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ORIGINAL ARTICLE

INCIDENCE OF DIFFERENT TYPES OF IRRITABLE BOWEL SYNDROME IN PATIENTS WITH NONALCOHOLIC FATTY LIVER

UČESTALOST RAZLIČITIH TIPOVA SINDROMA IRITABILNOG KOLONA KOD PACIJENATA SA NEALKOHOLNOM MASNOM JETROM

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Abstract

Introduction: Non-alcoholic fatty liver (NAFLD) is an excessive accumulation of fat, detected by imaging methods or histologically, in people who haven`t consumed alcohol, associated with insulin resistance and metabolic syndrome. Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder, diagnosed by Rome IV criteria, with no morphological disorders in the digestive system.

Aim: Detecting frequency between different types of IBS in different grades of steatosis to distinguish possible association between the two diseases.

Material and methods: In retrospective study at the Clinic for Gastroenterohepatology of the University Clinical Center of Serbia, from January to June 2020, a number of 49 patients over 18 years were diagnosed with NAFLD and IBS. Based on the ultrasound examination, patients are classified into those with grades I, II and III of steatosis, and according to the Roma IV criteria, into IBS-C, IBS-D and IBS-M type. Body Mass Index (BMI), hyperglycemia, cholesterol, triglycerides, ALT, AST, γGT, Diabetes Mellitus (DM), arterial hypertension, Gastroesophageal Reflux Disease (GERD) and cholelithiasis are examinated.

Results: In retrospective study at the Clinic for Gastroenterohepatology of the University Clinical Center of Serbia, from January to June 2020, a number of 49 patients over 18 years were diagnosed with NAFLD and IBS. Based on the ultrasound examination, patients are classified into those with grades I, II and III of steatosis, and according to the Roma IV criteria, into IBS-C, IBS-D and IBS-M type. Body Mass Index (BMI), hyperglycemia, cholesterol, triglycerides, ALT, AST, γGT, Diabetes Mellitus (DM), arterial hypertension, Gastroesophageal Reflux Disease (GERD) and cholelithiasis are examinated.

Conclusion: Patients with NAFLD and IBS are predominantly female. Non-alcoholic fatty liver is associated with metabolic syndrome, insulin resistance, GERD, and cholelithiasis. No association was shown between the grade of steatosis and the type of IBS, except in cholesterol, with the highest frequency in grade III of steatosis and the IBS-C type.

Keywords:
non-alcoholic fatty liver disease,
irritable bowel syndrome,
metabolic syndrome

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Sažetak

Uvod: Nealkoholna masna jetra (NAFLD) je preterana akumulacija masti koja se otkriva putem imidžing metoda ili histološki kod osoba koje nisu konzumirale alkohol. Povezana je sa insulinskom rezistencijom i metaboličkim sindromom. Sindrom iritabilnog kolona (IBS) je funkcionalni gastrointestinalni poremećaj, gde ne postoje morfološki poremećaji u digestivnom sistemu i čiju dijagnozu postavljamo na osnovu *Rome IV* kriterijuma.
Cilj: Cilj rada je utvrđivanje zastupljenosti različitih tipova IBS-a kod različitih stepena steatoze, radi razmatranja moguće povezanosti i međusobnog uticaja ove dve bolesti.
Materijal i metode: U retrospektivnoj studiji, sprovedenoj na Klinici za gastroenterohepatologiju Univerzitetskog kliničkog centra Srbije od januara do juna 2020, dijagnostikovana su 49 pacijenata, starosti preko 18 godina, sa dijagnozom NAFLD i IBS. Na osnovu ultrazvučnog pregleda pacijenti su klasifikovani na one sa I, II i III stepenom steatoze jetre, a prema *Rome IV* kriterijumima na IBS-C, IBS-D i IBS-M tip. Beleženi su podaci o: indeksu telesne mase (engl. *Body Mass Index*, BMI), hiperglikemiji, vrednostima holesterola, triglicerida, alanin (ALT) i aspartat aminotransferaze (AST) i gama glutamine transferaze (γGT), *Diabetes melitus*-u (DM), arterijskoj hipertenziji, gastroezofagusno-refluksnoj bolesti (GERB) i holelitijazi.
Rezultati: Ukupan broj ispitanika sa NAFLD i IBS je bio 49, prosečne starosti 52,02 ± 13,44 godine, 63% žena i 37% muškaraca. Kod žena su bili više zastupljeniji IBS-C i IBS-D tip (69% i 91%), a kod muškaraca IBS-M tip (75%). Razlika u učestalosti tipova IBS-a prema stepenu NAFLD nije bila statistički značajna. Visoko povišen BMI, hiperglikemija, holesterol, trigliceridi, ALT, AST, γGT, DM, GERB i holelitijaza pretežno su bili zastupljeni u II i III stepenu steatoze, dok prisustvo arterijske hipertenzije nije pokazalo statističku značajanu razliku. Statistički značajna razlika je postojala samo kod pacijenata sa povišenim holesterolom, sa najvećom zastupljenošću kod IBS-C tipa (77%).
Zaključak: Pacijenti oboleli od NAFLD i IBS-a su pretežno ženskog pola. Nealkoholna masna jetra je povezana sa metaboličkim sindromom, insulinskom rezistencijom, GERB-om i holelitijazom. Nije pokazana povezanost između stepena steatoze jetre i tipa IBS-a, osim povišenih vrednosti holesterola sa III stepenom steatoze i IBS-C tipom.

