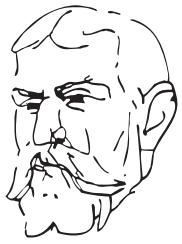
Wiadomości Lekarskie

Official journal of the Polish Medical Association



Memory of
dr Władysław
Biegański

VOLUME LXXIV, ISSUE 10 PART 2, OCTOBER 2021

Since 1928

ALUNA Publishing House

Wiadomości Lekarskie is abstracted and indexed in: PUBMED/MEDLINE, SCOPUS, EMBASE, INDEX COPERNICUS, POLISH MINISTRY OF EDUCATION AND SCIENCE, POLISH MEDICAL BIBLIOGRAPHY

CONTENTS

ORIGINAL ARTICLES

ORIGINAL ARTICLE

INSULIN RESISTANCE AS AN INDICATOR OF DIFFERENTIATION FOR THE FORMATION OF RISK GROUPS FOR NON-ALCOHOLIC FATTY LIVER DISEASE IN PATIENTS WITHOUT TYPE 2 DIABETES MELLITUS, AS A PART OF ONTOLOGICAL MODEL OF NON-ALCOHOLIC FATTY LIVER DISEASE

DOI: 10.36740/WLek202110212

Natalia O. Nosko, Viacheslav V. Kharchenko
SHUPYK NATIONAL HEALTHCARE UNIVERSITY OF UKRAINE, KYIV, UKRAINE

ABSTRACT

The aim: Using cluster analysis, to identify a high-risk group for NAFLD and develop a differential approach to examination, treatment and prevention of the disease based on IR indices, among NAFLD and non-NAFLD patients without type 2 diabetes mellitus (T2DM).

Materials and methods: Clinical, anthropometric, laboratory methods, ultrasound, computational and statistical techniques were applied.

Results: Cluster analysis was performed on the laboratory tests results: glucose, insulin, HOMA-IR index, HOMA2 Calculator (%B – beta-cell function, %S – insulin sensitivity, IR – insulin resistance). 5 groups of patients were formed, according to increasing HOMA-IR index and IR. Group II was found to be transient in IR formation, it included the majority of non-NAFLD patients (87%), and we consider it to be the risk group for NAFLD. Group V – with the highest IR scores, where 92% of patients had NAFLD and 73% had a high Fatty Liver Index – is considered to be a very high-risk group for developing T2DM.

Conclusions: 1. According to the results of cluster analysis, 5 groups of patients with different IR levels were identified. 2. In the second group, where non-NAFLD patients predominate, insulin resistance begins to form. 3. Groups III and IV – patients with high HOMA-IR index – had significant ultrasound findings indicating hepatic steatosis. 4. Group V included patients with NAFLD, with high HOMA-IR index and the highest risk of developing T2DM.

KEY WORDS: NAFLD, insulin resistance, HOMA-IR index, HOMA2 Calculator, ontology

Wiad Lek. 2021;74(10 p.II):2593-2598

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a chronic disease characterized by excessive accumulation of fat in the liver [1-6]. In most patients, NAFLD is associated with metabolic comorbidities such as obesity, type 2 diabetes mellitus (T2DM) and dyslipidemia [1-6]. According to a meta-analysis of epidemiological studies on NAFLD in 2016, the overall regional incidence of NAFLD in Asia is 52.34 per 1,000 person-years, while the incidence in the West is estimated at 28 per 1,000 person-years [7]. The global prevalence of NAFLD confirmed by computed tomography is about 25.24% [5, 7]. According to the American Association for the Study of Liver Diseases (AASLD), the prevalence of NAFLD in the general population ranges from 1.5% to 6.45% [5, 7, 8].

We analyzed and systematized the data from a 2016 article by Buzzetti E et al. [9], which set out a new perspective on NAFLD pathogenesis and revisited the previous "two-hit theory". Currently, a "multiple-hit theory" of NAFLD pathogenesis is predominant, the "hits" being lipotoxicity [10, 11]and insulin resistance (IR), microbiota impact ("gut-liver axis") [12, 13], dietary [14, 15], epigenetic [16, 17], genetic factors [17], adipose tissue dysfunction [18, 19], IL-6 and TNF-α, endoplasmic reticular stress [20, 21] and mitochondrial dysfunction[9, 22-25].

