

ORIGINAL PAPER



Triglyceride and glucose index: a useful tool for non-alcoholic liver disease assessed by liver biopsy in patients with metabolic syndrome?

ANCA MARIA AMZOLINI¹), MIRCEA CĂTĂLIN FORȚOFOIU¹), ANCA BARĂU ABU-ALHIJA¹), IONELA MIHAELA VLADU²), DIANA CLENCIU²), ADINA MITREA²), MARIA FORȚOFOIU³), DANIELA MATEI⁴), VIORELA ENĂCHESCU⁵), OCTAVIAN ION PREDESCU⁶), ELENA SIMONA MICU¹)

¹)Department of Internal Medicine, Medical Semiology, University of Medicine and Pharmacy of Craiova, Romania

²)Department of Diabetes, Nutrition and Metabolic Diseases, University of Medicine and Pharmacy of Craiova, Romania

³)Department of Emergency Medicine, University of Medicine and Pharmacy of Craiova, Romania

⁴)Department of Physiotherapy, University of Medicine and Pharmacy of Craiova, Romania

⁵)Department of Family Medicine, University of Medicine and Pharmacy of Craiova, Romania

⁶)Department of Nursing, Faculty of Nursing, Târgu Jiu Subsidiary, Titu Maiorescu University, Bucharest, Romania

Abstract

Introduction: Non-alcoholic fatty liver disease (NAFLD) is associated with metabolic impairments, being a component of metabolic syndrome. Considering the involvement of fat accumulation and insulin resistance in NAFLD, triglyceride and glucose (TyG) index was proposed as a marker of NAFLD progression. The “gold standard” for the evaluation of liver lesions characteristic for NAFLD remains the liver biopsy. The aim of this study was to establish the links between TyG index, assessing insulin resistance, and histopathological lesions of liver samples obtained by liver biopsy in patients with metabolic syndrome. **Patients, Materials and Methods:** We conducted a study over a period of three years, including 113 adult patients with metabolic syndrome in whom hepatic disorders were assessed by liver biopsy and insulin resistance was evaluated by TyG index. **Results and Discussions:** In our study, steatosis had a frequency of 92.03%, being identified 26 cases with mild steatosis, 48 with moderate steatosis and 31 with severe steatosis. Regarding non-alcoholic steatohepatitis (NASH), the frequency of this disorder in our study group was 29.2% in the subjects with liver steatosis, while liver fibrosis had a frequency of 53.09%. When we analyzed the relationships between TyG index and the presence of each type of lesion necessary for NASH diagnosis, we obtained statistically significant differences for the presence of hepatocyte ballooning ($p=0.01$) and a high statistically significance for the NAFLD activity score (NAS) ($p<0.0001$). **Conclusions:** TyG index is a facile tool that can be used to identify patients at risk for advanced NAFLD lesions evaluated by liver biopsy.

Keywords: liver biopsy, non-alcoholic liver disease, triglyceride and glucose index, metabolic syndrome.

Introduction

Metabolic syndrome is defined by the association between hyperglycemia, arterial hypertension, dyslipidemia [triglycerides above the normal limits and low high-density lipoprotein (HDL)–cholesterol levels], increased abdominal circumference [1]. Non-alcoholic fatty liver disease (NAFLD), a disorder that covers a spectrum of liver lesions (steatosis, non-alcoholic steatohepatitis – NASH, fibrosis, cirrhosis) that appear in the absence of alcohol consumption or minimal alcohol consumption and in the absence of other causes of liver disease, has been associated with metabolic impairments [2].

NAFLD, often presented as the hepatic manifestation of metabolic syndrome, is recognized as the key driver of this condition; furthermore, metabolic syndrome is a multi-organ syndrome, associating endocrine, cardiovascular and renal elements, the hepatic involvement being another

component [3]. Recent studies have suggested that the fatty liver may be the main pathogenic determinant of metabolic syndrome, and not just a component, as it was reported in older studies published in the medical literature [4].