Ključne reči:
nealkoholna masna jetra,
sindrom iritabilnog kolona,
metabolički sindrom

Introduction

Non-alcoholic fatty liver disease (NAFLD) is defined as excessive accumulation of fat, detected by imaging methods or histologically, in people who have not consumed alcohol (1). Within NAFLD, simple steatosis (80%) can be distinguished, which is reversible, and nonalcoholic steatohepatitis (20%), which usually progresses further to fibrosis, cirrhosis, or hepatocellular carcinoma (2).

It is associated with insulin resistance and metabolic syndrome, consisted of the following conditions: obesity, i.e. increased BMI (Body Mass Index), dyslipidemia (elevated triglycerides and reduced HDL), arterial hypertension and hyperglycemia (3).

Irritable Bowel Syndrome (IBS) is defined as a functional gastrointestinal disorder or, according to a newer definition, a disorder of the brain-gut axis (4, 5). Diagnosis is based on Roma IV criteria and there are no morphological disorders in the digestive system, detected by clinical, biochemical or microbiological tests, as well by colonoscopy findings.

The etiology of IBS is still incompletely defined, but there are pathophysiological mechanisms that could explain its occurrence: disorders of epithelial permeability, levels of bile acids and intestinal microflora, as well as previous infections, which could lead to activation of the intestinal immune system, change influence on the enteric nervous system and affect the brain-gut axis (6).

The aim of this study is to determine the frequency of IBS types in patients with certain grades of NAFLD and to analyze the frequency of certain parameters in patients with NAFLD and IBS. That would contribute to understanding the possible existence of a common pathogenesis and the mutual influence of these two diseases.

Material and methods

Study population

A retrospective study was conducted at the Clinic for Gastroenterohepatology of the University Clinical Center of Serbia, from January to June 2020.

The study involved 49 patients (18 men and 31 women), over the age of 18, with a diagnosis of NAFLD and IBS. Patients with NAFLD are classified into three groups, with grades I, II or III of steatosis. In relation to the IBS type, these patients are classified into three categories: IBS-C (with predominant constipation), IBS-D (with predominant diarrhea) and IBS-M (with mixed symptoms). According to BMI values, patients were divided into categories with normal (< 25), slightly elevated (25-29) and high BMI (> 29). Laboratory analyzes in serum were recorded: elevated glycemia (> 6.1 mmol / l), cholesterol (> 5.5 mmol / l), triglycerides (> 1.7 mmol / l),

ALT (> 41 IU / l), AST (> 38 IJ / l), γGT (> 40 U / l), as well as the existence of other diseases: Diabetes Mellitus (DM) type 1 and 2, arterial hypertension, gastroesophageal reflux disease (GERD) and cholelithiasis.

