| Fişa suspiciunii de plagiat / Sheet of plagiarism's suspicion | Indexat la: 100/07 |
|---|---|

| Opera suspicionată (OS)<br>Suspicious work | Opera autentică (OA)<br>Authentic work |
|---|---|

| | |
|---|---|
| OS | PANTEA, I; LEAŞU, T. Non-alcoholic steatohepatitis – a possibile definition criterion for metabolic syndrome. *Bulletin of the Transilvania University of Braşov*, Series VI: Medical Sciences, 2009, Vol. 2, No.51, p.81-86. |
| OA | MARCHESINI, G.; BUGIANESI, E.; FORLANI, G.; CERRELLI, F.; LENZI, M.; MANINI, R.; NATALE, S.; VANNI, E.; VILLANOVA, N.; MELCHIONDA, N. and RIZZETTO, M. Nonalcoholic Fatty Liver, Steatohepatitis, and the Metabolic Syndrome. *Hepatology*, April 2003, Vol. 37, No. 4, p.917-923. |

| Incidența minimă a suspiciunii / Minimum incidence of suspicion | |
|---|---|
| p.81:01s-p.81:09s | p.917:01s-p.917:06s |
| p.81:09d-p.81:18s | p.917:01d – p.917:07d |
| p.81:01d-p.81:06d | p.917:08d-p.917:11d |
| p.81:07d-p.81:21d | p.917:13d – p.918:01s |
| p.82:01s-p.82:13s | p.918:04s-p.918:06s;p.918:12s-p.918:18s |
| p.82:14s-p.82:41s | p.918:19s – p.918:18d |
| p.82:42s-p.82:11d | p.919:01s-p.919:09s |
| p.82:12d-p.82:32d | p.919:14s-p.919:29d |
| p.82:33d-p.83:06s | p.919:40s-p.920:19s |
| p.83:Fig.1 | p.920:Fig.1 |
| p.83:Fig.2 | p.920:Fig.2 |
| p.84:Fig.1 | p.920:Fig.3 |



Sursa de informație primară: http://antiplagiarism2014blog.wordpress.com.

## *Retraction of articles:*

1. **PANTEA, I.; LEASU, T. NON-ALCOHOLIC STEATOHEPATITIS–A POSSIBILE DEFINITION CRITERION FOR METABOLIC SYNDROME.** ***Bulletin of the Transilvania University of Braşov, Series VI: Medical Sciences*****, 2009, 2: 51, 81:86**

**Autorii au solicitat retragerea articolelor publicate in B*ulletin of the Transilvania University of Brasov, Series VI: Medical Sciences* datorită faptului că articolele sunt sub suspiciunea de plagiat.**

**Comitetul ştiinţific a decis retragerea acestor articole la cererea autorilor, decizie validata şi în Consiliul Facultăţii de Medicină din 25.06.2013.**

**Braşov**

**25.06.2013**

Bulletin of the *Transilvania* University of Braşov • Vol. 2 (51) - 2009
Series VI: Medical Sciences

# NON-ALCOHOLIC STEATOHEPATITIS – A POSSIBILE DEFINITION CRITERION FOR METABOLIC SYNDROME

**I. PANTEA[1]** **T. LEASU[1]**

***Abstract*:** *A frequency evaluation of diseases associated with steatohepatitis in order to propose including non-alcoholic steatohepatitis (NASH) among the definition criteria for the metabolic syndrome. A screening study has been carried out including patients who had been admitted for 2 months to the Astra Medical Clinic within the Clinic Emergency Hospital in Braşov. The study included 59 patients diagnosed with non-alcoholoc steatohepatitis (29 women and 30 men) between 40 - 80 of age. These preliminary results lead us to the idea that non-alcoholic steatohepatitis might be another definition criterion for the metabolic syndrome.*

***Key words:*** *Non alcoholic steatohepatitis, metabolic syndrome, nonalcoholic fatty liver disease.*

## 1. Introduction

There is a growing concern for nonalcoholic fatty liver disease (NAFLD) in clinical hepatology. A recent survey indicates that NAFLD may account for approximately 80% of cases with elevated liver enzyme levels in the American population, and that 1 in 4 or 5 American adults actually has NAFLD [5], [8]. Although in most cases fatty liver does not progress to more severe liver diseases, approximately 20% to 30% of patients have histologic signs of fibrosis and necroinflammation, indicating the presence of non-alcoholic steatohepatitis (NASH) [2], [6], [17], [20].

