the period ≥1 to 6 months prior to the enrolment. The diagnosis of a recent acute myocardial infarction was based on the results of an ECG, troponin test, echocardiography, and coronary angiography performed during hospitalization within the period ≥1 to 6 months prior to the enrolment. Information about prior myocardial infarction, stroke or transient ischemic attack was taken from patient's medical documents, confirming hospitalization due to these conditions more than 6 months before the enrolment. Heart failure was diagnosed in the presence of typical signs and symptoms with further classification according to the left ventricular ejection fraction value: ≤40 % – heart failure with reduced ejection fraction; 41-49 % – heart failure with mildly reduced ejection fraction; ≥50▫% – heart failure with preserved ejection fraction. Echocardiographic assessment of left ventricular mass was performed using linear method:

$$LVM\ (g) = 0.8 \times (1.04 \times [(IVS + LVID + PWT)^3 - LVID^3]) + 0.6\ g,$$

where IVS is interventricular septum; LVID is internal diameter; PWT is inferolateral wall thickness [11]; LVM was indexed to the height in meters$^{2.7}$; values ≤47 g/m$^{2.7}$ for women and ≤50 g/m$^{2.7}$ for men were considered normal. Kidney Disease Improving Global Outcomes (KDIGO) staging system was used to classify chronic kidney disease after calculation of estimated glomerular filtration rate by Cockcroft-Gault equation (D. Cockcroft, M. Gault, 1976). Peripheral artery disease was diagnosed after Doppler ultrasound of the peripheral arteries (e.g., carotid or lower extremities).

Evaluation of MAFLD. Hepatic steatosis was diagnosed after ultrasonography that was performed according to a unified protocol after overnight fasting when the following criteria were met: diffuse hyperechoic structure of the liver, increased echogenicity of the liver compared to the kidneys, poor visualization of portal veins walls, and dorsal attenuation of echo signal. Liver function tests included aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamyl transferase (GGT), bilirubin, albumin, and fibrinogen. Plasma hsCRP levels were measured by ELISA.

Anthropometry (i.e., measurement of height, body weight, waist and hip circumferences) was performed according to World Health Organization recommendations (1995). The body mass index (BMI) was calculated by dividing a patient's weight in kilograms by the height in metres squared. Metabolic syndrome was diagnosed when ≥3 International Diabetes Federation criteria were met. A standard oral glucose tolerance test (OGTT) was performed after an overnight fast during ≥8 hours. Venous blood samples were taken at fasting state and at 30, 60 and 120 minutes after oral glucose load (75 g of glucose dissolved in water). In these samples, plasma glucose was measured using the glucose oxidase method; a solid phase two-site enzyme immunoassay was used to determine serum insulin concentrations with standard Kit DRG Instrumentals GmbH, Germany. The concentration of

glycated haemoglobin (HbA1c) was determined in fasting venous blood samples using ion exchange chromatography. Prediabetes and type 2 diabetes was diagnosed after OGTT according to the criteria proposed for MAFLD [7]. To assess beta cell secretion and insulin sensitivity, the following indices were calculated:

- Area under the curve of insulin during OGTT (AUC $I_{0'\text{-}120'}$) using trapezoid rule;
- $HOMA-IR = I_{0'} \times G_{0'}/22.5$, where $I_{0'}$ is fasting insulin, μU/mL, $G_{0'}$ is fasting glucose, mmol/L (D. Matthews et al., 1985);
- $\text{Cederholm index} = [75000 + (G_{0'} - G_{120'}) \times 1.15 \times 180 \times 0.19 \times m]/[120 \times \log(I_{mean}) \times G_{mean}]$, where G is glucose in mmol/L; I is insulin in μU/mL; m is body mass in kg; $_{0'}$ is fasting; $_{120'}$ is 120 minutes after glucose load, $_{mean}$ is average during OGTT (J. Cederholm, L. Wibell, 1990);
- $\text{Matsuda index} = 10000/\sqrt{(I_{0'} \times G_{0'}) \times (I_{mean} \times G_{mean})}$, where G is glucose in mg/dL, I is insulin in μU/mL; $_{0'}$ is fasting; $_{120'}$ is 120 minutes after glucose load, $_{mean}$ is average during OGTT (M. Matsuda, R. DeFronzo, 1999);
- $\text{Disposition index} = \text{the incremental AUC } I_{0'-120'}/\text{the incremental AUC } G_{0'-120'} \times \text{Matsuda index}$ (M. Abdul-Ghani et al., 2006)

Serum total cholesterol (TC), triglycerides (TG) and high-density lipoprotein cholesterol (HDL-C) were measured by colorimetric methods. Low-density lipoprotein cholesterol (LDL-C) was calculated according to the Fridewald's formula: $\text{LDL cholesterol}, \frac{\text{mmol}}{\text{L}} = \text{total cholesterol} - \text{HDL cholesterol} - (\text{triglycerides}/2.2)$. Non-HDL-C was calculated as the difference between TC and HDL-C. The logarithmic value of TG/HDL-C ratio was determined as an indicator of low-density lipoprotein particle size [14]. Lipid accumulation product (LAP), a marker of ectopic lipid deposition, was calculated as follows: $LAP = (WC - 58) \times TG$ for women; $LAP = (WC - 65) \times TG$ for men, where WC is waist circumference in cm, TG is serum triglycerides level in mmol/l [12].