Distribution of age and gender in relation to the grade of NAFLD and different types of IBS was examined. Also, the frequency of other listed parameters was recorded in those patients and data on its statistical significance were obtained.

Diagnostic criteria for NAFLD

Diagnosis was made during ultrasound examination, visualizing changes related to: hepato-renal index, liver echogenicity, clarity of visualization of blood vessels and visibility of surrounding deeper structures (7). The changes were graded as: 0-normal liver, I-mild steatosis (slight and diffuse increase of liver echogenicity with normal visualization of the diaphragm and of the portal vein wall), II-moderate steatosis (moderate increase of liver echogenicity with slightly impaired appearance of the portal vein wall and the diaphragm) and III-severe steatosis (increased echogenicity with poor or no visualization of portal vein wall, diaphragm, and posterior part of the right liver lobe) (8).

Diagnostic criteria for IBS

Diagnosis is based on Roma IV criteria, which are defined as the presence of abdominal pain, at least once a week, last three months, and is associated with two or more of the following criteria: defecation, stool frequency change, and stool shape change. Patients were divided into 3 categories: IBS-C (with predominant constipation), IBS-D (with predominant diarrhea) and IBS-M (with mixed symptoms) (9, 10).

Statistical analysis

The arithmetic mean for the standard deviation was used to describe the numerical data, and the absolute and relative number for the categorical variables. One-factor ANOVA with TUCKEY intergroup comparison was used to compare the three independent groups according to mean age. The categorical variables were compared by the Chi square test. Complete statistical analysis was performed in IBM SPSS ver.21. All statistical methods were considered significant for the selected $\alpha = 0.05$.

Results

The total number of subjects with NAFLD and IBS is 49. The average age was 52.02 ± 13.44 years. Among the patients, females were dominant with 63%, while males were represented in a smaller percentage - 37 % (**Figure 1**).

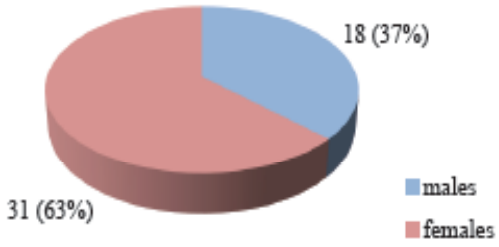

Figure 1. Gender distribution among all patients.

From 49 subjects with NAFLD, 19 had grade I, 16 had grade II, and 14 had grade III of steatosis. The average age of the subjects, in relation to the grade of steatosis, didn't show a statistically significant difference (p = 0.479) (**Table 1**). There wasn't statistically significant difference in the frequency of genders according to the grade of steatosis (p = 0.165), although in patients with grades I and II of steatosis the female gender dominated, and in grade III of steatosis the representation of male and female gender is almost the same (**Table 2**).

From the total number of subjects, 26 had IBS-C, 11 IBS-D, and 12 IBS-M type of IBS. The average age of

Table 1. The average age of the subjects according to the degree of steatosis

Degree of steatosis	Arithmetic mean $\bar{x}$	Standard deviation sd	p *	I vs. II	I vs. III	II vs. III
I	49.37	13.87	0.479	0.782	0.451	0.848
II	52.44	13.65				
III	55.14	12.81				

* for significance level 0.05, one-factor ANOVA

Table 2. Gender distribution according to the degree of steatosis

Gender	Degree of steatosis			p *
	I	II	III	
Male	5(26.3)	5(31.3)	8(57.1)	0.165
Female	14(73.7)	11(68.8)	6(42.9)	

* for significance level 0.05, Chi square test

Table 3. Average age of patients according to IBS type

IBS type	Arithmetic mean	Standard deviation	p *	IBS-C vs. IBS-D	IBS-C vs. IBS-M	IBS-D vs. IBS-M
IBS-C	53.08	13.12				
IBS-D	49.73	14.29	0.792	0.775	0.963	0.928
IBS-M	51.83	14.24				

* for significance level 0.05, one-factor ANOVA

the subjects, in relation to the IBS type, is shown in **Table 3**, with no statistically significant difference (p = 0.792). Distribution of gender in relation to the IBS type (**Figure 2**), showed statistically significant difference (p = 0.003). Type IBS-C was more prevalent in women than in men (69% *vs*. 31%), as well as type IBS-D (91% *vs*. 9%), while type IBS-M was more common in males than in females (75% *vs*. 25%).