These patients are at higher risk of developing cirrhosis, [19] terminal liver failure, [19] and hepatocellular carcinoma [4].

NAFLD is mainly associated with obesity, [15], [25] diabetes, [2], [15], [20] hyperdyslipemia, [2], [6], [13], [16] and insulin resistance, [16], [22] which are the main features of the recently characterized metabolic syndrome [1].

Only recently, the Third Report of the National Cholesterol Education Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III [ATPIII]) [7] has provided a working definition of the metabolic syndrome, based on a combination of 5 categorical and discrete risk factors (central obesity, hypertension, hypertriglyceridemia, low levels of high-density lipoprotein [HDL]-cholesterol, and hyperglycemia), derived from the guidelines of the International Societies or the statements of World Health Organization [1], [7], [10].

[1] Faculty of Medicine, *Transilvania* University of Brasov.

The metabolic syndrome is highly prevalent in the general population (approximately 22%), with differences in relation to race, gender, and age [9]. The aim of the present report is 2-fold:

(1) to measure the prevalence of the metabolic syndrome, based on predefined ATPIII criteria, in a large series of NAFLD patients without overt diabetes; and (2) to verify whether the presence of multiple metabolic disorders, as in the case of metabolic syndrome, carries a higher risk of the potentially progressive NASH.

## 2. Materials and Methods

In the period from September 2008 to December 2008 101 NAFLD patients without a previous diagnosis of diabetes mellitus were consecutively observed. Patients had either been referred to a liver unit for a comprehensive assessment of a previously detected liver disease or were found to have elevated aminotransferase levels during a screening of patients attending a unit for metabolic diseases for a weight-reducing program. All cases had chronic hypertransaminasemia (alanine aminotransferases [ALT] > 1.5X upper normal values for 3 months or more), negative hepatitis B and C viral markers, absence of autoantibodies indicative of autoimmune hepatitis or celiac disease, and negative or negligible alcohol consumption (<140 g/wk). Alcohol abuse was also excluded by interviewing patients' relatives.

All cases underwent a complete clinical, anthropometric, and laboratory investigation and an ultrasound scan of the liver. Brightness and posterior attenuation were considered indices of the extent of fatty infiltration and fibrosis [23].

The five components of the metabolic syndrome were available in all patients, and subjects having three or more of the following criteria were labelled as metabolic syndromes 23: (1) fasting glucose >110 mg/dL; (2) central obesity (waist circumference >102 cm [men] and >88 cm [women]); (3) blood pressure >130/85 mm Hg or pharmacologically treated; (4) triglyceride levels >150 mg/dL or current use of fibrates; and (5) HDL-cholesterol <40 mg/dL (men) and <50 mg/dL (women).

Body weight was measured in light clothing and without shoes to the nearest half kilogram. Height was measured to the nearest half centimetre. Body mass index (BMI) was calculated as weight (kg) divided by height (m). Waist circumference (at the nearest half centimetre) was measured at the midpoint between the lower border of the rib cage and the iliac crest, whereas hip circumference was similarly obtained at the widest point between hip and buttock.

Three blood pressure readings were obtained at 1-minute intervals, and the second and third systolic and diastolic pressure readings were averaged and used in the analyses.

Plasma glucose, both in the fasting state and in response to a standard glucose load, was measured in duplicate with an automated analyzer.

Liver biopsy was scored according to Brunt et al., [3] with minor modifications. The amount of fat, always present in our biopsies, was graded 1 to 3, according to the percentage of cells with fatty droplets (1, 0%-33%; 2,34%-66%; 3, 67%-100%). Fibrosis was graded 0 (absent) to 4 (1, perisinusoidal/ pericellular fibrosis; 2, periportal fibrosis; 3, bridging fibrosis; 4, cirrhosis).

Necroinflammation was graded 0 (absent) to 3 (1, occasional ballooned hepatocytes and no or very mild

inflammation; 2, ballooning of hepatocytes and mild-to-moderate portal inflammation; 3, intra-acinar inflammation and portal inflammation). NASH was defined by the presence of fibrosis (grade 1 or more) or necroinflammation (grade 2 or more).