The role of insulin resistance in the development of NAFLD is still controversial, although its presence was sustained as one of the important pathogenic pathways involved in the NAFLD–metabolic syndrome association. Between non-alcoholic liver disorders and insulin resistance a bidirectional relationship was described, insulin resistance is exacerbated by the liver dysfunction, leading to the development of overt diabetes, while hyperinsulinism secondary to insulin resistance increases the lipid accumulation in the liver [5, 6]. In addition, inflammation, through cytokine production, mitochondrial dysfunction, and gut microbiome dysbiosis, also plays a role in the association between insulin resistance, NAFLD and other metabolic related diseases [7].

Considering the involvement of fat accumulation (triglycerides) and insulin resistance in NAFLD, triglyceride and glucose (TyG) index was proposed as a marker of NAFLD progression in later life, studies showing an important correlation between this index and fatty liver in different populations [8, 9]. Commonly, insulin resistance is assessed by the homeostasis model assessment of insulin resistance (HOMA-IR), but some recent studies found a better predictive role of TyG index in NAFLD development, compared to HOMA-IR [8]. Moreover, TyG index was correlated with severe liver steatosis as well as with the presence of different degrees of liver fibrosis, assessed using transient elastography [9, 10].

The “gold standard” for the evaluation of liver lesions characteristic for NAFLD remains the liver biopsy, which appreciates the subtypes, the severity, and the progression of liver disease, and also the presence of liver fibrosis [11]. Liver biopsy is an invasive painful method, which has many disadvantages, ranging from bleeding to death in rare cases, limiting the clinical utility of this technique, therefore newer non-invasive tests are studied to improve the diagnosis of chronic liver diseases. Furthermore, the ideal non-invasive test should consider the metabolic components of NAFLD, being understandable why tests that also evaluate insulin resistance are proposed for the study of NAFLD progression [12].

Aim

The aim of this study was to establish the links between TyG index, assessing insulin resistance, and histopathological (HP) lesions of liver samples obtained by liver biopsy in patients with metabolic syndrome.

Patients, Materials and Methods

We conducted an epidemiological, cross-sectional, non-interventional study over a period of three years (2018–2020) that included 113 adult patients with metabolic syndrome, in whom hepatic disorders were assessed by liver biopsy. The study used the following inclusion criteria: patients aged over 18 years old, that accepted liver biopsy and met at least three criteria for metabolic syndrome. Patients that reported important alcohol consumption and patients diagnosed with different liver diseases were excluded from the study.

All the participants enrolled in the study signed the informed consent form. The study was conducted in accordance with the ethical principles, stipulated in the Helsinki Declaration, in accordance with good clinical practice, respecting the right to integrity, confidentiality, following approval granted by the Medical Ethics Committee of the Filantropia Municipal Hospital of Craiova, Romania (Approval No. 18086/07–11–2017).

We registered the demographic characteristics, clinical findings, and laboratory findings for all the patients included in the study. Waist circumference, weight and height were measured in all the patients, body mass index (BMI) was calculated, and patients were classified accordingly into normal weight (BMI <25 kg/m²), overweight (BMI ≥25 kg/m² and <30 kg/m²) and obese (BMI ≥30 kg/m²). The mean value of the three blood pressure measurements was recorded in the study database.

The laboratory tests performed in this study were fasting plasma glucose (FPG), lipid profile and liver enzymes.

TyG index was calculated to assess insulin resistance, using the formula reported in the medical literature [13].

The Menghini technique was used for liver biopsy, to establish the presence and the degree of liver steatosis, necro-inflammatory activity, and fibrosis. Percutaneous liver biopsy was performed in the intercostal space corresponding to the maximum liver dullness, between the anterior and posterior axillar lines. Biopsy samples of at least 2.5 cm were taken and they were fixed in 10% formalin to impair the destruction of the hepatocytes and to prepare the tissues for adequate staining. The tissue was fixed for 36–48 hours, at the temperature of 20–25°C, afterwards being washed out for 30 minutes in running water. The processed samples were embedded in paraffin. 3–5 μm slices were performed at the microtome and then processed with Hematoxylin–Eosin (HE) and Goldner–Szekely (GS) trichrome staining.