Table 2 – Liver function tests and C-reactive protein in study participants

Parameter, units	Gender	Group 1	Group 2	P value
Total bilirubin, μmol/l	women	12.8 [10.4; 16.4]	12.4 [10.4; 16.5]	0.454
	men	13.6 [10.4; 17.1]	12.4 [10.4; 16.4]	0.592
ALT, U/l	women	29.4 [25.8; 33.6]	22.8 [13.8; 33.6]	0.027
	men	37.8 [28.2; 45.0]	29.1 [16.8; 37.2]	0.011
Elevated ALT*, n (%)	women	16 (50.0 %)	2 (10.5 %)	0.006†
	men	21 (46.7 %)	2 (10.0 %)	0.005†
AST, U/l	women	25.2 [20.1; 29.4]	22.8 [13.8; 29.4]	0.489
	men	29.1 [24,0; 37,5]	25.2 [21,0; 33,6]	0.331
Elevated AST*, n (%)	women	5 (15.6 %)	4 (21.0 %)	0.711
	men	12 (26.7 %)	3 (15.0 %)	0.369
GGT, U/l	women	33.5 [25.2; 43.1]	30.2 [19.3; 38.3]	0.300
	men	48.3 [34.4; 64.2]	54.4 [35.8; 67.5]	0.647
Elevated GGT, n (%)	women	18 (56.3 %)	7 (36.8 %)	0.249
	men	22 (48.9%)	11 (55.0 %)	0.789
Albumin, g/l	women	40.2 [38.4; 49.2]	38.9 [36.4; 50.2]	0.781
	men	43.4 [39.8; 50.0]	44.1 [38.1; 51.3]	0.882
Fibrinogen, g/l	women	3.8 [3.0; 4.0]	3.0 [2.8; 3.6]	0.068
	men	3.8 [3.0; 4.1]	3.6 [2.9; 4.4]	0.871
C-reactive protein, mg/l	women	9.0 [5.7; 10.8]	8.9 [1.8; 10.3]	0.211
	men	8.7 [6.8; 9.4]	8.9 [6.5; 10.9]	0.687

*Notes: * Below the thresholds for steatohepatitis;*
† *Statistically significant after Bonferroni correction (P < 0.007)*

Statistical analysis was performed using the program "Statistica for Windows 6.0" (Statsoft, USA) and nonparametric methods, since the underlying error distribution of the most analysed variables was not Gaussian. Relative values were presented as percentages, groups were compared using Fisher's exact test. Quantitative values were presented as the median [25th percentile; 75th percentile], comparison of two independent group was performed using the Mann-Whitney test; Kruskal-Wallis ANOVA and median test were used to compare multiple independent groups. Correlation analysis was performed using Kendall's coefficient (τ). P-values from two-sided tests less than 5 % were considered statistically significant. To reduce the chance of type I error, Bonferroni correction was applied when multiple variables were compared.

Results. Although elevated ALT was much more common findings among patients with MAFLD, none of the participants met the criteria for steatohepatitis, as transaminase elevation did not exceed 1.5 times the upper reference limit. Elevated AST usually was detected among patients with a recent acute myocardial infarction. Many participants had elevated GGT. Albumin, fibrinogen and CRP levels did not differ between the groups (Table 2).

The median age at the time of ASCVD diagnosis was almost 10 years earlier than in women without MAFLD (Table 3). Although all participants had long-term history of arterial hypertension, were on continuous triple antihypertensive therapy with no significant differences in median blood pressure levels between the groups (Table 1), the median value of LVM index was the highest in women with MAFLD in comparison with median value of LVM index in women without MAFLD and men of both groups (Table 3, Kruskal-Wallis ANOVA P <0.0001; median test P = 0.002). Besides, the vast majority of woman with MAFLD had calcification of cardiac valves (Table 3). Although in our study all female participants were post-menopausal, women with MAFLD significantly more often had early menopause before 45 years of age; majority of these cases were caused by ovariohysterectomy (Table 3). Hormone replacement therapy was not performed after the intervention.