## 3. Results

There were significant differences in clinical, laboratory, and anthropometric data in relation to gender. Female patients were older, had a higher BMI and higher blood glucose, arterial pressure, and transaminase levels

The prevalence of positive criteria for the metabolic syndrome was exceedingly variable in the whole population, ranging from 11% (hyperglycemia, men) to 77% (hypertension, women). According to increased BMI class (Fig.1), hyperglycemia nearly doubled from 20% to 40% (P=.120), hypertriglyceridemia was as high as 80% (P= .002), a low HDL-cholesterol level was present in 59% of cases and the arterial pressure criteria were fulfilled in 90% of cases.

Finally, waist circumference exceeded the threshold for abdominal obesity in the large majority of obese patients, but also in 42% of overweight subjects and 6% of patients with normal BMI.

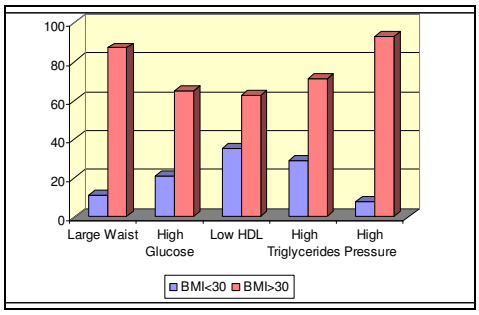


Fig. 1. *Prevalence of metabolic alterations fitting the criteria of the metabolic syndrome in patients with NAFLD*

Only a few patients did not satisfy any criteria of the metabolic syndrome (Fig. 2).

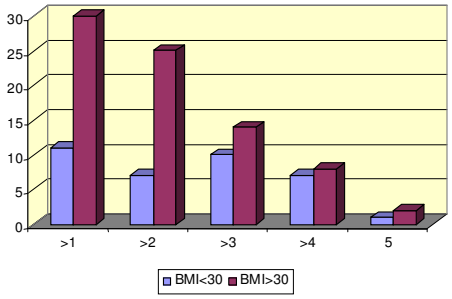


Fig. 2. *Prevalence of positive criteria for the metabolic syndrome in patients with NAFLD*

The cumulative presence of positive criteria was diagnostic for the metabolic syndrome (3 or more criteria) in (10% of normal weight subjects, and 12% obese). In 7 cases (2.3%, 2 normal weight, 5 obese) all 5 criteria were fulfilled. The prevalence of the metabolic syndrome also increased with increasing age (26% in subjects aged less than 40 years to 45% in subjects aged 40 or more; P=.0005).

The presence of the metabolic syndrome was significantly associated with female sex (OR, 3.08; 95% CI, 1.57-6.02) and age (OR, 1.54; 95% CI, 1.23-1.93 per 10 years) after adjustment for BMI class. Among individual criteria for the metabolic syndrome, only the prevalence of large waist was different and lower in the liver biopsy group (50% vs. 70%; P=.038, Fisher's exact test) (Fig.3), but the overall prevalence of the metabolic syndrome was not different (47% in liver biopsy patients vs. 53%; P=.151).

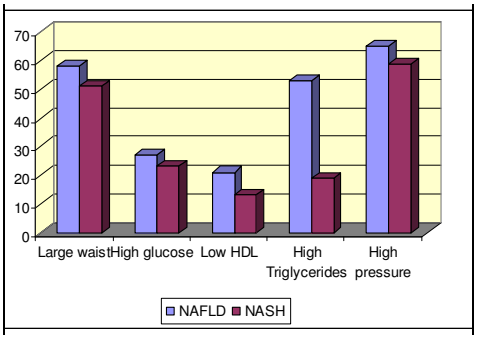


Fig. 3. *Prevalence of positive criteria for the metabolic syndrome in NAFLD and NASH patients*

However, NASH patients had a more severe metabolic disorder and a larger prevalence of criteria for the metabolic syndrome, compared with subjects with pure fatty liver (Table 1).