Insulin resistance is one of the key factors in steatosis and non-alcoholic steatohepatitis (NASH) development and leads to increased hepatic de novo lipogenesis (DNL) and impaired inhibition of lipolysis resulting in increased fatty acid uptake by the liver [9, 26-28]. Insulin resistance contributes to adipose tissue dysfunction which leads to altered production and secretion of adipokines and inflammatory cytokines [9, 29]. The "Consensus document. Management of non-alcoholic fatty liver disease (NAFLD) Clinical practice guideline" published in 2018 states that insulin resistance is a trigger factor in liver damage, which causes fat deposition in its tissue [5]. IR is an abnormal biological response of insulin effector tissues (liver, muscle and adipose tissue) and is reflected by plasma insulin levels above 20 μU/ml, associated with adverse cardiovascular events and NAFLD progression [5]. The consensus also states that IR is associated with reticular and oxidative stress which induces serine and threonine phosphorylation at insulin receptors, resulting in reduced efficiency of the insulin signaling cascade [5].

Table I. Patients distributed into groups according to cluster analysis

N 151	Group I	Group II	Group III	Group IV	Group V
n (%)	34 (23%)	45(30%)	27(1%)	19(13%)	26(17%)
male (%) female (%)	13(38) 21(62)	23(51) 22(49)	12(44) 15(56)	9(47) 10(53)	19(73) 7(27)
NAFLD(%)	3 (9%)	10 (22%)	17(22%)	17(89%)	24(92%)
Without NAFLD (%)	31 (91%)	35(78%)	35(78%)	2(11%)	2(8%)

We focused on studying insulin resistance in NAFLD patients and non-NAFLD patients who do not have T2DM, by utilizing the indirect IR measures recommended in 2014 "Surrogate measures of insulin sensitivity vs the hyperinsulinaemic-euglycaemic clamp: a meta-analysis" and others [30, 31].

THE AIM

Using cluster analysis, to identify patients that form a risk group for NAFLD and further develop a differential approach to examination, treatment and prevention of the disease based on IR indices, among patients with confirmed NAFLD and without NAFLD who do not have type 2 diabetes mellitus (T2DM).

MATERIALS AND METHODS

We analyzed results from 151 patients' examinations in the "INTO-SANA" clinic (according to the agreement on scientific cooperation between Shupyk National Healthcare University of Ukraine and Medisvit Medical Centers MMC) throughout 2018 – 2020. Prior consent for data processing had been obtained. We analyzed data from patients with NAFLD without T2DM (n 71), including 44 males (61%) and 54 females (39%), as well as patients without NAFLD who do not have T2DM (n 80), including 32 males (40%) and 48 females (60%). The diagnosis of NAFLD was established according to the National Ukrainian Unified Clinical Protocol for Primary and Secondary (Specialized) Medical Care "Non-Alcoholic Steatohepatitis".

Clinical, anthropometric, laboratory methods, as well as ultrasound, computational and statistical techniques were applied.

The workup algorithm included examination of patients with the assessment of anthropometric parameters (body weight, height, body mass index (BMI), waist circumference (WC)), laboratory tests (complete blood count (CBC), alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), fasting glucose, fasting insulin, total cholesterol, triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), atherogenic index of plasma (AIP), HBsAg, total anti-HCV antibodies.

HOMA-IR is a laboratory alternative for the "gold standard" of IR diagnosis – hyperinsulinaemic-euglycaemic clamp test. The HOMA-IR index is calculated using the following formula [30, 31]:

fasting glycaemia (mmol/l) x fasting insulin (μOD/ml))/22.5.

Values: no IR – <1.82; prediabetic (IR) – ≥1.82 – <3.63; diabetic (high IR) ≥ 3.63. The values are valid for adult middle-aged Europeans [32].

To calculate the HOMA2 index (%B – beta-cell function, %S – insulin sensitivity, IR – insulin resistance), an on-line calculator was utilized [33]. This model has been calibrated to obtain %B and %S values of 100% for healthy young people using currently available insulin assays.