The degree of the liver steatosis, necro-inflammation and fibrosis was established according to Kleiner’s & Brunt’s classification (2005) [14], staging of steatosis (S) ranging from absent (S0) to severe (S3), inflammation (I) from I0 to I3 and fibrosis (F) being quantified from stage F0 to F4. The NAFLD activity score (NAS) [15] ranging from 0 to 8 was calculated for all the analyzed samples, defining NASH as a NAS score equal or greater than 5, NAS scores of 3 to 4 including the patients in borderline NASH, NAS scores equal or less than 2 being suggestive for the absence of NASH.

All the registered data were statistically analyzed using one-way analysis of variance (ANOVA) test of the Statistical Package for the Social Sciences (SPSS) software, version 26.0 (SPSS Inc., Chicago, IL, USA). The statistical significance was considered for *p*-value <0.05, while high statistical significance was defined as *p*<0.0001.

Results

The patients enrolled in the study (41 males and 72 females) were aged between 24 and 79 years old. Considering the metabolic syndrome criteria, the mean value of waist circumference was 105.41±12.02 cm in men, 101.94±33.23 cm in females, the mean value of triglycerides was 107.98±27.57 mg/dL and the mean value for HDL–cholesterol was 48.01±1.62 mg/dL. A number of 68 (60.16%) patients had arterial hypertension in their personal medical history, while 43 (38.05%) patients had type 2 diabetes. Most of the patients were overweight with a mean BMI of 27.45±3.16 kg/m². TyG index had a mean value of 9.02±0.5 in females and a mean value of 8.88±0.03 in males. The clinical and biological parameters of the studied patients are summarized in Tables 1 and 2.

The comparative analysis of TyG index in term of ponderal status, showed a mean value of 9.07±0.14 in patients with obesity, 8.91±0.03 in patients with overweight and 8.48±0.87 in the patients with normal weight, the differences reaching statistical significance (*p*<0.0001).

Table 1 – Clinical parameters of the patients

Parameter	Mean ± SD
Age [years]	51.57±4.14
Waist circumference in males [cm]	105.41±12.02
Waist circumference in females [cm]	101.94±33.23
BMI [kg/m ²]	30.55±17.17
Blood pressure [mmHg]	145/90

BMI: Body mass index; SD: Standard deviation.

Table 2 – Biological parameters of the patients

Parameter	Mean ± SD
Triglycerides [mg/dL]	164±105.14
FPG [mg/dL]	107.98±27.57
ALT [U/L]	35.09±21.92
AST [U/L]	44.41±39.03
TyG index	8.83±1.45

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; FPG: Fasting plasma glucose; SD: Standard deviation; TyG: Triglyceride and glucose.

Liver biopsy samples were analyzed, establishing the degree of liver steatosis, inflammation, degenerative ballooning and fibrosis.

Liver steatosis (Figure 1) was recognized by the accumulation of lipid drops in the hepatocyte, pushing the nucleus to the cell periphery. In the study group, the frequency of mild steatosis (S1) was 23%, moderate steatosis (S2) was observed in 42.47% of the patients, 27.43% of the patients being diagnosed with severe steatosis (S3). Only 7.07% of the patients presented less than 5% steatosis on the liver samples analyzed. Patients with S0 steatosis had a mean BMI of 25.56±4.24 kg/m², only four patients being overweight. However, all of them had a waist circumference above the upper limit.

