sciendo

The correlation between Body Mass Index and histological features of Nonalcoholic Fatty Liver Disease

ANA CALIN-NECULA[1,2], VLAD ENCIU[1,2], PRISCILA OLOGEANU[1,2], ALEXANDRU CONSTANTIN MOLDOVEANU[1,2], CARMEN FIERBINTEANU BRATICEVICI[1,2]

[1] Internal Medicine II and Gastroenterology Department, "Carol Davila" University of Medicine and Pharmacy Bucharest
[2] Emergency University Hospital Bucharest

Abstract

Introduction: NAFLD is strongly associated with metabolic syndrome, and for many years, fatty liver was an exclusive feature of obese patients. The study tries to assess whether the body mass index (BMI) and body circumference is correlated to steatosis, fibrosis, or inflammatory activity of the liver.

Methods: 81 patients with recent hepatic biopsy were included in the study and were weighed and measured. The biopsy results were compared to the measurements.

Results: The average BMI overall for the whole lot was 30.16. There was a significant difference in BMI across the inflammatory activity categories ($p = 0.009$): groups with higher necro inflammatory activity tended to have higher BMI values (average values per grade: 0–28, 1–29, 2–33, 3–32, 4–29). There was no significant difference for grades of steatosis ($p = 0.871$). With regards to waist circumference, the overall average was 90.70cm/35.70in. There was a significant difference across the steatosis categories ($p < 0.001$): groups with higher steatosis scores had higher waist circumferences (average values per grade: 1–77cm / 30 in, 2–95 cm / 37 in, 3–94 cm / 37 in). There was no significant difference for grades of activity ($p = 0.058$).

Conclusion: BMI and waist circumference are easy to measure, non-invasive parameters, which could be useful in screening patients at higher risk for necro inflammatory activity or severe steatosis.

Keywords: Non-alcoholic Fatty Liver Disease; Body Mass Index; Weist circumference, Liver biopsy, Inflammatory activity, Steatosis, Fibrosis.

What is New? What is Important?

Body mass index and waist circumference are easy to measure parameters that could be useful in predicting patients at risk for necroinflamatory activity and steatosis. Until now, there were no proven correlations of these clinical parameters with histological findings in NAFLD.

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is a common hepatic disorder characterized by excessive accumulation of fat in the liver cells, which can lead to inflammation, fibrosis, and ultimately cirrhosis or liver cancer if left untreated. NAFLD is now recognized as the most prevalent liver disease worldwide, affecting around 25% of the general population and up to 70% of obese individuals [1]. The association between NAFLD and obesity is well established, as adipose tissue dysfunction and insulin resistance are major contributors to the pathogenesis of NAFLD. However, the prevalence of NAFLD in non-obese individuals is also significant and raises questions about the etiology, prognosis, and management of this condition. The pathogenesis of NAFLD is multifactorial suggesting that other factors such as genetic predisposition, dietary habits, and physical inactivity may play a role in the development of hepatic steatosis and its progression to nonalcoholic steatohepatitis (NASH) and advanced fibrosis [2].

Understanding the differences between NAFLD in lean and obese individuals is crucial for

 DOI: 10.2478/rjim-2023-0011

the diagnosis, monitoring, and treatment of this condition [1, 2]. The aim of this study is to examine the correlation between body mass index and waist circumference and histological features of NAFLD, specifically steatosis, fibrosis, and inflammatory activity, in a cohort of patients who underwent liver biopsy. We will review the existing literature on NAFLD and its association with metabolic syndrome and obesity, highlight the significance of lean NAFLD, and discuss the limitations and gaps in the current knowledge. The findings of this study may provide valuable insights into the role of BMI and waist circumference as non-invasive predictors of NAFLD severity and help identify patients at higher risk for disease progression and complications.

MATERIALS AND METHODS

Patients with NAFLD were followed up between October 2014 and September 2017. Inclusion criteria were represented by patient consent and recent biopsy performed for NAFLD as evaluated by abdominal ultrasound and liver function tests (liver citolysis). Patients with viral hepatitis, alcohol abuse, autoimmune liver disease, or other known causes of liver disease were excluded from the study. The remaining patients with biopsy proven NAFLD were included in the study.

A total of 81 patients were included in the study. All patients were adults (age 18 years or older) and had undergone liver biopsy for evaluation of suspected NAFLD. Patients with incomplete medical records or missing data were excluded from the study. The patients' demographic information, medical history, and laboratory data were collected from their medical records. Informed consent was obtained from all patients included in the study.