Table 3 – Clinical features and risk factors in study participants

Parameter, units	Gender	Group 1	Group 2	P value
Age, years	women	63.0 [57.0; 70.5]	71.0 [65.0; 75.0]	0.008
	men	58.0 [52.0; 67.0]	62.0 [54.5; 70.5]	0.165
Age when ASCVD was diagnosed, years	women	58.5 [53.0; 64.0]	68.0 [63.0; 69.0]	0.002†
	men	53.0 [49.0; 60.0]	54.5 [49.5; 67.5]	0.267
Cardiac valve calcinosis, n (%)	women	31 (96.9 %)	9 (47.4 %)	0.0001†
	men	35 (77.8 %)	13 (65.0 %)	0.361
Left ventricular mass index, g/m^{2,7}	women	84.0 [72.5; 89.5]	63.0 [50.6; 74.0]	<0.0001†
	men	67.0 [55.1; 74.0]	63.9 [50.0; 73.5]	0.340
Menopause before 45 years of age, n (%)	women	15 (46.9 %)	1 (5.3 %)	0.0019†
Surgical menopause, n (%)	women	12 (40.6 %)	1 (0 %)	0.018
Smoking, n (%)	women	2 (6.25 %)	0 (0 %)	0.523
	men	26 (57.8 %)	10 (50.0 %)	0.598
Alcohol*, n (%)	women	6 (18.7 %)	4 (21.0 %)	1.00
	men	29 (64.4 %)	12 (60.0 %)	0.785
Obesity**, n (%)	women	21 (65.6 %)	3 (15.8 %)	0.001†
	men	34 (75.6 %)	6 (30.0 %)	0.0008†
Body weight, kg	women	88.0 [71,5; 93,5]	69.0 [65.0; 75,0]	0.0001†
	men	95.0 [88,0;107,0]	85.5 [78.0; 95.5]	0.009
Body mass index, kg/m^2	women	32.9 [28,4; 36,7]	26.8 [25.3; 29.2]	0.0004†
	men	30.9 [30.1; 34.1]	27.7 [26.4; 30.9]	0.006
Waist circumference, cm	women	109 [94; 117]	93 [88; 97]	0.002†
	men	110 [106; 118]	106 [101; 108]	0.100

*Notes: * ≤ 30 mL of ethanol per day for men ≤ 15 ml per day for women;*
*** Body mass index ≥30 kg/m^2;*
† Statistically significant after Bonferroni correction (P < 0.004);
ASCVD = atherosclerotic cardiovascular disease

Unlike women, men in both groups often were smokers and reported moderate alcohol consumption (Table 3). Gender differences were significant among patients with MAFLD (P<0.0001 for smoking, P=0.0001 for alcohol) and among patients without MAFLD (P = 0.0004 for smoking, P=0.0023 for alcohol). Excessive alcohol use denied all study participants.

Among study participants, 113 persons (97.4 %) had abdominal obesity basing on WC values, 64 patients (55.2 %) had BMI ≥30 kg/m^2 (obesity), and 43 patients (33.1 %) had BMI within the ranges from 25.01 kg/m^2 to 29.99 kg/m^2 (overweight). However, the proportion of obesity was significantly higher in patients with MAFLD (Table 3).

Median values of LAP were significantly higher in patients with MAFLD. In addition, higher median values of triglycerides and log (TG/HDL-C) were found in men with MAFLD (Table 4).

Table 4 – Lipid profile in study participants

Parameter, units	Gender	Group 1	Group 2	P value
Total cholesterol, mmol/l	women	5.85 [5.15; 6.40]	5.30 [4.50; 6.00]	0.122
	men	5.30 [4.60; 6.40]	5.75 [4.65; 6.10]	0.827
HDL-C, mmol/l	women	1.06 [0.94; 1.68]	1.17 [0.99; 1.80]	0.348
	men	0.96 [0.87; 1.24]	1.09 [0.89; 1.27]	0.333
LDL-C, mmol/l	women	3.79 [2.54; 4.37]	2.47 [2.26; 3.75]	0.084
	men	3.29 [2.80; 4.08]	3.27 [2.17; 4.07]	0.800
Non-HDL-C, mmol/l	women	4.46 [3.70; 5.28]	3.43 [2.70; 4.61]	0.037
	men	4.22 [3.52; 5.15]	4.49 [3.48; 4.89]	0.794
Triglycerides, mmol/l	women	1.81 [1.29; 2.29]	1.58 [1.11; 1.90]	0.153
	men	1.72 [1.40; 2.23]	1.30 [0.89; 1.59]	0.0004†
Log (TG/HDL-C)	women	0.18 [-0.03; 0.34]	0.01 [-0.20; 0.21]	0.065
	men	0.25 [0.07; 0.38]	0.11 [-0.15; 0.21]	0.002†
Lipid accumulation product, cm×mmol/l	women	90.3 [72.2; 112.5]	45.2 [35.5; 92.5]	0.002†
	men	79.2 [66.0; 100.7]	48.6 [38.8; 68.8]	0.0001†

Notes: †Statistically significant after Bonferroni correction (P < 0.007).