Fatty Liver Index was calculated using the following formula [34]:

$(FLI) = e^y / (1 + e^y) \times 100$

$y = 0.953 \times \ln(TG, mg/dL) + 0.139 \times BMI, kg/m2 + 0.718 \times \ln(GGT, U/L) + 0.053 \times WC, cm - 15.745$

FLI <30 – low risk, hepatic steatosis ruled out; FLI = 30 – <60 – the risk is uncertain, steatosis possible; FLI ≥ 60 – high risk, hepatic steatosis ruled in.

Laboratory tests were performed and results identified according to the unified methods approved by the Ministry of Health of Ukraine.

All patients were examined with an abdominal ultrasound (US). Ultrasound criteria for hepatic steatosis are: parenchymal hyperechogenicity due to diffuse fatty infiltration, fine- or medium-grain echoes, deep beam attenuation, portal vessels hypoechogenicity, hepatomegaly; sometimes within the fatty infiltration pattern areas of reduced echogenicity may be seen – reflecting patches of normal parenchyma.

An online calculator "The alcoholic liver disease/Non-alcoholic fatty liver disease index (ANI)" was used to differentiate between NAFLD and alcoholic liver disease (ALD). This is a statistical model that takes into account alanine aminotransferase (ALT), aspartate aminotransferase (AST), mean erythrocyte volume (MCV), patient's body weight, height and sex. An index value greater than zero was assessed as alcoholic liver disease (ALD) and less than zero as NAFLD.

Patients taking statins were excluded from the study.

Cluster analysis was performed using the results of laboratory tests: glucose, insulin, HOMA-IR index, HOMA2 values (%B, %S, IR).

The calculations were performed with the SPSS Statistics 26 program, using cluster analysis. When evaluating indicators with normal distribution M ± SD [95% CI] was applied, and for indicators with a non-normal distribution – Me [Q1 25%; Q3 75%].

RESULTS

By conducting cluster analysis (Fig. 1), the following groups were formed with characteristic differences in certain indicators:

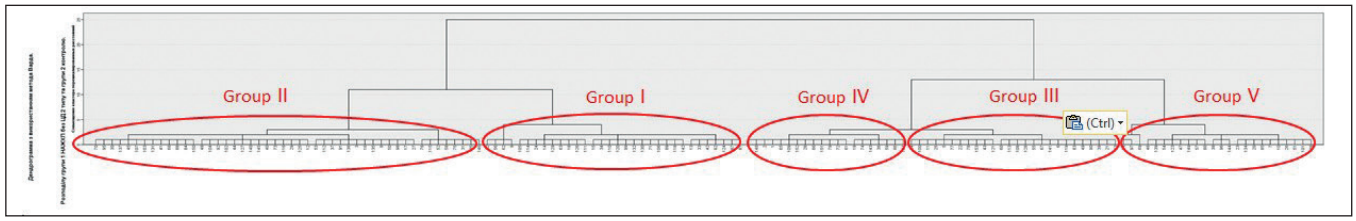


Fig. 1. Cluster analysis-grouping results.

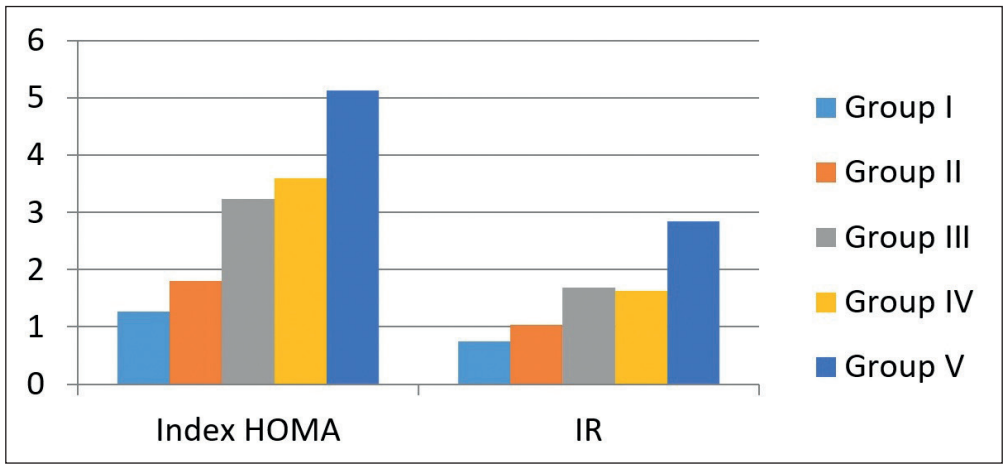


Fig. 2. HOMA and IR values in each group.