Ultrasound imaging was performed on all followed patients using the Acuson S2000 (Siemens AG) to classify the presence and severity of hepatic steatosis (HS) based on a four-point scale of hyperechogenity ranging from absent (0) to severe (3). The spleen volume was estimated by spleen longitudinal diameter (SLD) measured by a senior physician with 20 years of experience using postero-lateral scanning. All followed patients underwent a percutaneous liver biopsy performed by a senior physician using the Menghini technique with a 1.4-mm-diameter needle (Hepafix; Braun, Germany). The liver biopsy specimens were analyzed by an expert pathologist with 20 years of experience using the SAF classification and FLIP Diagnosis Algorithm to establish a positive diagnosis for non-alcoholic steatohepatitis (NASH). The length of each liver biopsy was established in millimeters, and only liver fragments of at least 2.0 cm in length that included 8 portal tracts were considered for histological assessment. The pathologist was blinded to the patients' clinical results [22].

The patients' body weight and height were measured at the time of their hospital visit. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Waist circumference was measured at the level of the umbilicus using a flexible tape measure.

Descriptive statistics were used to summarize the demographic and clinical characteristics of the study population. The Kruskal-Wallis test was used to compare the differences in BMI and waist circumference across the categories of steatosis, activity, and fibrosis. Correlation of variables was assessed using the Kendall Tau-B test. The level of statistical significance was set at $p < 0.05$. All statistical analyses were performed using IBM SPSS version 25 and python using sci-py, sklearn, stats-models and pandas libraries.

RESULTS

The study included 81 patients with NAFLD. The average BMI overall for the whole lot was 30.16. There was a significant difference in BMI across the inflammatory activity categories, but not by steatosis grade (Table 1).

With regards to waist circumference, the overall average was 90.70 cm/35.70 in. There was a significant difference across the steatosis categories, but not across inflammatory activity (Table 2).

Table 1

Univariate analysis by activity group

Variable	A0	A1	A2	A3	A4	Method	p-value
Body mass index	27.88 (SD = 6.01)	29.2 (SD = 6.03)	33.4 (SD = 4.74)	32.36 (SD = 4.7)	29.67(SD = 3.06)	ANOVA	0.009
Waist Circumference	90.0 [65–104]	99.0 [72–110]	91.0 [64–131]	95.0 [91–108]	88.0 [75–95]	KW	0.059

SD = standard deviation, ANOVA = One Way Analysis of Variance, KW = Kruskal-Wallis test

Table 2

Univariate analysis by steatosis group

Variable	S1	S2	S3	Method	p-value
Body mass index	29.56 (SD = 5.73)	30.69 (SD = 5.87)	29.83 (SD = 5.56)	ANOVA	0.871
Waist Circumference	77.0 [64–110]	95.0 [73–131]	94.0 [82–96]	KW	< 0.001

SD = standard deviation, ANOVA = One Way Analysis of Variance, KW = Kruskal-Wallis test

We also analyzed correlations to fibrosis grade but found no statistically significant differences for BMI and waist circumference (Table 3).

Table 3

Univariate analysis by fibrosis group

Variable	F0	F1	F2	F3	F4	Method	p-value
Body mass index	28.81 (SD = 6.2)	31.5 (SD = 6.55)	30.88 (SD = 6.49)	30.58 (SD = 4.42)	31.16 (SD = 5.53)	ANOVA	0.575
Waist Circumference	91.0 [65–104]	91.0 [82–107]	95.0 [74–131]	94.0 [76–131]	92.0 [64–110]	KW	0.697

standard deviation, ANOVA = One Way Analysis of Variance, KW = Kruskal-Wallis test

BODY MASS INDEX

The distribution of the patients included in the study according to the body mass index is Gaussian (p = 0.819), with an average of 30.16 and a standard deviation of 5.85.

The average body mass index does not differ statistically significantly according to the degree of hepatic steatosis (p = 0.871) – Chart 1.

Correlation tests show a moderate correlation between body mass index and activity and no correlation with the other two parameters (Table 4).

The mean body mass index differed statistically significantly according to the degree of liver inflammatory activity (p = 0.009) – Chart 2.

