Indian Journal of Basic and Applied Medical Research; December 2022: Vol.-12, Issue- 1 , P. 33-38
DOI: 10.36855/IJBAMR/2022/98215.55547

Original article:

Non-Alcoholic Fatty Liver Disease (NAFLD): A review of pathophysiology with Clinical correlation Grade 1 and Grade 2 NAFLD

***Jaspreet Kaur Gujral [1] , Dr. Busi Karunanand [1] , Dr. Monu Sarin[2], Dr. Abhishek Gaurav [3] , Preeti Kashyap[4]**

[1] Department of Biochemistry SGT Medical College, Hospital and Research Institute Budhera, Gurugram
[2] Department of Radiology SGT Medical College, Hospital and Research Institute Budhera, Gurugram
[3] Department of Medicine SGT Medical College, Hospital and Research Institute Budhera, Gurugram
[4] Department of Biochemistry SGT Medical College, Hospital and Research Institute Budhera, Gurugram
Corresponding author*

Abstract

Non-alcoholic fatty liver disease (NAFLD) is one of the most chronic hepatic diseases in the world and occurs in about 25% of individuals worldwide. It is considered as the manifestation of metabolic syndrome in liver, and its development and progression is influenced by complex interaction of environmental and genetic factors. In this review we discuss the pathophysiology, risk factors, imaging in NAFLD, differential diagnoses, and the commonly used grading and staging systems of NAFLD. Diagnosis of NAFLD is defined as presence of hepatic steatosis, ballooning and lobular inflammation with or without fibrosis. Weight loss, dietary modification, and the treatment of underlying metabolic syndrome remain the mainstays of therapy once the diagnosis is recognized. Dietary recommendations and lifestyle interventions, weight loss, and the treatment of underlying metabolic syndrome remain the mainstays of therapy once the diagnosis is established with promising results but are difficult to maintain.

Keywords: NAFLD, Non-alcoholic fatty liver disease, Weight management, Fatty liver, Non-alcoholic steatohepatitis, metabolic syndrome, fibrosis.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is a common cause of chronic liver disease worldwide. NAFLD means without significant alcohol intake which defined as less than approximately 30 g/day for women and 40 g/day for men by the American Association for the Study of Liver Disease (AASLD) **[1]** In NAFLD, hepatic steatosis is present without evidence of inflammation, whereas in NASH, hepatic steatosis is present with lobular inflammation and apoptosis that can lead to fibrosis and cirrhosis **[2]**. NAFLD is becoming more common chronic liver disease in Western industrialized countries, particularly in patients with central obesity, T2DM, dyslipidaemia, and metabolic syndrome**[3]**.

Epidemiology

The prevalence of NAFLD varies among different populations and is influenced by the methods of diagnosis, includes serum biochemistry, imaging and histologic examination. The prevalence of liver disease (NAFLD) has risen rapidly in Western countries, with a worldwide prevalence of 25% **[3]**. The global prevalence of NAFLD diagnosed by imaging was reported to be 25.24%. The highest prevalence was in Middle East (37.19%) and

South America (30.45), followed by Asia (27.17%), North America (24.13%), Europe (23.17%) and Africa (13.48%) **[4]**.

The World Health Organization Global Health Observatory data in 2014 indicates that globally obesity occurs in 15% of women and 11% of men aged 18 and over **[5].**

Pathophysiology of Non- Alcoholic Fatty liver Disease

Pathophysiology of NAFLD mainly difference in dietary models (high fructose, high fat or methionine/ choline deficient diet (MCD) **[6]**. NAFLD can be divided into two distinct types. The first type of NAFLD has a narrow relationship with metabolic syndrome and the current beliefs are that insulin resistance is the primary pathophysiological mechanism. The second type of NAFLD has a relationship with infectious pathologies that can lead to the occurrence of liver steatosis. In this case infections like hepatitis C and HIV can be a cause, but it is also associated with medication (total parenteral nutrition, glucocorticoids, tamoxifen, tetracycline, amiodaron, methotrexate, valproic acid, vinyl chloride) and specific toxins or inherited/acquired metabolic diseases (e.g. lipodystrophy or cachexia or intestinal bypass surgery) **[7,8]**.