Liver inflammation consisted of steatosis associated with intralobular inflammatory infiltration (Figure 2) and was identified in 54.86% of the patients enrolled in the study, 33.62% presenting mild inflammation (I1), 18.58%

showing moderate inflammation (I2) and in 2.65% of the analyzed patients, severe inflammation (I3) was described. 57.89% of the patients with mild inflammation were staging as moderate steatosis. They have a mean waist circumference of 105.85±29.69 cm in males and a mean value of 102.84±24.64 cm in females. From the other criteria for metabolic syndrome, the value of serum triglycerides ranged between 103 mg/dL and 293 mg/dL, with a mean value of 169±32.52 mg/dL and the mean value of HDL-cholesterol was 45.6±14.42 mg/dL.

Hepatocyte granulovacuolar degeneration (Figure 3) was observed in 49.55% of the patients, important ballooning (B2) being met in 16.81% of the cases. In all the cases, granulovacuolar degeneration was associated with moderate and severe steatosis. The B2 subgroup of patients fulfilled at least four criteria for metabolic syndrome, 68.48% of them being diagnosed with type 2 diabetes and 63.15% with arterial hypertension. The mean calculated BMI was 31.64±13.29 kg/m², 47.36% of these patients being overweight and 21.25% with third degree obesity. None of them presented normal BMI. The mean value of serum triglycerides was 182±20.2 mg/dL.

Fibrosis (Figure 4) was present in 53.09% of the subjects, with the predominance of periportal lesions (31.85%), corresponding to stage F1 fibrosis. None of the studied patients presented stage F4 fibrosis. The mean age of these patients was 54.6±38.18 years old, and the mean BMI was 31.11±1.41 kg/m².

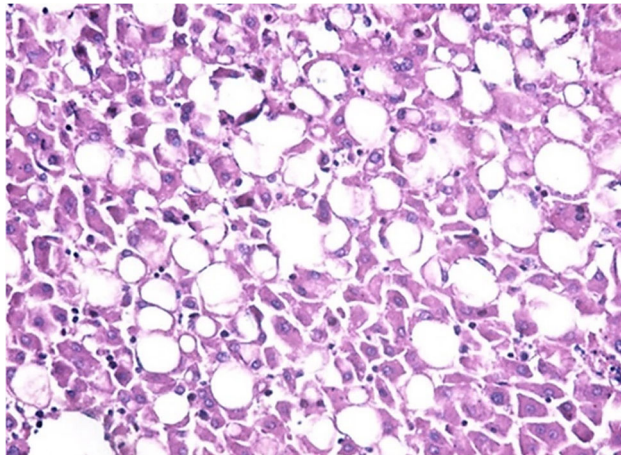


Figure 1 – Macrovesicular liver steatosis. HE staining, ×200. HE: Hematoxylin–Eosin.

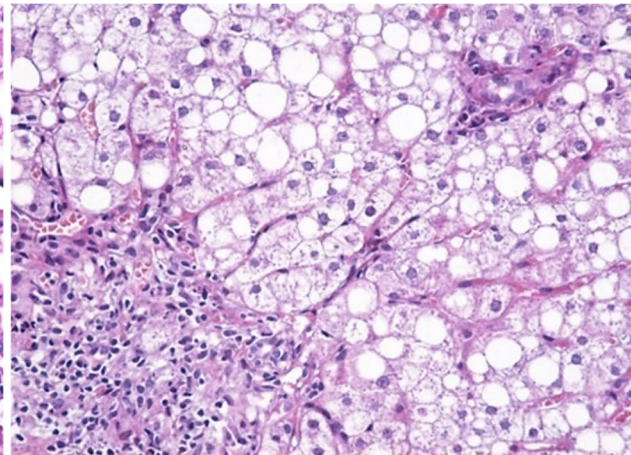


Figure 2 – Moderate intralobular inflammatory infiltrate. HE staining, ×200.