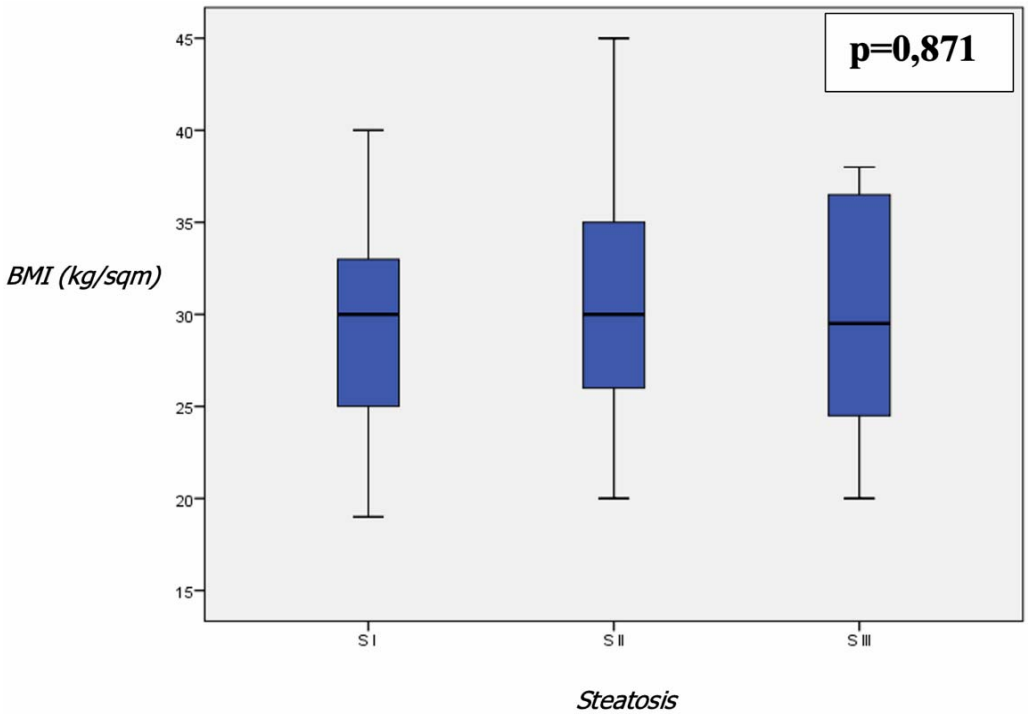


Figure 1. BMI and steatosis presence.

Table 4

Kendall correlation and Jonckheere-Terpstra Test

Variable 1	Variable 2	Kendall Tau-B	Jonckheere-Terpstra	p-value
Fibrosis	Body Mass Index	0.12	1386	0.147
Activity	Body Mass Index	0.28	1566	0.001
Steatosis	Body Mass Index	0.02	1028	0.793
Fibrosis	Waist Circumference	0.09	1347	0.267
Activity	Waist Circumference	0.15	1401	0.078
Steatosis	Waist Circumference	0.26	1312	0.004

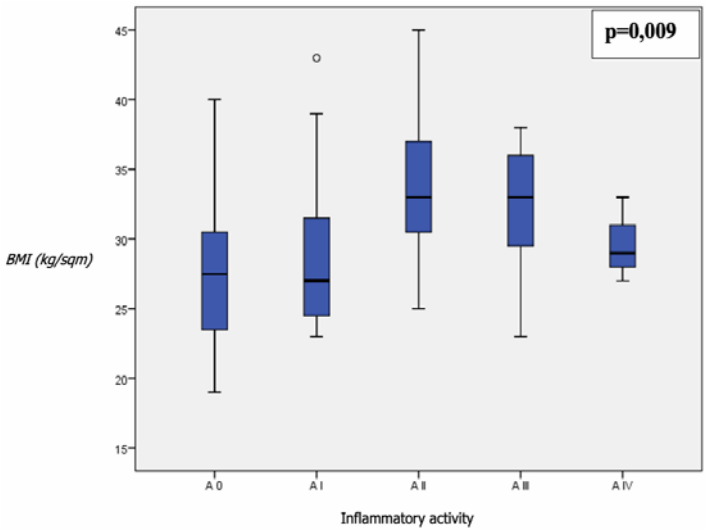


Figure 2. Association between inflammatory activity and BMI.