Risk Factors

People with NAFLD generally have characteristics of MS, with the associated cardiovascular disease risk factors **[9,10].** As stated earlier NAFLD related to metabolic syndrome and obesity, type 2 diabetes mellitus (T2DM), and dyslipidaemia are considered to be important risk factors for NAFLD **[11]**. NAFLD than without, with coronary, cerebrovascular and peripheral vascular disease was greater among those with NAFLD than among those without this disease, aside from normal CVD risk factors, medication use and diabetes-related variables **[12]**.

Smoking was considered an independent risk factor for the development of NAFLD **[13],** however, a cross-sectional study of 933 patients (368 smokers and 565 non-smokers as controls) found no difference in the prevalence of NAFLD in the two groups (22.2% versus 29%), nor with heavy smokers (> 20 packs of cigarettes per year) **[14]** .

Signs and symptoms

Patients with NAFLD do not experience any symptoms, however some of them may complain of fatigue, right upper quadrant discomfort, hepatomegaly, acanthosis nigricans, and lipomatosis. A significant amount of patients with cirrhosis can be present themselves with end-stage liver disease **[15]**. Although clinical related of chronic liver failure are rarely seen in this population, one study showed that at the time of diagnosis splenomegaly was present in 25% of the patients **[15]**.

Laboratory Findings

In patients with NAFLD, ALT elevations are more common than elevations of AST. The ALT levels tend to be higher in NASH than in simple steatosis. Elevated serum ferritin levels are commonly elevated in patients with NAFLD, and increased transferrin saturation is found in 6–11% of patients **[16-18].** Other markers of interest are alkaline phosphatase (ALP) and clotting factors. Although albumin and bilirubin levels may be high in patients who have developed chronic progressive disease. In cirrhotic patients laboratory measurements of clotting times can be abnormal. Most of the time patients who have developed cirrhosis have a prolonged prothrombin time, thrombocytopenia, and a concomitant neutropenia **[16-18]**.

Grading of NAFLD

In 1999 Brunt et al. first proposed a grading and staging system for NASH based on the liver biopsies from 51 adult patients **[19]**. A three-tiered grading system was built based on the compilation of steatosis, lobular and portal inflammation, and ballooning degeneration (Table A). Fibrosis is staged based on the location and extent. Stage 1 represents zone 3 perisinusoidal/pericellular fibrosis; stage 2 is assigned when there is stage 1 plus periportal fibrosis; bridging fibrosis is designated as stage 3; and stage 4 is established where there is evidence of cirrhosis (Table B).

Grade	Steatosis	Ballooning	Inflammation
1 (Mild)	1-2 (up to 66%)	Minimal	L: 1-2 P: None-mild
2 (Moderate)	2-3 (>33%, may be >66%)	Present	L: 2 P: Mild-moderate
3 (Severe)	2–3	Marked	L: 3 P: Mild-moderate

Steatosis Grade 1: ≤33%; Grade 2: >33% < 66%; Grade 3: ≥66%.
L (lobular): 0, None; 1, <2 foci/20X objective; 2, 2–4 foci/20X objective; 3, >4 foci/20X objective.
P: portal.

TABLE A

Stage	Zone 3, peri-sinusoidal	Portal-based	Bridging	Cirrhosis
1	Focal or extensive	0	0	0
2	Focal or extensive	Focal or extensive	0	0
3	Bridging septa	Bridging septa	+	0
4	±	±	Extensive	+

TABLE B

Imaging in NAFLD

In liver diseases such as NAFLD and NASH, various imaging modalities can be used to substantiate the diagnosis, however none of them are routinely used for differentiating between (histological) subtypes of NAFLD or NASH **[20].** Computed tomography (CT) scans, abdominal ultrasound (US), or Magnetic Resonance Imaging (MRI) can detect these liver diseases. Imaging findings in patients with NAFLD include increased echogenicity on ultrasound, decreased hepatic attenuation on CT, and an increased fat signal on MRI **[20].**

Ultrasound

The sensitivity and the specificity of US are respectively 89 and 93% in detecting increased fibrosis and steatosis **[21]**. However, the US is the cheapest method and has been the most common modality used in clinical practice. The sensitivity of US is decreased in patients with obesity **[22, 23]**. The US showing hyperechogenic liver tissue in contrast to the spleen or kidney echogenicity is suggestive of steatosis. However, the sensitivity of the US is only 60–94% in these instances **[24].**

Vibration-controlled transient Elastography (VCTE)

VCTE is a non-invasive method for excluding advanced fibrosis in measuring liver stiffness with VCTE **[25–27]**. A meta-analysis of 19 biopsy-controlled studies including over 2700 patients, the optimal cut-off value for steatosis grade > S0 was 248 dB/m (95% Confidence Interval (CI) 237-261) and for steatosis grade > S1 was 268 dB/m (95% CI 257-284) **[26]**.