Abbreviations: HDL-C = high density lipoprotein cholesterol; LDL-C = low density lipoprotein cholesterol; Log (TG/HDL-C) = the logarithmic value of triglycerides-to-high-density lipoprotein cholesterol ratio

Among study participants, 90 persons (77.6 %) met criteria for metabolic dyslipidaemia. Among patients with MALFD, there were 30 cases (38.96 %) of combined metabolic dyslipidaemia with elevated TG and low HDL-C versus 6 cases (15.38 %) in group 2 (P < 0.01). Among men with MAFLD there were 11 cases of moderate hypertriglyceridemia with TG levels above 2.3 mmol/l (24.4 %) that was not observed among men without MAFLD (P = 0.013); among women, there was no difference in the proportion of persons with moderate hypertriglyceridemia – 25.0 % and 21.0 %, respectively (Figure 1). Despite atorvastatin use at the dose of 40 mg for at least 3 months prior to enrolment, none of the participants reached recommended by National standards [10] LDL-C target <1.8 mmol/l for patients with very high risk (Figure 1). Significant direct correlations were observed between MALFD and LAP: τ = 0.352, P = 0.0003 in women; τ = 0.385, P < 0.0001 in men; and between MALFD and log (TG/HDL-C): τ = 0.216, P = 0.025 in women; τ = 0.309, P = 0.0003 in men. In addition, there was direct correlation between MALFD and non-HDL-C in women τ = 0.242, P = 0.012; and direct correlation between MAFLD and TG in men (τ = 0.354, P < 0.0001).

The results of OGTT met criteria for normal glucose regulation only in 8 persons (10.4 %) with MAFLD versus 16 persons (41.0 %) in group 2 (P = 0.0002 for all participants; P = 0.003 for women; P = 0.023 for men). Thus, majority of patients with MAFLD had diabetes or prediabetes (Figure 2). Women with MAFLD had significantly higher median values of HbA_{1c}, 2-hour post-load plasma glucose level, fasting insulin levels than woman without MAFLD. Men with MAFLD had significantly higher median values of fasting glycaemia, fasting and post-load serum insulin levels than men without MAFLD, as well as higher prevalence of both fasting and post-load hyperinsulinemia. There were significant higher median values of HOMA-IR and significantly lower median values of Matsuda index in women and men with MAFLD (Table 5). Significant direct correlations were observed between MALFD and HOMA-IR: τ = 0.364, P = 0.0002 in women;

Table 5 – Parameters of glucose regulation and insulin sensitivity indices in study participants

Parameter, units	Gender	Group 1	Group 2	P value
Glycated haemoglobin (HbA_{1c}), %	women	5.3 [4.5; 6.2]	4.4 [4.1; 4.7]	0.002†
	men	5.6 [5.1; 6.0]	5.2 [4.3; 5.8]	0.030
Fasting plasma glucose, mmol/l	women	6.3 [5.9; 6.8]	5.2 [4.4; 6.4]	0.030
	men	6.4 [5.2; 6.9]	5.2 [4.5; 6.1]	0.004†
Two-hour post-load plasma glucose, mmol/l	women	10.6 [7.5; 11.7]	6.6 [6.0; 8.4]	0.002†
	men	8.8 [6.8; 10.8]	7.4 [5.7; 8.7]	0.050
Fasting serum insulin, μU/ml	women	15.8 [13.1; 20.0]	10.6 [7.1; 13.7]	0.002†
	men	18.8 [13.4; 26.0]	11.4 [6.1; 15.5]	0.0003†
Two-hour post-load serum insulin, μU/ml	women	68.6 [45.0; 92.8]	51.4 [28.1; 64.6]	0.023
	men	67.1 [45.1; 92.7]	36.0 [17.9; 54.5]	0.0003†
Fasting hyperinsulinemia, n (%)	women	16 (50.0 %)	4 (21.0 %)	0.074
	men	28 (62.2 %)	3 (15.0 %)	0.0005†
Two-hour post-load hyperinsulinemia, n (%)	women	20 (62.5 %)	4 (21,0 %)	0.008
	men	26 (57,8 %)	2 (10,0 %)	0.0003†
HOMA-IR index	women	4,56 [3,24; 6,78]	2,38 [1,51; 4,47]	0.002†
	men	5,36 [3,81; 7,55]	2,51 [1,60; 4,24]	<0.0001†
Matsuda index	women	3,26 [2,40; 4,10]	5,69 [3,53; 8,06]	0.0006†
	men	2,90 [2,16; 3,86]	5,75 [4,12; 7,90]	<0.0001†

Note: † Statistically significant after Bonferroni correction (P < 0.005).