ABDOMINAL CIRCUMFERENCE

The distribution of the patients included in the study according to the abdominal circumference is Gaussian ($p = 0.370$), with a mean of 90.70 cm and a standard deviation of 12.76.

The mean abdominal circumference differed statistically significantly according to the degree of hepatic steatosis ($p < 0.001$) – Chart 3.

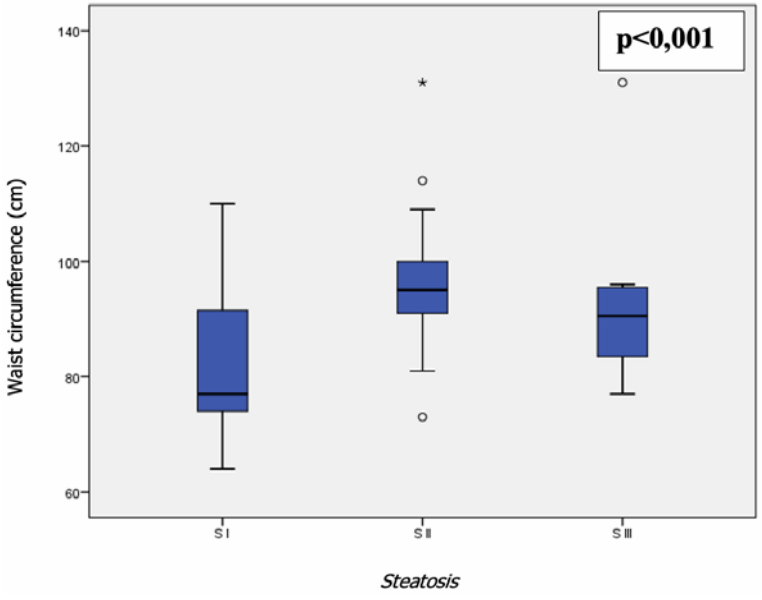


Figure 3. Association between steatosis and waist circumference.

The mean abdominal circumference does not differ statistically significantly according to the degree of liver inflammatory activity (p = 0.059) – Chart 4.

Correlation tests show a moderate correlation between waist circumference and steatosis and no correlation with the other two parameters (Table 4).

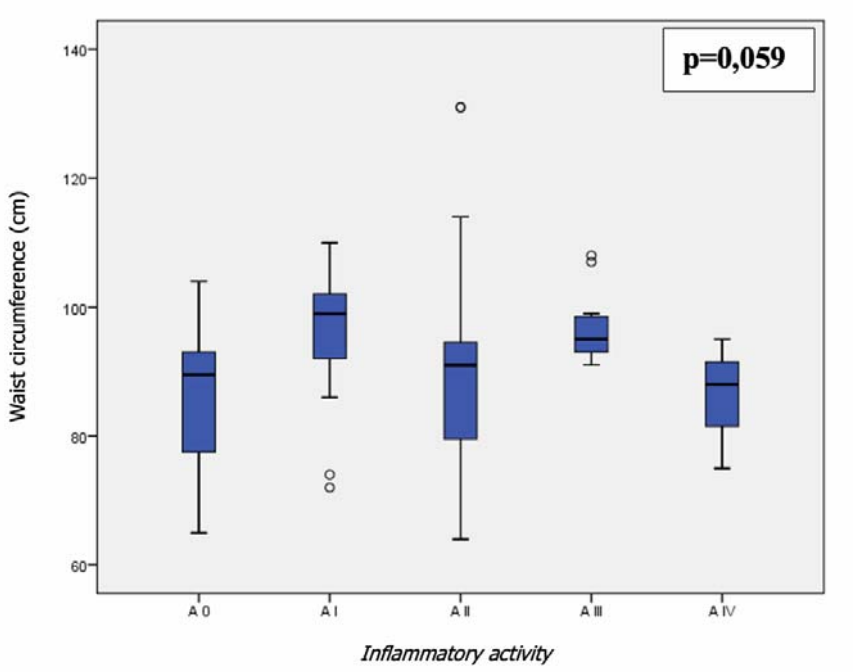


Figure 4. Association between inflammatory activity and waist circumference.

DISCUSSION

NAFLD is the main responsible factor for the exponential increase in burden of chronic liver disease in the future [3].

The modeling approach of the epidemic of NAFLD predicted that the number of individuals with cirrhosis and its complications will increase 2-3-fold by 2030 if the present tendency cannot be stopped [4]. Therefore, it becomes absolutely necessary to identify individuals with NAFLD and risk for disease progression for effective interventions.