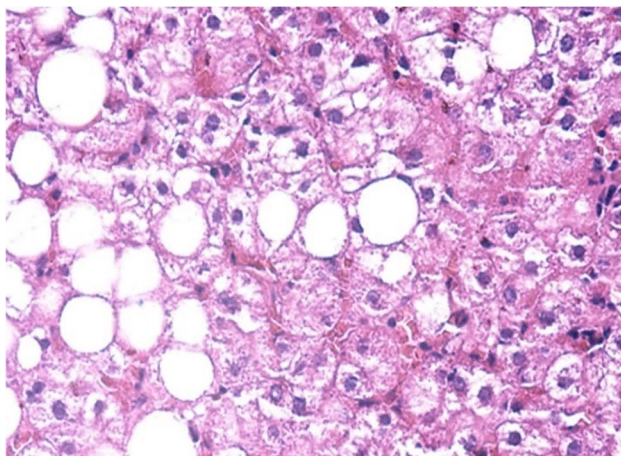


Figure 3 – Hepatocyte granulovacuolar degeneration on a liver steatosis background. HE staining, ×200.

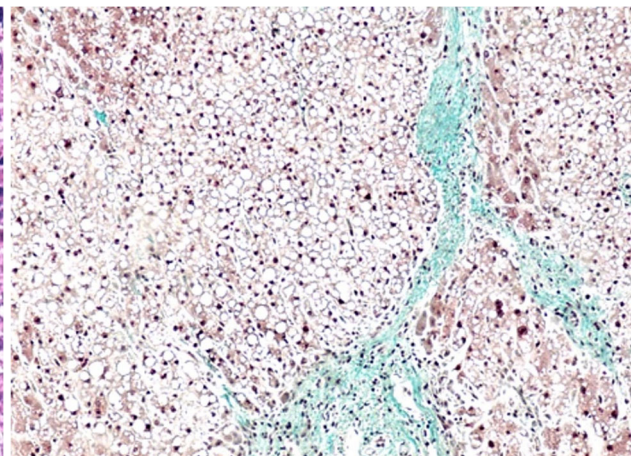


Figure 4 – Peri-portal and porto-central liver fibrosis. GS trichrome staining, ×100. GS: Goldner–Szekely.

Representing the sum of scores for steatosis, hepatocyte ballooning and lobular inflammation, NAS was calculated in all the patients. According to this score, in 33 (29.2%) patients we considered the diagnostic of NASH, "borderline NASH" was observed in 37 (32.74%) patients, while in 44 (38.05%) subjects NASH was excluded.

Regarding the biological assessment of liver function, only 37.16% of the patients had abnormal liver enzymes, with a mean value of 72.73 ± 18.2 U/L for alanine aminotransferase (ALT) and a mean value of 65.22 ± 30.9 U/L for aspartate aminotransferase (AST). The higher values of ALT were found in the patients with severe steatosis (53.41 ± 12.42 U/L), while the higher values of AST were detected in patients with stage F3 fibrosis (54.2 ± 30.3 U/L).

The TyG index was analyzed in relationship with the presence of liver lesions described by the anatomopathological exam, as well as with the NAFLD categories. Table 3 reports the associations between TyG index and the degree of liver steatosis (mean TyG index value for mild steatosis was 8.97 ± 0.02 , 8.97 ± 0.9 for moderate steatosis and 8.95 ± 0.81 for severe steatosis), lobular inflammation (mean TyG index value for mild lobular inflammation was 8.99 ± 0.07 , 9.07 ± 1.19 for moderate lobular inflammation and 8.92 ± 0.03 for severe lobular steatosis), ballooning (mean TyG index value for stage B1 hepatocyte ballooning was 8.92 ± 0.9 and 9.28 ± 0.5 for stage B2 hepatocyte ballooning) and fibrosis (mean TyG index value for mild fibrosis was 8.95 ± 0.08 , 9.32 ± 0.24 for moderate fibrosis and 9.35 ± 0.85 for severe fibrosis). We found statistically significant differences between TyG index according to the degree of hepatocyte ballooning ($p=0.01$) and a higher statistically significant difference between TyG index according to the degree of fibrosis ($p<0.0001$).