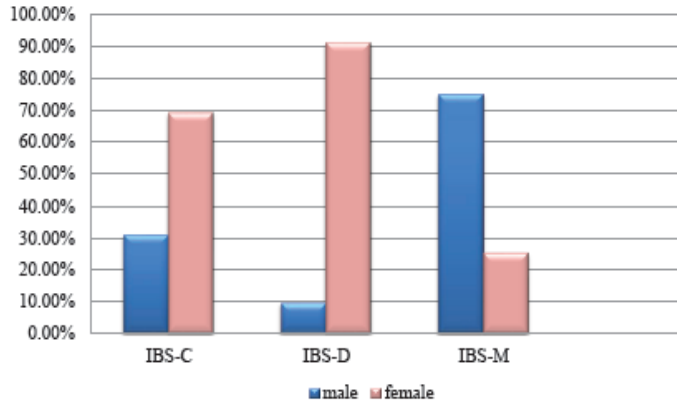

Figure 2. Gender distribution according to type of IBS (*for significance level 0.05, Hi square test, p = 0.003)

The prevalence of different IBS types, depending on the grade of steatosis, is shown in **Table 4**. All three types of steatosis were almost equally represented in patients with IBS (19 patients with grade I, 16 with grade II, and 14 with grade III). However, most of the patients with steatosis had IBS-C type (53%). The other two types of IBS were almost equally represented in patients with steatosis (22% with IBS-C and 24.5% with IBS-M). There was no statistically significant difference in the frequency of IBS types, according to the grade of NAFLD (p = 0.332).

The frequency of the examined parameters, in relation to the grade of steatosis, is shown in **Table 5**. Frequency of subjects with BMI > 29 was significantly higher in patients with grade II (56%) and grade III (43%) than in those with grade I of NAFLD (16%), which showed a statistically significant difference (p = 0.040). The frequency of patients with normal and slightly elevated BMI was not statistically significant in relation to the grade of steatosis (p = 0.062 *vs*. p = 0.980). The presence of NAFLD patients with elevated glycemia was highest in grade III (64%), slightly lower in grade II (37%), and lowest in grade I of steatosis (5%). This difference was statistically significant (p = 0.001). Elevated cholesterol was significantly more often present in subjects with grade II (75%) and grade III (79%) than in subjects with grade I (37%) and the data show a statistically significant difference (p = 0.020). There is also a statistically significant difference (p <0.001) for elevated triglyceride values, and they are the most prevalent in the group of patients with grade III (79%), slightly less in grade II (56%), and significantly less in subjects with grade I of steatosis (5%). Elevated values of ALT and AST were present in grade II (37% and 31%) and grade III (29% and 21%) of steatosis, significantly higher in these two stages than in I grade (p = 0.016 and p = 0.037). Elevated γGT values were most common in grade II (44%), with a statistically significant difference compared to grades I and III (p = 0.006). Type 1 of DM was present in approximately the same percentage in the group of patients with grade II and III (37% *vs*. 29%), while it was not recorded at all among patients with degree I of steatosis (p = 0.016). Type 2 of DM was most prevalent in grade III (43%), while this percentage was much lower in grade I (5%) and II (6%) of steatosis, with a statistically significant difference (p = 0.006). Additionally, GERD was more prevalent in grade II (31%) and III (50%) than grade I (5%) of steatosis, with a statistically significant difference (p = 0.014). Cholelithiasis was most common in grade II (37%), slightly lower in grade III (14%), and least in grade I (5%), with a significant statistical difference (p = 0.044). The presence of arterial

Table 4. Distribution of IBS types according to the degree of steatosis

IBS type	Degree of steatosis				p *
	I	II	III		
IBS C	9(47.4)	10(62.5)	7(50.0)	26(53.1)	
IBS D	7(36.8)	2(12.5)	2(14.3)	11(22.4)	0.332
IBS M	3(15.8)	4(25.0)	5(35.7)	12(24.5)	
	19(100)	16(100)	14(100)	49(100)	