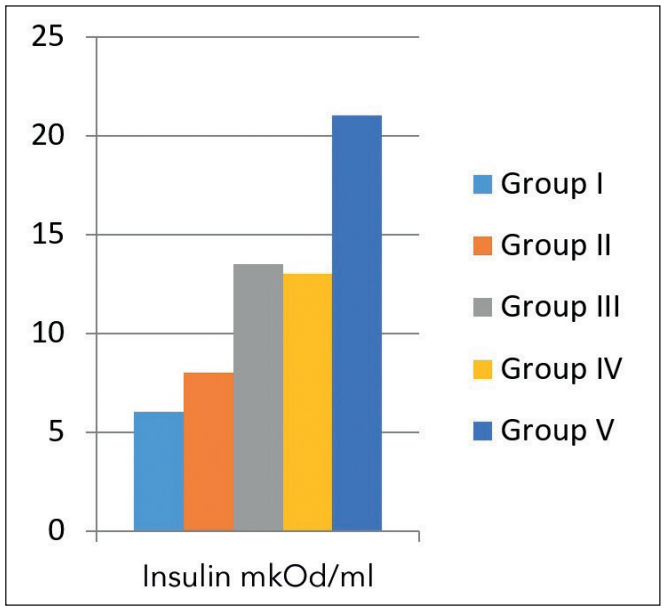


Fig. 3. Insulin levels in each group.

• *Group I*: n 34 (23%), 13 males (38%) and 21 females (62%). Among them 31 (91%) from the non-NAFLD group, 3 (9%) from the NAFLD group with mean HOMA-IR – 1.3, %B – 78%, %S – 135%, IR – 0.8, glucose – 5, insulin – 6,2; 26 patients (77%) with low FLI, 8 (23%) with indeterminate FLI, 0 with high FLI.

• *Group II*: n 45 (30%), 23 males (51%) and 22 females (49%). Among them, 35 (78%) non-NAFLD patients, 10 (22%) NAFLD patients with mean HOMA-IR – 1.8, %B – 105%, %S – 95%, IR – 1.1, glucose – 5.9, insulin – 8; 29 patients (64%) with low FLI, 12 (27%) with indeterminate FLI and 4 (8%) with high FLI.

• *Group III*: n 27 (18%), 12 males (44%) and 15 females (56%). Among them 10 (37%) non-NAFLD patients, 17 (63%) NAFLD patients with mean HOMA-IR – 3.8, %B – 122%, %S – 58%, IR – 1.7, glucose – 5.3, insulin – 13,5; 7 patients (26%) with low FLI, 7 (26%) with indeterminate FLI, 13 (48%) with high FLI.

• *Group IV*: n 19 (13%), 9 males (47%) and 10 females (53%). Among them 2 (11%) non-NAFLD patients, 17 (89%) NAFLD patients with mean HOMA-IR – 3.6, %B – 99%, %S – 56%, IR – 1.8, glucose – 6, insulin – 13.7; 3 patients (16%) with low FLI, 3 (16%) with indeterminate FLI, 13 (68%) with high FLI.

Group V: n 26 (17%), 19 males (73%) and 7 females (27%). Among them 2 non-NAFLD patients, 24 (92%) NAFLD patients with mean HOMA-IR – 5, %B – 174%, %S – 41%, IR – 6.5, glucose – 5.3, insulin – 21; 0 patients (0%) with low FLI, 7 (27%) with intermediate FLI, 19 (73%) with high FLI. (Tabl.I)

Applying cluster analysis (Fig. 1), all patients were divided into groups based on HOMA-IR values (Fig. 2).

Between groups II and III there is a cut-off transition from patients with normal HOMA-IR index (0.8 ± 0.3) in group II to the values indicating IR (3.23 ± 0.83) in group III. In group III, the HOMA-IR index is already (3.23 ± 0.83), in group IV it is (3.6 ± 1.5), which indicates high IR, in group V it is (5.13 ± 2, 15). The IR index calculated with HOMA2 Calculator also increases with each group: 0.75 [0.69; 0.8] in group I, 1.04 [0.95; 1.18] in group II, 1.68 [1.56; 2.1] in group III, 1.63 [1.45; 1.81] in group IV, 2.84 [2.18; 4.2] in group V (Fig. 2). Between groups II and III there is a cut-off transition from the normal IR index of 1.04 [0.95; 1.18] to an increased value – 1.68 [1.56; 2.1]. Insulin levels progressively increase from group I (6 ± 2.71) to group V (21 ± 7.46) (Fig. 3).