Regarding the relationship between TyG index and NASH, we analyzed the statistical differences between TyG index according to NAS, demonstrating a statistically significant difference ($p=0.04$), presented in Table 4, the higher TyG index mean value being met in patients with $NAS \geq 5$ (9.16 ± 0.98).

Table 3 – The relationship between TyG index and the degree of liver lesions

Histopathological lesion	Staging	TyG index (mean \pm SD)	F ANOVA	p ANOVA
Steatosis	S0	8.44 ± 0.23	1.282	0.284
	S1	8.97 ± 0.02		
	S2	8.97 ± 0.9		
	S3	8.95 ± 0.81		
Lobular inflammation	I0	8.82 ± 0.81	0.690	0.560
	I1	8.99 ± 0.07		
	I2	9.07 ± 1.19		
Hepatocyte ballooning	I3	8.92 ± 0.03	4.855	0.01
	B0	8.82 ± 0.10		
	B1	8.92 ± 0.9		
Fibrosis	B2	9.28 ± 0.5	28.613	<0.0001
	F0	8.73 ± 0.2		
	F1 (1a, 1b, 1c)	8.95 ± 0.08		
	F2	9.32 ± 0.24		
	F3	9.35 ± 0.85		

ANOVA: Analysis of variance; SD: Standard deviation; TyG: Triglyceride and glucose.

Table 4 – The relationship between TyG index and NAS

NAS	TyG index (mean \pm SD)	F ANOVA	p ANOVA
0–2	8.85 ± 0.34	3.324	0.04
3–4	8.81 ± 0.43		
≥ 5	9.16 ± 0.98		

ANOVA: Analysis of variance; NAS: Non-alcoholic fatty liver disease (NAFLD) activity score; SD: Standard deviation; TyG: Triglyceride and glucose.

Discussions

Many studies have described the liver lesions present in patients with metabolic diseases, such as obesity, type 2 diabetes and metabolic syndrome, showing an important triglyceride accumulation in the liver, explaining why NAFLD, an important public health issue, is regarded also as an obesity-associated disease [16, 17].

The prevalence increasing trend described for obesity and type 2 diabetes is also met for the prevalence of NAFLD. It is estimated that NAFLD affects 20–40% of the general adult population, reaching 73–92% in subjects that present obesity [18]. Studies performed in subjects with obesity that underwent bariatric surgery and in whom liver biopsy was performed, reported a prevalence of liver steatosis ranging between 84% to 96%, 25–50% of the subjects presented lesions characteristic for NASH, 34–47% presented incipient fibrosis, while 2–12% presented bridging fibrosis and cirrhosis [19]. Regarding NASH, its prevalence is estimated at 2–7% of the general population, 34–40% in the patients with elevated transaminases levels and in the absence of viral hepatitis markers, reaching 37% in patients with morbid obesity, but not all these data were pathologically confirmed [20]. The real evaluation of the progression of fibrosis in NASH patients is limited by the fact that most of the studies are retrospective and only a small percentage of patients underwent liver biopsy during the study follow-up. Regardless of the presence of HP lesions of NASH, other predictive factors for the progression of liver fibrosis were also reported, including obesity, type 2 diabetes, ages over 45 years old, arterial hypertension, elevated ALT, triglycerides, and iron levels [21]. Other studies reported advanced liver fibrosis in 6.6% in patients with moderate or severe steatosis, numbers that almost doubled in patients with metabolic syndrome, reaching 30% in the patients that met all the five metabolic syndrome criteria [22].