Abbreviations: HOMA-IR – *Homeostasis Model Assessment of Insulin Resistance index*

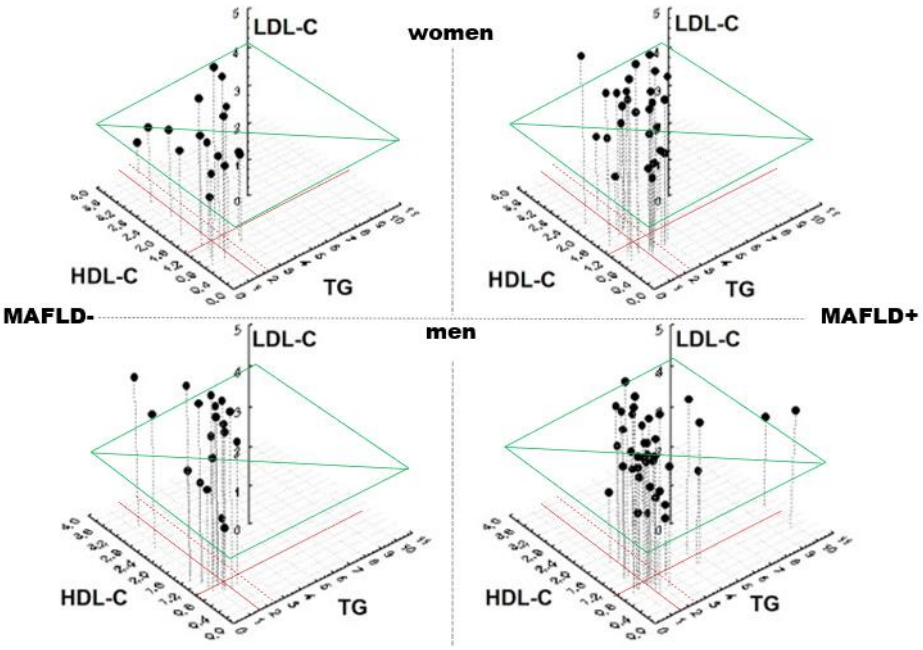

Figure 1 – Patterns of dyslipidaemia in women (top) and men (bottom) without MAFLD (left) and with MAFLD (right)

Notes: red lines show cut-off values between normal and abnormal levels of high-density lipoprotein cholesterol (HDL-C) levels and triglycerides (TG) levels; green lines show the cut-off value between normal and abnormal levels of low-density lipoprotein cholesterol (LDL-C). MAFLD = metabolically associated fatty liver disease