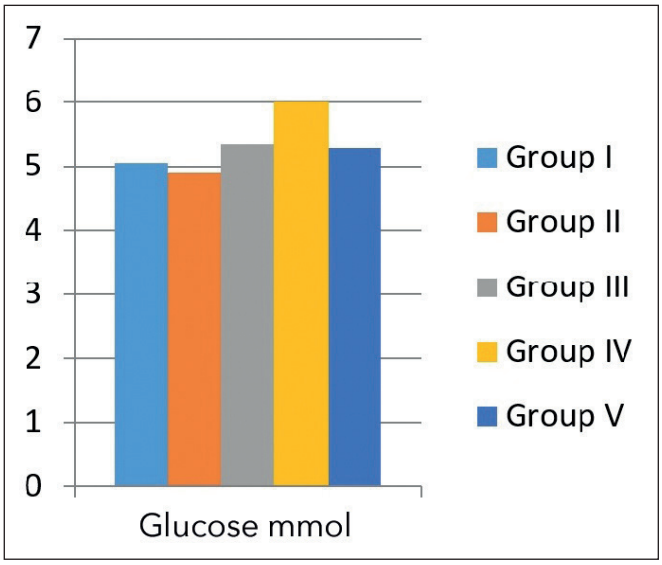


Fig. 4. Glucose levels in each group.

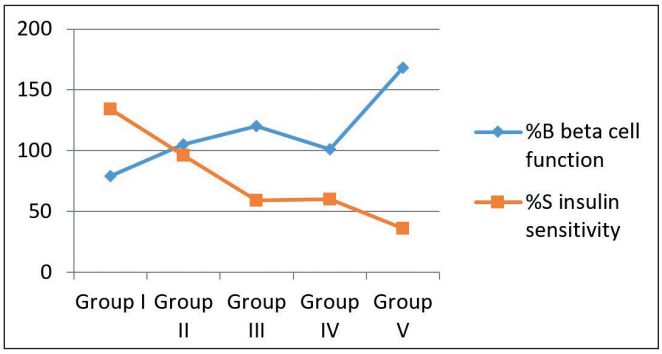


Fig. 5. %B and %S in each group.

Patients' blood glucose levels in all these groups were normal. Only group V had borderline values – 6 mmol/l (Fig.4).

Similarly, other HOMA2 Calculator indicators (%B – B-cell function, %S – insulin sensitivity) in the groups change expectedly (Fig. 5). %B increases from 78% in group I to 174% in group V, %S – insulin sensitivity – decreases from 135% in group I to 41% in group V. Transition from normal to abnormal high IR occurs between groups II and III, as shown in Figure 5.

It is important to note that in our study the criteria for the metabolic syndrome associated with NAFLD [1], such as TG (> 1.7 mmol/l) and HDL-C (<1 in males/1.3 mmol/l in females) were identified only starting from group IV for TG, and from group V in females for HDL-C.

DISCUSSION

In our study, having applied cluster analysis, we performed an original distribution between patients not by a known NAFLD differentiation cluster, such as hepatic steatosis on ultrasound, but by IR measures. The key was that patients with T2DM and those taking statins were excluded from the study. We found the transition between groups II and III to be the most valuable, since it indicated the transition from normal insulin sensitivity to low sensitivity. It was significant that these groups included patients with both existing NAFLD and without it. Given that the correction of IR, with existing NAFLD or without it (taking into account that the ultrasound method might not detect steatosis in the liver with a fat content <20% [1-6], includes a lifestyle modification, regular exercise and nutrition correction, we consider it important to actively identify patients with insulin resistance who do not yet have NAFLD, to prevent its development [1-6]. It can be concluded that testing for fasting blood glucose without checking insulin level makes it impossible to detect patients who are already developing insulin resistance, but have no ultrasound findings characteristic for hepatic steatosis. Based on the obtained data, the future works will be focusing on anthropometric indicators for all five groups of patients with the development of an algorithm for clinical decision-making depending on measured anthropometric, clinical and laboratory indicators, which may be of practical importance.