CT, MRI, and magnetic resonance spectroscopy (MRS)

Both imaging modalities are able to detect steatosis, but lack sensitivity to detect inflammatory or fibrotic process of the liver **[27]**. Unfortunately MRS has a higher sensitivity to detect the earlier mentioned pathological processes it is (not yet) widely available **[28].** In general the sensitivity of CT, MRI and MRS to detect steatosis of the liver was 33, 50, and 88%, respectively. Specificity of all three for detection of hepatic steatosis was 100, 83, and 63%, respectively **[29-30]**.

Treatment

The treatment of NAFLD and related diseases (including but not limited to components of MS) consists of several tiers of which conservative and surgical therapies are known treatments. Very often the treatment of patients with NAFLD consists of a multimodal intervention targeting multiple aspects like weight loss, lifestyle modifications and possible medication optimisation.

Conclusions

With the growing obesity pandemic and the rising prevalence of comorbid conditions like T2DM and NAFLD, the management of these patients has become even more complex. There are some treatment methods, however there is lack of high-quality studies that compared different treatment methods with each other. Considering that bariatric surgery is an increasingly utilized, prospective study answering the remaining questions on the connection of insulin resistance, fatty liver, and fibrosis progression should become available in the near future.

References:

1. Chalasani N, Younossi Z, Lavine JE, Charlton M, Cusi K, Rinella M, et al. The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the American Association for the Study of Liver Diseases. Hepatology 2018; 67(1):328e57.
2. Machado MV, Diehl AM. Pathogenesis of nonalcoholic Steatohepatitis. Gastroenterology. 2016;150(8):1769–77.
3. Browning JD, Szczepaniak LS, Dobbins R, Nuremberg P, Horton JD, Cohen JC, et al. Prevalence of hepatic steatosis in an urban population in the United States: impact of ethnicity. Hepatology (Baltimore, Md). 2004;40(6):1387–95.
4. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver diseasedmeta-analytic assessment of prevalence, incidence, and outcomes. Hepatology 2016;64(1):73e84.
5. Edmison J, McCullough AJ. Pathogenesis of non-alcoholic steatohepatitis: human data. Clin Liver Dis. 2007;11(1):75–104, ix.
6. Lau JK, Zhang X, Yu J. Animal models of non-alcoholic fatty liver disease: current perspectives and recent advances. J Pathol. 2017;241(1):36–44.
7. Chitturi S, Farrell GC. Etiopathogenesis of nonalcoholic steatohepatitis. Semin Liver Dis. 2001;21(1):27–41.
8. Fromenty B, Pessayre D. Impaired mitochondrial function in microvesicular steatosis. Effects of drugs, ethanol, hormones and cytokines. J Hepatol. 1997;26(Suppl 2):43–53.