Overweight reflected by BMI is among the main risk factors for developing non-alcoholic fatty liver disease and body fat distribution (characterized by increased truncal subcutaneous fat – waist circumference and visceral fat) is the most important driver of disease progression [5]. Histological evaluation of NAFLD should provide three important information: diagnosis, severity grading of necroinflammatory activity, and staging of fibrosis [6].

While liver biopsy is decisive in determining the histological features in chronic liver disease, it is not an appropriate test in most general practice settings. This is because liver biopsy is resource-intensive, invasive, and carries some morbidity and rare but real mortality risk. Therefore, we tried to find a non-invasive correspondence between the main histological features (steatosis, inflammation, and fibrosis) and the most accessible clinical parameters (anthropometric findings), in order to help clinicians in their daily general practice regarding the approach of patients with NAFLD.

With this scenario the aim of our study was to provide evidence for the correlation between BMI and waist circumference with histological features of NAFLD.

Specifically, our results show that higher BMI values are associated with higher levels of inflammatory activity in the liver, while higher waist circumferences are associated with higher levels of steatosis. Regarding the BMI and inflammatory activity, these findings are consistent with previous research on the relationship between obesity (including degrees of obesity) and NAFLD [7] or NASH in both prospective [8] and retrospective studies [9] as well as several geographic locations [1, 10, 11]. There also appears to be a significant correlation to future risk of developing NAFLD in patients with increased BMI, and, while the results are significantly influenced by other risk factors such as sex and diabetes [12,13], BMI does appear

to be an independent predictor [14,15]. While most studies have only separated patients in low BMI / high BMI categories, others have performed a more in-depth analysis which suggests a linear association [16]. We also know that some scores have successfully made use of BMI as a predictive factor for NAFLD future evolution [17].

Previous research also shows a connection between NAFLD and waist circumference [10]. This may be due a common physiopatological mechanism like poor eating habits [18,19] or other comorbidities – other components of the metabolic syndrome [19–21]. Furthermore, a reduction in weight (which may correlate with abdominal circumference decrease) has led to improved histology results [22].

In our study, with respect to waist circumference there was no significant difference for grades of activity and fibrosis. Whether the amount of steatosis has an important impact in other histological outcomes is a topic of intense debate. We found that increasing waist circumference were not associated with worse histology, suggesting probably a dissociation between the amount of steatosis and inflammatory activity or fibrosis. In line with these findings, imaging studies have shown that quantification of intrahepatic fat content by using MR-based techniques could not predict the severity of histology [23].

Regarding the relationship between steatosis and fibrosis in NAFLD, our study considers the multifactorial pathogenesis of fibrosis in NAFLD: it can occur not only via steatosis and also by non-steatosis pathways as suggested by another study [24].

One of the main limitations of this study is the small sample size, which may have limited the generalizability of the findings. Additionally, there may have been potential confounding factors that were not accounted for in the analysis, including lifestyle factors or comorbidities. A further limitation is that we did not evaluate fibrosis and did not follow-up the patients for longer term monitoring. Longer term histopathological monitoring could be a future research direction, as only a few studies have had this approach, but we expect the study enrolment to be difficult due to the invasive nature of the procedure.

CONCLUSIONS

In conclusion, our study found a significant correlation between BMI and waist circumference with certain histological features of NAFLD. Specifically, higher BMI values were associated with higher levels of necro inflammatory activity, while higher waist circumference was associated with higher levels of steatosis. These findings highlight the importance of addressing obesity and metabolic syndrome as risk factors for NAFLD. Clinicians should consider measuring BMI and waist circumference as part of the diagnostic evaluation of patients with suspected NAFLD, and interventions to address obesity should be included as part of the management of the disease.