HOMA-IR provides a surrogate estimate of IR in persons without diabetes and can therefore be recommended provided proper reference values have been established (A1 recommendation), according to EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease [1]. Its use was limited due to the absence of established age-adjusted reference values for Ukraine. According to Horáková D et al. 2019 study, we may use their defined HOMA-IR cut-offs for middle-aged Europeans to improve T2DM prevention. [32] There are also published HOMA-IR reference values for Turkey, Brazil and other regions [35, 36].

In July 2020 Eslam M. et al. published an article [37] suggesting to redefine non-alcoholic fatty liver disease (NAFLD) as a metabolic dysfunction-associated fatty liver disease (MAFLD). HOMA-IR ≥ 2,5 is one of the diagnostic criteria for MAFLD in patients with confirmed hepatic steatosis and body mass index < 25 kg/m2 in Caucasians and < 23 kg/m2 in Asians. Aligning these values, we determine that individuals with HOMA- IR ≥1,82 and <2,5 already have insulin resistance, but they do not yet fit into NAFLD criteria – therefore, they are a risk group.

According to the American Diabetes Association (ADA) "Standards of Medical Care in Diabetes 2020", fasting plasma glucose (FPG), oral glucose tolerance test (OGTT), or A1C criteria are recommended for diabetes and prediabetes screening. HOMA-IR is not mentioned in the guideline. "Prediabetes" is the term used for individuals whose glucose levels do not meet the criteria for diabetes but are too high to be considered normal. Prediabetes is not viewed as a clinical entity in its own right but rather as an increased risk for diabetes and cardiovascular disease. Prediabetes is associated with obesity (especially abdominal or visceral obesity), dyslipidemia with high triglycerides and/or low HDL cholesterol, and hypertension. [38].

As we see, early insulin resistance detection and prevention are highlighted in all guidelines for in insulin resistance-associated diseases, emphasizing the fundamental diet and lifestyle modification.

CONCLUSIONS

1. According to the obtained results of cluster analysis, 5 groups of patients with different levels of insulin resistance were identified.
2. It was found that from group II, where non-NAFLD patients predominate, 35 (78%) begin to from insulin resistance.
3. Groups III and IV – patients with high HOMA-IR index – had significant ultrasound findings indicating hepatic steatosis. In group III the characteristic findings were seen in 1/2 of patients, while in group IV – in 2/3 of patients.
4. Group V included patients with NAFLD (24 92%), with high HOMA-IR index (5.13 ± 2.15), IR 2.84 [2.18; 4.2] and %B – beta-cell function of 174%. Insulin sensitivity %S was only 41%. This group of patients is at a very high risk of developing T2DM.
6. Systematization of knowledge, as the basis for the ontological model of NAFLD, regarding the importance of testing for blood insulin level to identify insulin resistance in patients without T2DM allows to identify a risk group for NAFLD, prevent the disease and improve care for patients.