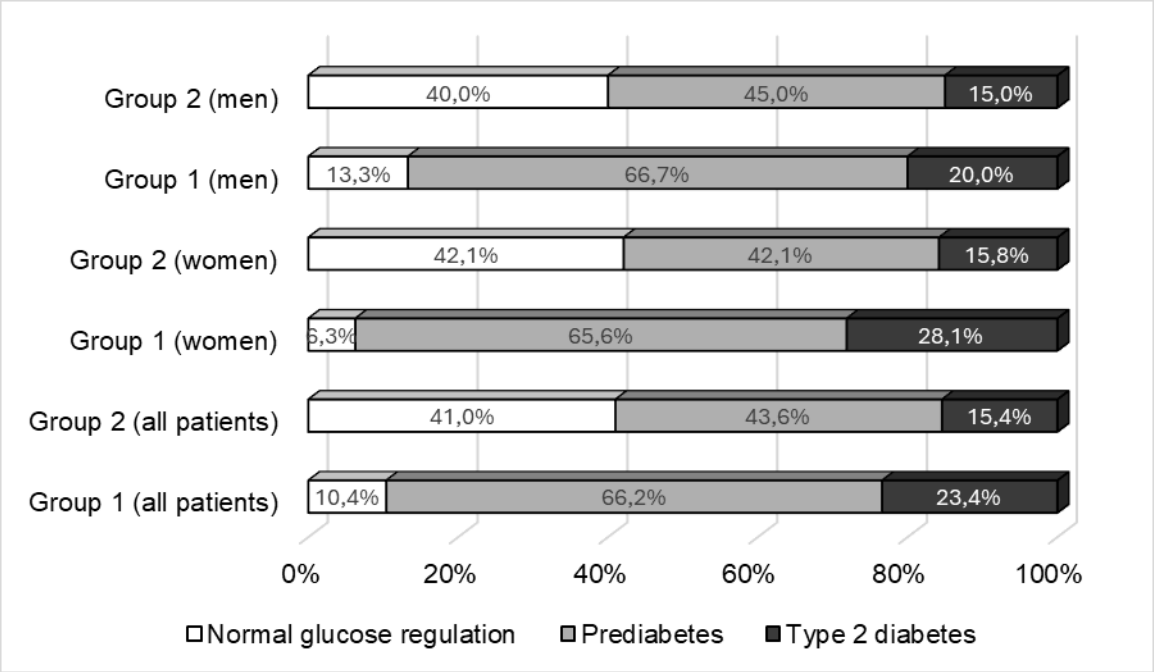

Figure 2 – The results of oral glucose tolerance test in study participants

τ = 0.427, P < 0.0001 in men. Negative correlations were observed between MALFD and insulin sensitivity indices, such as Cederholm index (τ = -0.411, P < 0.0001 in women; τ = -0.341, P < 0.0001 in men), Matsuda index (τ = -0.338, P = 0.0001 in women; τ = -0.449, P < 0.0001 in men), disposition index (τ = -0.284, P = 0.003 in women; τ = -0.177, P < 0.037 in men).

Although vast majority of participants met criteria for metabolic syndrome (96.1 % and 87.2% in group 1 and group 2, respectively, P > 0.05), patients with MAFLD much more commonly met 4 or 5 criteria than those without MAFLD (Figure 3), indicating more severe and complex metabolic disturbances in patients with MAFLD.

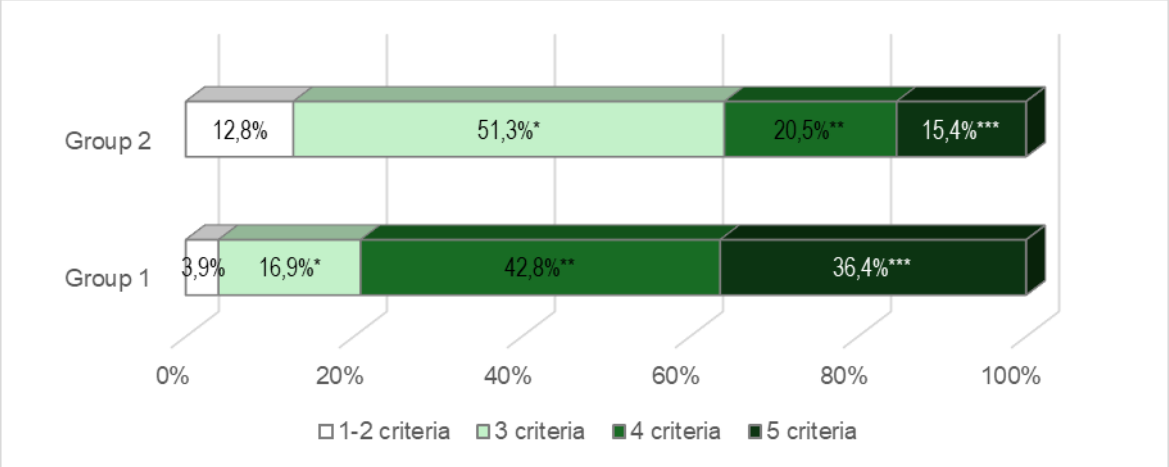

Figure 3 – The proportions of participants with different number of metabolic syndrome criteria

*Notes: * P = 0.0002; ** P = 0.023; *** P = 0.030*

Discussion. In our study the prevalence of MAFLD was 66.4% among patients with very high cardiovascular risk that is much higher than the prevalence in general population. The prevalence of obesity in men and women with MAFLD was significantly higher than in those without MAFLD. The results of a multi-ethnic study of atherosclerosis showed that both WC and BMI are important risk factors for NAFLD [13]. Unlike BMI, which is considered an indicator of general obesity, WC is a surrogate marker of abdominal obesity and visceral fat accumulation, which is a recognized prognostic risk factor for a

number of complications. A recent meta-analysis found that every 10 cm increase in WC increases the risk of ASCVD by 3.4 % in women and by 4.0 % in men [14].