Table 1

*Clinical and laboratory data in patients with NAFLD and NASH*

| | NAFLD | NASH | P |
|---|---|---|---|
| Enlarged waist circumference | 57% | 73% | =0.037 |
| Hypertension | 53% | 72% | =0.011 |
| HDL cholesterol | 57% | 76% | =0.019 |
| Hypertriglyceridemia | 58% | 72% | =0.054 |
| Hyperglycemia | 60% | 91% | =0.004 |

## 4. Discussion

The present report further highlights the association of NASH with features of the metabolic syndrome. Obesity, diabetes, hypertension, and hyperlipidemia have been repeatedly reported in NAFLD, but their simultaneous presence significantly increases the risk of more severe stages of liver disease.

A correct identification of subjects with the metabolic syndrome is mandatory, because these patients are generally at higher risk of cardiovascular disease, [11], [14] particularly in the presence of diabetes [12]. Considering that the median age of our patients was 40 years old, the prevalence of the metabolic syndrome may be approximately doubled in NAFLD compared with the general population.

The presence of the metabolic syndrome was significantly associated with insulin resistance. A central role for insulin resistance in the pathogenesis of NAFLD is supported by physiopathologic considerations, clinical association, and laboratory investigations.

The prevalence of individual criteria for the metabolic syndrome was not systematically different in patients who received a liver biopsy, who were fairly representative of the whole series. It is also possible that only cases with more severe or more prolonged forms of liver disease were seen at specialized centers, thus increasing the relative prevalence of NASH. This conclusion is supported by significant differences in enzyme levels between pure fatty liver and NASH.

In obesity, ALT levels did not predict the extent of histologic severity of liver disease [21]; in a previous series of NAFLD, aminotransferase levels did not differ in relation to the severity of steatosis, necroinflammatory infiltration, and fibrosis [24]. Accordingly, aminotransferase levels cannot be confidently used as surrogate markers of disease in intervention studies, which constitutes a severe limit in the assessment of the effects of lifestyle changes, dieting, and drugs on disease progression.

The association of the metabolic syndrome with NASH and with more severe necroinflammatory activity and fibrosis is particularly relevant in epidemiologic terms. The prevalence of obesity is dramatically increasing in the western world, assuming the character of an epidemic [26].

Obesity in turn increases the prevalence of diabetes, [18] dyslipidemia, hypertension, and ultimately of the metabolic syndrome. Our analysis underlines the existence of an exceedingly large population at risk of forthcoming liver failure in the next decades, provided they survive the burden of cardiovascular disease mortality [14].

## References


1. Alberti, K.G.; Zimmet, P.Z. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus. Provisional report of a WHO consultation. In: *Diabet Med* 1998;15, p. 539-553.
2. Bacon, B.R.; Farahvash, M.J.; Janney, C.G.; Neuschwander-Tetri, B.A. Nonalcoholic steatohepatitis: an expanded clinical entity. In: *Gastroenterology* 1994;107, p. 1103-1109.
3. Brunt EM, Janney CG, Di Bisceglie AM, Neuschwander-Tetri BA, Bacon BR. Nonalcoholic steatohepatitis: a proposal for grading and staging the histological lesions. Am J Gastroenterol 1999;94, p. 2467-2474.
4. Bugianesi, E.; Leone, N.; Vanni, E.; Marchesini, G.; Brunello, F.; Carucci, P.; Musso, A. et al. Expanding the natural history of nonalcoholic steatohepatitis: From cryptogenic cirrhosis to hepatocellular carcinoma. In: *Gastroenterology* 2002;123, p.134-140.
5. Clark, J.M.; Brancati, F.L.; Diehl, A.M. Nonalcoholic fatty liver disease. In: *Gastroenterology* 2002;122, p. 1649-1657.
6. Dieh, A.M.; Goodman, Z.; Ishak, K.G. Alcohollike liver disease in nonalcoholics. A clinical and histologic comparison with alcohol-induced liver injury. In: *Gastroenterology* 1988; 95, p. 1056-1062.
7. Expert Panel on Detection Evaluation and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). In: *JAMA* 2001;285, p. 2486-2497.
8. Falck-Ytter, Y.; Younossi, Z.M.; Marchesini, G.; McCullough, A.J. Clinical features and natural history of nonalcoholic steatosis syndromes. In: *Semin Liver Dis* 2001;21, p. 17-26.
9. Ford, E.S.; Giles, W.H.; Dietz, W.H. Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. In: *JAMA* 2002;287, p. 356-359.
10. Guidelines Subcommittee. 1999 World Health Organization-International Society of Hypertension Guidelines for the Management of Hypertension. In*: J Hypertens* 1999;17, p. 151-183.
11. Isomaa, B.; Almgren, P.; Tuomi, T.; Forsen, B.; Lahti, K.; Nissen, M.; Taskinen, M.R. et al. Cardiovascular morbidity and mortality associated with the metabolic syndrome. In: *Diabetes Care* 2001;24, p. 683-689.
12. Isomaa, B.; Henricsson, M.; Almgren, P.; Tuomi, T.; Taskinen, M.R.; Groop, L. The metabolic syndrome influences the risk of chronic complications in patients with type II diabetes. In: *Diabetologia* 2001;44, p. 1148-1154.
13. Itoh, S.; Yougel, T.; Kawagoe, K. Comparison between non-alcoholic steatohepatitis and alcoholic hepatitis. In: *Am J Gastroenterol* 1987;82, p. 650-654.