REFERENCES

1. Marchesini G., Day C.P., Dufour J-F. et al. EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. Journal of Hepatology. 2016;64(6):1388-402.
2. National Guideline C. National Institute for Health and Care Excellence: Guidance. Non-Alcoholic Fatty Liver Disease: Assessment and Management. London: National Institute for Health and Care Excellence (UK) Copyright. National Institute for Health and Care Excellence. 2016.
3. Wong VW-S., Chan W-K., Chitturi S. et al. Asia-Pacific Working Party on Non-alcoholic Fatty Liver Disease guidelines. Definition, risk factors and assessment. Journal of Gastroenterology and Hepatology. 2017;1:34.
4. Lonardo A., Nascimbeni F., Targher G. et al. AISF position paper on nonalcoholic fatty liver disease (NAFLD): Updates and future directions. Digestive and Liver Disease. 2017;49(5):471-83. 5. Chalasani N., Younossi Z., Lavine J.E. et al. The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. Hepatology. 2018;67(1):328-57.
6. Leoni S., Tovoli F., Napoli L. at al. Current guidelines for the management of non-alcoholic fatty liver disease: A systematic review with comparative analysis. World Journal of Gastroenterology. 2018;24(30):3361-73.
7. Lonardo A., Byrne C.D., Caldwell S.H. at al. Global Epidemiology of Nonalcoholic Fatty Liver Disease: Meta-Analytic Assessment of Prevalence, Incidence, and Outcomes. Hepatology. 2016;64(4):1388-9.
8. Golabi P., Sayiner M., Fazel Y. at al. Current complications and challenges in nonalcoholic steatohepatitis screening and diagnosis. Expert Review of Gastroenterology & Hepatology. 2016;10(1):63-71.
9. Buzzetti E., Pinzani M., Tsochatzis E.A. The multiple-hit pathogenesis of non-alcoholic fatty liver disease (NAFLD). Metabolism-Clinical and Experimental. 2016;65(8):1038-48. doi: 10.1016/j.metabol.2015.12.012.
10. Rives C., Fougerat A., Ellero-Simatos S. et al. Oxidative Stress in NAFLD: Role of Nutrients and Food Contaminants. Biomolecules. 2020;10(12).
11. Notarnicola M., Osella A.R., Caruso M.G. et al. Nonalcoholic Fatty Liver Disease: Focus on New Biomarkers and Lifestyle Interventions. International Journal of Molecular Sciences. 2021;22(8).
12. Jennison E., Byrne C.D. The role of the gut microbiome and diet in the pathogenesis of non-alcoholic fatty liver disease. Clinical and Molecular Hepatology. 2021;27(1):22-43.
13. Tsai H-J., Tsai Y-C., Hung W-W. at al. Gut Microbiota and Non-Alcoholic Fatty Liver Disease Severity in Type 2 Diabetes Patients. Journal of Personalized Medicine. 2021;11(3).
14. Mirabelli M., Chiefari E., Arcidiacono B. et al. Mediterranean Diet Nutrients to Turn the Tide against Insulin Resistance and Related Diseases. Nutrients. 2020;12(4).
15. Valenzuela R., Videla L.A. Impact of the Co-Administration of N-3 Fatty Acids and Olive Oil Components in Preclinical Nonalcoholic Fatty Liver Disease Models: A Mechanistic View. Nutrients. 2020;12(2).
16. Huypens P., Sass S., Wu M. et al. Epigenetic germline inheritance of diet-induced obesity and insulin resistance. Nature Genetics. 2016;48(5):497-9.
17. DiStefano J.K. Fructose-mediated effects on gene expression and epigenetic mechanisms associated with NAFLD pathogenesis. Cellular and Molecular Life Sciences. 2020;77(11):2079-90.
18. Hendrikx T., Binder C.J. Oxidation-Specific Epitopes in Non-Alcoholic Fatty Liver Disease. Frontiers in Endocrinology. 2020;11.
19. de Oliveira dos Santos A.R., de Oliveira Zanuso B., Miola V.F.B. et al. Adipokines, Myokines, and Hepatokines: Crosstalk and Metabolic Repercussions. International Journal of Molecular Sciences. 2021;22(5).
20. Fernandes-da-Silva A., Miranda C.S., Santana-Oliveira D.A. et al. Endoplasmic reticulum stress as the basis of obesity and metabolic diseases: focus on adipose tissue, liver, and pancreas. European Journal of Nutrition. 2021. doi: 10.1007/s00394-021-02542-y.
21. Flessa C-M., Kyrou I., Nasiri-Ansari N. et al. Endoplasmic Reticulum Stress and Autophagy in the Pathogenesis of Non-alcoholic Fatty Liver Disease (NAFLD): Current Evidence and Perspectives. Current Obesity Reports. 2021;10(2):134-61.
22. Babak O., Bashkirova A. Results of correction of the hepatic steatosis on the background of hypertension and overweight with help of essential phospholipid complex. Georgian medical news. 2019;288:86-91.
23. Marchisello S., Di Pino A., Scicali R. et al. Pathophysiological, Molecular and Therapeutic Issues of Nonalcoholic Fatty Liver Disease: An Overview. International Journal of Molecular Sciences. 2019;20(8).
24. Gerges S.H., Wahdan S.A., Elsherbiny D.A. at al. Non-alcoholic fatty liver disease: An overview of risk factors, pathophysiological mechanisms, diagnostic procedures, and therapeutic interventions. Life Sciences. 2021;271. doi: 10.1016/j.lfs.2021.119220.
25. Ota T. Molecular Mechanisms of Nonalcoholic Fatty Liver Disease (NAFLD)/Nonalcoholic Steatohepatitis (NASH). Carotenoids: Biosynthetic and Biofunctional Approaches. 2021;1261:223-9.
26. Rehman K., Akash M.S.H. Mechanisms of inflammatory responses and development of insulin resistance: how are they interlinked? Journal of Biomedical Science. 2016;23. doi: 10.1186/s12929-016-0303-y.
27. Gastaldelli A. Insulin resistance and reduced metabolic flexibility: cause or consequence of NAFLD? Clinical Science. 2017;131(22):2701-4.
28. Kron V., Verner M., Smetana P. et al. The Changes of Cholesterol Profile at the Different Insulin Resistance Range in the Czech Republic. Medicina-Lithuania. 2021;57(3).
29. Peverill W., Powell L.W., Skoien R. Evolving Concepts in the Pathogenesis of NASH: Beyond Steatosis and Inflammation. International Journal of Molecular Sciences. 2014;15(5):8591-638.
30. Otten J., Ahren B., Olsson T. Surrogate measures of insulin sensitivity vs the hyperinsulinaemic-euglycaemic clamp: a meta-analysis. Diabetologia. 2014;57(9):1781-8.