Introducere: *NAFLD este o patologie strâns asociata cu sindromul metabolic şi a fost considerată o caracteristică exclusiv a pacienţilor obezi. Studiul nostru încearcă să stabilească dacă indicele de masă corporală (BMI) şi circumferinţa abdominală se corelează cu steatoza, fibroza sau activitatea inflamatorie a ficatului.*

Metode: *81 de pacienţi cu biopsie hepatică recentă au fost incluşi în studiu şi a au fost măsuraţi şi cântăriţi. Rezultatele biopsiei au fost comparate cu măsurătorile.*

Rezultate: *BMI-ul mediu pentru întregul lot a fost 30,16. Diferenţa de BMI între categoriile de activitate necroinflamatorie a fost semnificativă statistic (p = 0,009): grupele cu activitate crescută tind să aibă valori mai mari a BMI (valori medii per grad: 0–28, 1–29, 2–33, 3–32, 4–29). Nu a existat diferenţă semnificativă pentru gradele de steatoză (p = 0,871). În ceea ce priveşte circumferinţa abdominală, media a fost de 90.70 cm / 35.70 in. Diferenţa între categoriile de steatoză a fost semnificativă statistic (p < 0,001): grupurile cu scoruri mai mari de steatoză au avut circumferinţe abdominale mai mari (valori medii per grad: 1–77 cm / 30 in, 2–95 cm / 37 in, 3–94 cm / 37 in). Diferenţa nu a fost semnificativă între gradele de activitate (p = 0,058).*

Concluzii: *BMI şi circumferinţa abdominală sunt parametrii uşor de măsuraţi, non-invazivi, ce ar putea fi utili în evaluarea pacienţilor cu risc crescut de activitate necro-inflamatorie şi steatoză.*

Correspondence to: Alexandru Constantin Moldoveanu, MD, Ph.D, Dionisie Lupu No. 37, Sector 2, Bucharest, 020021 and Splaiul Indepentenţei No. 169, Sector 5, Bucharest, 050098
Email: alexandru@moldoveanu.tel
Phone: +4 0742 224 204

Declaration of Interest: The authors declare no conflict of interest.