14. Lakka, H.M.; Laaksonen, D.E.; Lakka, T.A.; Niskanen, L.K.; Kumpusalo, E.; Tuomilehto, J.; Salonen, J.T. The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. In: *JAMA* 2002;288, p. 2709-2716.
15. Lee, R.G. Nonalcoholic steato-hepatitis: a study of 49 patients. In: *Hum Path* 1989;20, p. 594-598.
16. Marchesini, G.; Brizi, M,; Morselli-Labate, A.M.; Bianchi, G.; Bugianesi, E.; McCullough, A.J.; Forlani, G. et al. Association of nonalcoholic fatty liver disease with insulin resistance. In: *Am J Med* 1999;107, p. 450-455.
17. Matteoni, C.A.; Younossi, Z.M.; Gramlich, T.; Boparai, N.; Liu, Y.C.; McCullough, A.J. Nonalcoholic fatty liver disease: a spectrum of clinical and pathological severity. In: *Gastroenterology* 1999; 116, p. 1413-1419.
18. Mokdad, A.H.; Ford, E.S.; Bowman, B.A.; Dietz, W.H.; Vinicor, F,; Bales, V.S.; Marks, J.S. Prevalence of obesity, diabetes, and obesity-related health risk factors, 2001. JAMA 2003;289, p. 76-79.
19. Poonawala, A.; Nair, S.P.; Thuluvath, P.J. Prevalence of obesity and diabetes in patients with cryptogenic cirrhosis: a case-control study. In: *HEPATOLOGY* 2000; 32, p. 689-692.
20. Powell, E.E.; Cooksley, W.G.; Hanson, R.; Searle, J.; Halliday, J.W.; Powell, L.W. The natural history of nonalcoholic steatohepatitis: a follow-up study of forty-two patients for up to 21 years. In: *HEPATOLOGY* 1990;11, p. 74-80.
21. Ratziu, V.; Giral, P.; Charlotte, F.; Bruckert, E.; Thibault, V.; Theodorou, I.; Khalil, L. et al. Liver fibrosis in overweight patients. In: *Gastroenterology* 2000; 118, p. 1117-1123.
22. Sanyal, A.J.; Campbell-Sargent, C.; Mirshahi, F.; Rizzo, W.B.; Contos, M.J.; Sterling, R.K.; Luketic, V.A. et al. Nonalcoholic steatohepatitis: association of insulin resistance and mitochondrial abnormalities. In: *Gastroenterology* 2001; 120, p. 1183-1192.
23. Saverymuttu, S.H.; Joseph, A.E.; Maxwell, J.D. Ultrasound scanning in the detection of hepatic fibrosis and steatosis. In: *Br Med J* 1986; 292, p. 13-15.
24. Sonsuz, A.; Basaranoglu, M.; Ozbay, G. Relationship between amino-transferase levels and histopathological findings in patients with nonalcoholic steatohepatitis. In: *Am J Gastroenterol* 2000; 9:5, p. 1370-1371.
25. Wanless, I.R.; Lentz, J.S. Fatty liver hepatitis (steatohepatitis) and obesity: an autopsy study with analysis of risk factors. In: *HEPATOLOGY* 1990;12, p. 1106-1110.
26. World Health Organization. Preventing and managing the global epidemic: report of a WHO consultation. World Health Organization WHO Technical Report Series, 894, 2000.