9. Byrne CD, Targher G. NAFLD: a multisystem disease. J Hepatol. 2015;62(1):S47–64.
10. Anstee QM, Targher G, Day CP. Progression of NAFLD to diabetes mellitus, cardiovascular disease or cirrhosis. Nat Rev Gastroenterol Hepatol. 2013;10(6):330–44.
11. EASL. EASD&EASO clinical practice guidelines for the management of nonalcoholic fatty liver disease. J Hepatol. 2016;64(6):1388–402.
12. Targher G, Bertolini L, Padovani R, Rodella S, Tessari R, Zenari L, et al. Prevalence of nonalcoholic fatty liver disease and its association with cardiovascular disease among type 2 diabetic patients. Diabetes Care. 2007;30(5):1212–8.
13. Hamabe A, Uto H, Imamura Y, Kusano K, Mawatari S, Kumagai K, et al. Impact of cigarette smoking on onset of nonalcoholic fatty liver disease over a 10-year period. J Gastroenterol. 2011;46(6):769–78.
14. Chavez-Tapia NC, Lizardi-Cervera J, Perez-Bautista O, Ramos-Ostos MH, Uribe M. Smoking is not associated with nonalcoholic fatty liver disease. World J Gastroenterol. 2006;12(32):5196–200.
15. Bacon BR, Farahvash MJ, Janney CG, Neuschwander-Tetri BA. Nonalcoholic steatohepatitis: an expanded clinical entity. Gastroenterology. 1994;107(4):1103–9.
16. Mofrad P, Contos MJ, Haque M, Sargeant C, Fisher RA, Luketic VA, et al. Clinical and histologic spectrum of nonalcoholic fatty liver disease associated with normal ALT values. Hepatology (Baltimore, Md). 2003;37(6):1286–92.
17. Noguchi H, Tazawa Y, Nishinomiya F, Takada G. The relationship between serum transaminase activities and fatty liver in children simple obesity. Acta Paediatr Jpn Overseas Edition. 1995;37(5):621–5.
18. Charatcharoenwitthaya P, Lindor KD, Angulo P. The spontaneous course of liver enzymes and its correlation in nonalcoholic fatty liver disease. Dig Dis Sci. 2012;57(7):1925–31.
19. Brunt EM, Janney CG, DiBisceglie AM, Neuschwander-Tetri BA, Bacon BR. Nonalcoholic steatohepatitis: a proposal for grading and staging the histological lesions. Am J Gastroenterol 1999; 94(9):2467e74.
20. Schwenzer NF, Springer F, Schraml C, Stefan N, Machann J, Schick F. Non-invasive assessment and quantification of liver steatosis by ultrasound, computed tomography and magnetic resonance. J Hepatol. 2009;51(3):433–45.
21. Hernaez R, Lazo M, Bonekamp S, Kamel I, Brancati FL, Guallar E, et al. Diagnostic accuracy and reliability of ultrasonography for the detection of fatty liver: a meta-analysis. Hepatology (Baltimore, Md). 2011;54(3):1082–90.
22. Mottin CC, Moretto M, Padoin AV, Swarowsky AM, Toneto MG, Glock L, et al. The role of ultrasound in the diagnosis of hepatic steatosis in morbidly obese patients. Obes Surg. 2004;14(5):635–7.
23. de Moura AA, Cotrim HP, Barbosa DB, de Athayde LG, Santos AS, Bitencourt AG, et al. Fatty liver disease in severe obese patients: diagnostic value of abdominal ultrasound. World J Gastroenterol. 2008;14(9):1415–8.
24. Adams LA, Talwalkar JA. Diagnostic evaluation of nonalcoholic fatty liver disease. J Clin Gastroenterol. 2006;40(Suppl 1):S34–8.
25. Wong GL, Wong VW. Fat and fiber: how the controlled attenuation parameter complements noninvasive assessment of liver fibrosis. Dig Dis Sci. 2015;60(1):9–12.
26. Karlas T, Petroff D, Sasso M, Fan JG, Mi YQ, de Lédinghen V, et al. Individual patient data meta-analysis of controlled attenuation parameter (CAP) technology for assessing steatosis. J Hepatol. 2017;66(5):1022–30.
27. Shi KQ, Tang JZ, Zhu XL, Ying L, Li DW, Gao J, et al. Controlled attenuation parameter for the detection of steatosis severity in chronic liver disease: a meta-analysis of diagnostic accuracy. J Gastroenterol Hepatol. 2014;29(6):1149–58.
28. Rofsky NM, Fleishaker H. CT and MRI of diffuse liver disease. Semin Ultrasound CT MR. 1995;16(1):16–33.

29. Szczepaniak LS, Nurenberg P, Leonard D, Browning JD, Reingold JS, Grundy S, et al. Magnetic resonance spectroscopy to measure hepatic triglyceride content: prevalence of hepatic steatosis in the general population. Am J Physiol Endocrinol Metab. 2005;288(2):E462–8.
30. Borra RJ, Salo S, Dean K, Lautamäki R, Nuutila P, Komu M, et al. Nonalcoholic fatty liver disease: rapid evaluation of liver fat content with in-phase and out-of-phase MR imaging. Radiology. 2009;250(1):130–6.