* for significance level 0.05, Chi square test

Table 5. Frequency of examined parameters in patients with different degrees of steatosis

Parameter		Degree of steatosis			p *
		I	II	III	
BMI	<25	12(63.2)	4(25.0)	5(35.7)	0.062
	25-29	4(21.1)	3(18.8)	3(21.4)	0.980
	>29	3(15.8)	9(56.3)	6(42.9)	**0.040**
Glycemia (> 6.1mmol/l)		1(5.3)	6(37.5)	9(64.3)	**0.001**
Cholesterol (> 5.5mmol/l)		7(36.8)	12(75.0)	11(78.6)	**0.020**
Triglycerides (> 1.7mmol/l)		1(5.3)	9(56.3)	11(78.6)	< **0.001**
ALT (> 41IJ/l)		0(0.0)	6(37.5)	4(28.6)	**0.016**
AST (> 38IJ/l)		0(0.0)	5(31.3)	3(21.4)	**0.037**
γGT(> 40U/l)		1(5.3)	7(43.8)	1(7.1)	**0.006**
DM type 1		0(0.0)	6(37.5)	4(28.6)	**0.016**
DM type 2		1(5.3)	1(6.3)	6(42.9)	**0.006**
Arterial hypertension		3(15.8)	7(43.8)	4(28.6)	0.189
GERD		1(5.3)	5(31.3)	7(50.0)	**0.014**
Cholelithiasis		1(5.3)	6(37.5)	2(14.3)	**0.044**

* for significance level 0.05, Chi square test

hypertension in relation to the grade of steatosis showed no statistically significant difference (p = 0.189).

The frequency and statistical significance of the same parameters were also shown in patients with different types of IBS (**Table 6**). It was found that the only statistically significant difference existed in patients with elevated cholesterol levels compared to the type of IBS (p = 0.045), with the highest prevalence in patients with IBS-C type (77%), slightly less with IBS-M (50%) and at least with IBM-D (36.4%) type. The frequency of subjects with normal, slightly elevated and high BMI in relation to the type of IBS was not statistically significant (p = 0.784, p = 0.224, p = 0.350), nor in patients with elevated glycemia (p = 0.805) and triglycerides. p = 0.171). Elevated ALT, AST and γGT values were present in patients with IBS-C (27% *vs*. 19% *vs*. 27%) and IBS-M (25% *vs*. 25% *vs*. 17%) types, while they were not observed in patients with IBS-D, but the results didn't show a statistically significant difference (p = 0.161, p = 0.227, p = 0.152). The frequency of other parameters, the presence of DM type 1 (p = 0.346), DM type 2 (p = 0.397), arterial hypertension (p = 0.678), GERD (p = 0.326) and cholelithiasis (p = 0.258), didn't show a statistically significant difference compared to the type of IBS.

Table 6. Frequency of examined parameters in patients with different types of IBS

Parameter		IBS type			p *
		IBS C	IBS D	IBS M	
BMI	<25	10(38.5)	5(45.5)	6(50.0)	0.784
	25-29	5(19.2)	4(36.4)	1(8.3)	0.244
	>29	11(42.3)	2(18.2)	5(41.7)	0.350
Glycemia (> 6.1mmol/l)		9(34.6)	4(36.4)	3(25.0)	0.805
Cholesterol (> 5.5mmol/l)		20(76.9)	4(36.4)	6(50.0)	**0.045**
Triglycerides (> 1.7mmol/l)		13(50.0)	2(18.2)	6(50.0)	0.171
ALT (> 41IJ/l)		7(26.9)	0(0.0)	3(25.0)	0.161
AST (> 38IJ/l)		5(19.2)	0(0.0)	3(25.0)	0.227
γGT(> 40U/l)		7(26.9)	0(0.0)	2(16.7)	0.152
DM type 1		5(19.2)	1(9.1)	4(33.3)	0.346
DM type 2		6(23.1)	1(9.1)	1(8.3)	0.397
Arterial hypertension		8(30.8)	2(18.2)	4(33.3)	0.678
GERD		8(30.8)	1(9.1)	4(33.3)	0.326
Cholelithiasis		7(26.9)	1(9.1)	1(8.3)	0.258