Dyslipidaemia plays an important role in the pathogenesis of both ASCVD and MAFLD. In case of MAFLD, the accumulation of fat in the liver is caused by inadequate absorption of lipids from the circulation, increased hepatic lipogenesis de novo, insufficient fatty acids oxidation, and impaired export of lipids [15, 16]. As a result, "diabetic" or "metabolic" dyslipidaemia occurs, also typical for metabolic syndrome or type 2 diabetes. Criteria for metabolic dyslipidaemia include low HDL-C, hypertriglyceridemia, accumulation of triglyceride-enriched lipoproteins, and increased number of small dense LDL particles [15]. Our study showed significantly higher prevalence of metabolic dyslipidaemia as well as higher values of logarithmic index (TG/HDL-C) among patients with MALFD. Besides, almost quarter of men with MAFLD had moderate hypertriglyceridemia that was not observed among men without MAFLD. The results of the Look AHEAD study demonstrated a higher risk of cardiovascular complications in patients with metabolic dyslipidaemia, including events related to coronary artery disease [17]. The results of our previous study showed increased risk of diabetes and cardiovascular events in patients with hypertriglyceridemia [18].

Insulin resistance is another important contributor of dyslipidaemia in MAFLD. At the same time, insulin resistance results in hyperglycaemia, ectopic lipid deposition, systemic inflammation, oxidative stress, and endothelial dysfunction. All these mechanisms are engaged in atherogenesis and progression of atherosclerosis. We revealed significant direct correlations between MAFLD and HOMA-IR index and negative correlations with all insulin sensitivity indices in men and women. Insulin resistance increases lipogenesis in the liver, potentiating dyslipidaemia and increasing lipotoxicity [19]. The LAP is a parameter, reflecting ectopic lipid deposition and lipid toxicity. We observed direct and significant correlations between LAP and MAFLD in women and men. A recent systematic review and meta-analysis of 16 studies showed that the overall sensitivity of LAP for NAFLD screening was 94 % with a specificity of 85 % [12]. Taking into account easy calculation of LAP index in routine clinical practice and the possibility of simultaneous assessment of two important metabolic components (i.e., serum TG and WC, a parameter of abdominal obesity), we propose LAP as a simple tool to determine the need for MAFLD screening in patients with very high cardiovascular risk.

In our study, the majority of participants met metabolic syndrome criteria (i.e., long-term medically controlled hypertension in 100 %; abdominal obesity in 97.4 %; dyslipidaemia in 77.6 %; first detected prediabetes in 58.6 %, newly detected type 2 diabetes in 20.7 %). However, the prevalence of obesity, dyslipidaemia, prediabetes and type 2 diabetes, median values of HOMA-IR in patients with MAFLD were much higher than in the group 2. In addition, patients with MAFLD significantly more commonly met 4 or 5 criteria for metabolic syndrome than patients without MAFLD. That indicates more severe and complex metabolic disorders in patients with very high risk and associated MAFLD.

There is a report that NAFLD is associated with failure to achieve LDL-C targets [20]. In our study, despite long-term moderate-dose statin use, none of the participants reached recommended by National standards LDL-C target [10]. In this setting, intensification of lipid-lowering therapy is recommended with either high dose of statin or combination therapy with ezetimibe or PCSK9 inhibitor. From the other hand, in our study ALT elevation was much more common among patients with MAFLD, although in all cases the elevation was below thresholds characteristic for steatohepatitis. Elevated transaminases are often the reason for statin therapy discontinuation in routine clinical practice. Thus, further studies should assess benefits and risks of the proposed options of lipid-lowering therapy intensification in patients with very high cardiovascular risk associated with MAFLD.

Gender differences were found in the development and progression of NAFLD [21]. In our study, a direct correlation between MAFLD and non-HDL-C was observed in women. Non-HDL-C is a composite measure of cholesterol content in small, dense LDL particles, very low-density lipoproteins and intermediate density lipoproteins. There is emerging evidence that non-HDL-C levels may be elevated in NAFLD [22]. In addition, non-HDL-C can be an independent predictor of NAFLD [23] and a better predictor of ASCVD than LDL-C [24]. The resent study conducted by L. Lee et al. demonstrated a higher likelihood of NAFLD among individuals with increased non-HDL-C levels during the follow-up period [25].

There is evidence that lower prevalence of NAFLD in premenopausal women is explained by the protective effect of oestrogens [26]. Early menopause is also an established cardiovascular risk factor [10]. After menopause, the prevalence of both ASCVD and NAFLD in women is similar to that in men [10, 26]. All women in our study were post-menopausal, and 14 women underwent ovariohysterectomy before 45 years of age (of those, 13 women were in group 1). The study conducted by J. DiStefano et al. revealed a higher risk of NAFLD after ovariectomy, with increasing prevalence over time, from 14.1 % at 1 year to 38.4▫% at 5 years after the

intervention [27]. Early menopause in addition to more severe and complex metabolic disorders in women with MAFLD might explain why the median age of ASCVD diagnosis was almost 10 years earlier than in women without MAFLD (Table 3).