REFERENCES

1. YOUNOSSI; KOENIG; ABDELATIF; FAZEL; HENRY; WYMER. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology* 2016, **64**, 73–84, doi:10.1002/hep.28431.
2. CHRYSAVGIS; ZTRIVA; PROTOPAPAS; TZIOMALOS; CHOLONGITAS. Nonalcoholic fatty liver disease in lean subjects: Prognosis, outcomes and management. *World J Gastroenterol* 2020, **26**, 6514–6528, doi:10.3748/wjg.v26.i42.6514.
3. NEWSOME; SCHATTENBERG; SERFATY; AGHEMO; AUGUSTIN; TSOCHATZIS; et al. The economic cost and health burden of non-alcoholic steatohepatitis in the EU5 countries. *Digestive and Liver Disease* 2020, **52**, e33–e34, doi:10.1016/ j.dld.2019.12.121.
4. YOUNOSSI; TAMPI; RACILA; QIU; BURNS; YOUNOSSI; et al. Economic and Clinical Burden of Nonalcoholic Steatohepatitis in Patients With Type 2 Diabetes in the U.S. *Diabetes Care* 2020, **43**, 283–289, doi:10.2337/dc19-1113.
5. GASTALDELLI; CUSI. From NASH to diabetes and from diabetes to NASH: Mechanisms and treatment options. *JHEP Rep* 2019, **1**, 312–328, doi:10.1016/j.jhepr.2019.07.002.
6. BRUNT; KLEINER; CARPENTER; RINELLA; HARRISON; LOOMBA; et al. NAFLD: Reporting Histologic Findings in Clinical Practice. *Hepatology* 2021, **73**, 2028–2038, doi:10.1002/hep.31599.
7. CUSI. Nonalcoholic fatty liver disease in type 2 diabetes mellitus. *Curr Opin Endocrinol Diabetes Obes* 2009, **16**, 141–149, doi:10.1097/MED.0b013e3283293015.
8. HILLENBRAND; KIEBLER; SCHWAB; SCHEJA; XU; HENNE-BRUNS; et al. Prevalence of non-alcoholic fatty liver disease in four different weight related patient groups: association with small bowel length and risk factors. *BMC Res Notes* 2015, **8**, 290, doi:10.1186/s13104-015-1224-7.
9. MACHADO; MARQUES-VIDAL; CORTEZ-PINTO. Hepatic histology in obese patients undergoing bariatric surgery. *J Hepatol* 2006, **45**, 600–606, doi:10.1016/j.jhep.2006.06.013.
10. WONG; CHAN; CHITTURI; CHAWLA; DAN; DUSEJA; et al. Asia-Pacific Working Party on Non-alcoholic Fatty Liver Disease guidelines 2017 – Part 1: Definition, risk factors and assessment. *J Gastroenterol Hepatol* 2018, **33**, 70–85, doi:10.1111/jgh.13857.
11. CHALASANI; YOUNOSSI; LAVINE; CHARLTON; CUSI; RINELLA; 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**, 328–357, doi:10.1002/hep.29367.
12. LOOMIS; KABADI; PREISS; HYDE; BONATO; ST LOUIS; et al. Body Mass Index and Risk of Nonalcoholic Fatty Liver Disease: Two Electronic Health Record Prospective Studies. *J Clin Endocrinol Metab* 2016, **101**, 945–952, doi:10.1210/jc.2015-3444.
13. YOUNOSSI; GOLABI; DE AVILA; PAIK; SRISHORD; FUKUI; et al. The global epidemiology of NAFLD and NASH in patients with type 2 diabetes: A systematic review and meta-analysis. *J Hepatol* 2019, **71**, 793–801, doi:10.1016/j.jhep.2019.06.021.
14. ANGULO; KEACH; BATTS; LINDOR. Independent predictors of liver fibrosis in patients with nonalcoholic steatohepatitis. *Hepatology* 1999, **30**, 1356–1362, doi:10.1002/hep.510300604.
15. DIXON; BHATHAL; O'BRIEN. Nonalcoholic fatty liver disease: predictors of nonalcoholic steatohepatitis and liver fibrosis in the severely obese. *Gastroenterology* 2001, **121**, 91–100, doi:10.1053/gast.2001.25540.
16. EGUCHI; HYOGO; ONO; MIZUTA; ONO; FUJIMOTO; et al. Prevalence and associated metabolic factors of nonalcoholic fatty liver disease in the general population from 2009 to 2010 in Japan: a multicenter large retrospective study. *J Gastroenterol* 2012, **47**, 586–595, doi:10.1007/s00535-012-0533-z.
17. HAGSTROM; NASR; EKSTEDT; STAL; HULTCRANTZ; KECHAGIAS. Accuracy of Noninvasive Scoring Systems in Assessing Risk of Death and Liver-Related Endpoints in Patients With Nonalcoholic Fatty Liver Disease. *Clin Gastroenterol Hepatol* 2019, **17**, 1148–1156 e1144, doi:10.1016/j.cgh.2018.11.030.
18. GHAEMI; HOSSEINI; OSATI; NAGHIZADEH; DEHGHAN; EHRAMPOUSH; et al. Waist circumference is a mediator of dietary pattern in Non-alcoholic fatty liver disease. *Sci Rep* 2018, **8**, 4788, doi:10.1038/s41598-018-23192-x.
19. HUANG; GREENSON; CHAO; ANDERSON; PETERMAN; JACOBSON; et al. One-year intense nutritional counseling results in histological improvement in patients with non-alcoholic steatohepatitis: a pilot study. *Am J Gastroenterol* 2005, **100**, 1072–1081, doi:10.1111/j.1572-0241.2005.41334.x.
20. HAMAGUCHI; KOJIMA; TAKEDA; NAKAGAWA; TANIGUCHI; FUJII; et al. The metabolic syndrome as a predictor of nonalcoholic fatty liver disease. *Ann Intern Med* 2005, **143**, 722–728, doi:10.7326/0003-4819-143-10-200511150-00009.
21. BHATIA; CURZEN; CALDER; BYRNE. Non-alcoholic fatty liver disease: a new and important cardiovascular risk factor? *Eur Heart J* 2012, **33**, 1190–1200, doi:10.1093/eurheartj/ehr453.
22. PROMRAT; KLEINER; NIEMEIER; JACKVONY; KEARNS; WANDS; et al. Randomized controlled trial testing the effects of weight loss on nonalcoholic steatohepatitis. *Hepatology* 2010, **51**, 121–129, doi:10.1002/hep.23276.
23. BRIL; BARB; PORTILLO-SANCHEZ; BIERNACKI; LOMONACO; SUMAN; et al. Metabolic and histological implications of intrahepatic triglyceride content in nonalcoholic fatty liver disease. *Hepatology* 2017, **65**, 1132–1144, doi:10.1002/hep.28985.
24. SEO. Letter: Hepatic Fibrosis and Steatosis in Metabolic Syndrome (J Obes Metab Syndr 2022;31:61–9). *J Obes Metab Syndr* 2022, **31**, 350–351, doi:10.7570/jomes22049.

Received 23rd April 2023