31. Singh B., Saxena A. Surrogate markers of insulin resistance: A review. World journal of diabetes. 2010;1(2):36-47.
32. Horakova D., Stepanek L., Janout V. et al. Optimal Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) Cut-Offs: A Cross-Sectional Study in the Czech Population. Medicina-Lithuania. 2019;55(5). doi: 10.3390/medicina55050158.
33. Matthews D.R., Hosker J.P., Rudenski A.S. at al. Homeostasis model assessment – insulin resistance and beta-cell function from fasting plasma-glucose and insulin concentrations in man. Diabetologia. 1985;28(7):412-9.
34. Bedogni G., Bellentani S., Miglioli L. et al. The Fatty Liver Index: a simple and accurate predictor of hepatic steatosis in the general population. BMC Gastroenterology. 2006;6(1). doi: 10.1186/1471-230X-6-33.
35. Demir A.K., Sahin S., Kaya S.U. et al. Prevalence of insulin resistance and identifying HOMA1-IR and HOMA2-IR indexes in the Middle Black Sea region of Turkey. African Health Sciences. 2020;20(1):277-86.
36. Haueisen Sander Diniz M.F, Rezende Beleigoli A.M., Schmidt M.I. et al. Homeostasis model assessment of insulin resistance (HOMA-IR) and metabolic syndrome at baseline of a multicentric Brazilian cohort: ELSA-Brasil study. Cadernos De Saude Publica. 2020;36(8).
37. Eslam M., Newsome P.N., Sarin S.K. et al. A new definition for metabolic dysfunction-associated fatty liver disease: An international expert consensus statement. Journal of Hepatology. 2020;73(1):202-9.
38. Amer Diabet A. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2020. Diabetes Care. 2020;43:S14-S31.

The study was performed within the research work "Prevention, diagnosis and treatment of liver and intestinal diseases associated with the pathology of other organs and systems" (National registration number: 0117U000908) carried out by the Gastroenterology, Dietology and Endoscopy department of Shupyk National Healthcare University of Ukraine and is a fragment of research "Substantiation for the ontological model of care for patients with nonalcoholic fatty liver disease" (National registration number: 0118U100267).

ORCID and contributionship:
Viacheslav V. Kharchenko: 0000-0002-0294-9688 [A, E, F]
Natalia O. Nosko: 0000-0002-0732-8223 [A-D]

Conflict of interest:
The Authors declare no conflict of interest.

CORRESPONDING AUTHOR
Natalia O. Nosko
Shupyk National Healthcare University of Ukraine
9 Dorohozhytska St., 04112 Kyiv, Ukraine
tel: +380997093119
e-mail: natnosko77@gmail.com

Received: 01.07.2021
Accepted: 17.09.2021

A – Work concept and design, **B** – Data collection and analysis, **C** – Responsibility for statistical analysis, **D** – Writing the article, **E** – Critical review, **F** – Final approval of the article