* for significance level 0.05, Chi square test

Discussion

The examined population of patients with NAFLD and IBS proved to be a population in which the female gender is more prevalent than the male, with the average age of 52.02 ± 13.44 years. The prevalence of gender and age in patients with NAFLD in this study coincides with other studies showing that the incidence of NAFLD is higher in the female population and highest in the population aged between 50 and 60 (11, 12). This result can be explained by the postmenopausal stage in the life of women (reduction of protective estrogenic mechanisms, increased insulin resistance, hyperlipidemia and visceral fat accumulation). Therefore, females become more represented than males after the age of 50 (13, 14). The result of higher prevalence of women in the population with IBS can be explained by hormonal changes during life: bloating, more frequent stools and abdominal pain during menstrual cycle, effect of estrogen and progesterone on increased motility, increased visceral hypersensitivity, intestinal microflora, as well as on the brain-gut axis influencing to higher sensitivity, emotional response and stress (15–17). Our study also showed a higher incidence of IBS-C and IBS-D type in women compared to men, where IBS-M is more prevalent. Fatigue, anxiety and depression are more common in women, affecting their quality of life, especially in the ages of 48 to 57, which will lead to more women seeing doctors after the age of 50 (18). Since we do not have an insight into the duration of the disease at the moment of data collecting, the years of life in our study population coincide with these studies.

Our study didn't show an association between the prevalence of different types of IBS, in relation to the grade of hepatic steatosis, although the largest number of patients with NAFLD had IBS-C type. According to other studies, there is a theoretical link across obesity and the liver-gut axis, which explains the role of disturbed gut microflora and permeability in delivering substances to the liver and triggering inflammation, immune system and liver changes (19–21). In the literature, there was no previous research found on examining the association of IBS types with the grade of liver steatosis.

As expected, the results of the association of NAFLD with metabolic syndrome and insulin resistance were shown. Subjects with highly elevated BMI, hyperglycemia, elevated cholesterol, triglycerides, as well as patients with DM were most prevalent in grade II and III of steatosis. The frequency of arterial hypertension in patients with varying grades of steatosis didn't show a statistically significant difference. Various studies confirm these results among the subjects or explain the connection between obesity, metabolic flow disorders in the liver, leading to inflammatory processes and increased examined parameters (22–25). Confirming other researches, the study showed significant difference in the frequency of subjects with elevated liver enzymes (ALT, AST, γGT) between different grades of liver steatosis, with a higher presence of grade II and III (25, 26).

Additionally, in this study, there is a significant association of GERD in relation to the grade of steatosis, with the highest frequency of patients in grade II and III of liver steatosis. Previous researches suggest a link between steatosis and GERD through the theory that obesity affects on accumulation of visceral adipose tissue, increasing abdominal pressure and leading to regurgitation, but also creates proinflammatory cytokines that reduce sphincter tone and leads to GERD (27, 28).

The connection between the presence of cholelithiasis in patients with different grades of steatosis, with the highest frequency in grades II and III was determined. Cholelithiasis is more common in women over the age of 50, in obese people, people with DM and dyslipidemia, which together contribute to risk factors for NAFLD and explain their association (29, 30).

Cholesterol is the only parameter in the study that shows a statistically significant difference in relation to the type of IBS, with the highest prevalence in IBS-C type. None of the studies addressed the association of the presence of elevated cholesterol with the type of IBS. However, there are studies that analyze the association between obesity and pre-diabetic condition with IBS, within the parameter of elevated cholesterol in people with IBS is examined (31, 32).

It is believed that the limitation of this work is the small number of respondents since no significant difference in the frequency of other examined parameters in relation to the type of IBS was found.

Conclusion

The study confirmed that patients with NAFLD and IBS were predominantly female and that NAFLD was associated with components of metabolic syndrome, insulin resistance, GERD and cholelithiasis. There was no association in distribution of grades of NAFLD according to IBS types. The only parameter that showed a statistically significant difference in both diseases was cholesterol, with the highest incidence in grade III of hepatic steatosis and IBS-C type.

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