Echocardiographic evidence of mitral and/or aortic valve calcification was found in almost all women with MAFLD and less than half of women without MAFLD (Table 3). Calcification of cardiac valves is considered to be an endocardial equivalent of vascular atherosclerotic process [28]. The study conducted by A. Mantovani et al. demonstrated that NAFLD was an independent predictor of aortic and mitral valve calcification in patients with type 2 diabetes [29]. In our study diabetes was more common among women with MAFLD than among man (Figure 2). In addition, women with prediabetes were more likely to have combination of impaired fasting glucose with impaired glucose tolerance, whereas men with prediabetes usually had either impaired fasting glucose or impaired glucose tolerance. Median HbA1c level was significantly higher in women with MAFLD comparing to those without MAFLD (Table 5).

In our study the median value of LVM index in women with MAFLD was much higher than in all other groups (table 3). In the literature, there is evidence about the link between NAFLD and LVM index. A comparison of 660 patients with NAFLD detected by liver ultrasound and 791 patients without NAFLD showed significantly higher LVM index in patients with NAFLD (101.62 ± 34.48 g/m^2 vs. 88.22 ± 25.61 g/m^2, P < 0.0001) [30]. A prospective analysis that included 1962 participants of the Bogalusa Heart Study and 1547 participants of the Cardiovascular Risk in Young Finns Study (all without ASCVD) revealed significant direct correlations between fatty liver index and LVM index in both cohorts (both P < 0.001), but correlation was stronger in women than in men [31].

In our study men with MAFLD often had fasting and post-load hyperinsulinemia. Hyperinsulinemia is believed to play a key role in the pathogenesis of non-alcoholic steatohepatitis and associated cardiovascular risk. There is evidence that chronic hyperinsulinemia is a consequence of impaired insulin clearance, rather than insulin hypersecretion [32]. In the study conducted by F. Bril et al. liver histology was performed to assess the relationship between insulin clearance and hyperinsulinemia; it was found almost 30 % decrease in hepatic insulin clearance in patients with hepatic steatosis and steatohepatitis compared to those without NAFLD. Decreased hepatic insulin clearance was not associated with severity of inflammation, ballooning, or fibrosis. The authors concluded that hyperinsulinemia in NAFLD significantly correlated with impaired insulin clearance occurring during early stages of NAFLD due to the accumulation of fat in the liver [33].

Another feature observed in our study, was a significantly higher proportion of alcohol consumption and smoking among men than among women. According to the literature, extrinsic risk factors that contribute to fatty infiltration of the liver are more common in men [26, 34].

CONCLUSIONS / ВИСНОВКИ

1. Among patients with very high cardiovascular risk, the proportion of MAFLD was 66.7 %, which is significantly higher than the prevalence in the general population.
2. Concomitant MAFLD was associated with more severe metabolic disorders (i.e., obesity, metabolic dyslipidaemia, hyperglycaemia, insulin resistance), which usually combined.
3. The LAP index is a simple available tool that may be used in routine clinical practice to determine the need for MAFLD screening.
4. Women with MAFLD frequently had early menopause, cardiac valve calcification, and much higher median value of LVM index; direct correlation was observed between MAFLD and non-HDL-C. Men with MAFLD more often had moderate hypertriglyceridemia and fasting and/or post-load hyperinsulinemia.

PROSPECTS FOR FUTURE RESEARCH / ПЕРСПЕКТИВИ ПОДАЛЬШИХ ДОСЛІДЖЕНЬ

Concomitant MAFLD in patients with ASCVD need further study, as this comorbidity is associated with more severe complex metabolic disorders that contribute to earlier onset and more rapid progression of both conditions. A deeper understanding of the pathogenetic effects each metabolic disorder and their combinations, as well as gender differences in the pathogenesis of MAFLD and ASCVD, may disclose new opportunities for treatment and prevention. We consider that specific attention should be paid to investigation of lipid-lowering therapy intensification in this cohort as many patients do not achieve LDL-C goals and patients with MAFLD often have elevated liver enzymes that frequently lead to discontinuation of statin therapy in routine clinical practice. Thus, benefits and risks of high dose statin therapy or combination therapy with ezetimibe or PCSK9 inhibitor require further researches in this cohort.

CONFLICT OF INTEREST / КОНФЛІКТ ІНТЕРЕСІВ

The authors declare no conflict of interest.

FUNDING / ДЖЕРЕЛА ФІНАНСУВАННЯ

None.

AUTHOR CONTRIBUTIONS / ВКЛАД АВТОРІВ

All authors substantively contributed to the drafting of the initial and revised versions of this paper. They take full responsibility for the integrity of all aspects of the work.

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