In our study, steatosis had a frequency of 92.03%, being identified 26 (23%) cases with mild steatosis, 48 (42.47%) with moderate steatosis and 31 (27.43%) with severe steatosis. Furthermore, our results show a high percentage of liver steatosis in patients with normal BMI, explained by the fact that all the subjects include in the study met at least three metabolic syndrome criteria. The patients with normal BMI presenting liver steatosis had an abdominal circumference above the normal limit, evocative for visceral obesity, implying fat accumulation in the liver. Additionally, even subjects with normal BMI in the presence of abdominal obesity are at an increased risk for NAFLD development [23].

Studies proved that TyG index, a non-invasive marker of insulin resistance, is a good predictor for NAFLD [23, 24], demonstrating an association of fatty liver with TyG

index values above 8.5–8.85 [23, 25]. We found a TyG index mean value of 8.83 ± 1.45 .

Regarding NASH, the frequency of this disorder in our study group was 29.2% in the subjects with liver steatosis, while liver fibrosis had a frequency of 53.09%. We found no statistically significant difference between TyG index values analyzed according to the degree of liver steatosis ($p=0.284$). Other studies that assessed liver steatosis using non-invasive methods reported an association between TyG index and the severity of steatosis, explaining the lack of difference found in our study [26]. In this study, 7.07% of the patients had steatosis less than 5% on the examined samples, having a mean TyG index of 8.44 ± 0.23 , comparable to cut-off values reported in other studies [27].

When we analyzed the relationships between TyG index and the presence of each type of lesion necessary for NASH diagnosis, we obtained statistically significant differences for the presence of hepatocyte ballooning ($p=0.01$) and a high statistical significance for the NAS ($p<0.0001$). The limitation of our study was represented by the small number of patients with definite NASH, impeding us to establish a cut-off value for TyG index that could be used in clinical practice, further studies including a higher number of patients being necessary to achieve this desiderate.

The mean value of TyG index in patients with liver fibrosis described by the HP exam was 9.10 ± 2.25 and the highest value obtained in this group was 10.63. The patients that did not present fibrosis had a mean TyG index value of 8.73 ± 0.2 , between the two subgroups of patients identifying high statistically significant differences ($p<0.0001$). TyG index is a useful biological parameter for the evaluation of fibrosis progression, especially taking into consideration that this index was associated with liver fibrosis even in studies that assessed the presence of fibrosis using non-invasive tests [26, 28].

While chronic liver disease from chronic hepatitis B or C is declining, NASH is on the rise and is expected to become a global health problem in the coming years [29–31].

Conclusions

The HP exam performed after liver biopsy allowed us to assess a simple non-invasive test associated with liver steatosis, NASH and fibrosis in patients with metabolic syndrome. Our study proved an association between TyG index as a marker of insulin resistance and HP lesions of NAFLD. The most important association was between the TyG index and increasing severity of liver fibrosis. TyG index, an independent risk factor for liver fibrosis, is a facile tool that can be used to identify patients at risk for advanced NAFLD lesions, helping the clinician to implement early prevention measures in patients at risk for liver disease progression.

Conflict of interests

The authors declare no conflict of interests.

Institutional Review Board statement

The study was conducted according to the Guidelines of the Declaration of Helsinki in accordance with good clinical practice, respecting the right to integrity, confidentiality, the option of the subject to withdraw from the study at any time.

Informed consent statement

Informed consent was obtained from all subjects involved in the study.

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Corresponding authors

Ionela Mihaela Vladu, Assistant Professor, MD, PhD, Department of Diabetes, Nutrition and Metabolic Diseases, University of Medicine and Pharmacy of Craiova, 2 Petru Rareș Street, 200349 Craiova, Romania; Phone +40763–670 811, e-mails: ionela.vladu@umfcv.ro, mihmitzu@yahoo.com

Octavian Ion Predescu, Lecturer, MD, PhD, Department of Nursing, Faculty of Nursing, Târgu Jiu Subsidiary, Titu Maiorescu University, Bucharest, 100 Ecaterina Teodoroiu Avenue, 210106 Târgu Jiu, Romania; Phone +40766–219 418, e-mail: octavian_predescu@yahoo.com

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