

NONALCOHOLIC FATTY LIVER DISEASE BRAZILIAN SOCIETY OF HEPATOLOGY CONSENSUS

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ABSTRACT - The prevalence of obesity-related metabolic syndrome has rapidly increased in Brazil, resulting in a high frequency of nonalcoholic fatty liver disease, that didn't receive much attention in the past. However, it has received increased attention since this disease was identified to progress to end-stage liver diseases, such as cirrhosis and hepatocellular carcinoma. Clinical practice guidelines for the diagnosis and treatment of nonalcoholic fatty liver disease have not been established in Brazil. The Brazilian Society of Hepatology held an event with specialists' members from all over Brazil with the purpose of producing guideline for Nonalcoholic Fatty Liver Disease based on a systematic approach that reflects evidence-based medicine and expert opinions. The guideline discussed the following subjects: 1-Concepts and recommendations; 2-Diagnosis; 3-Non-medical treatment; 4-Medical treatment; 5-Pediatrics - Diagnosis; 6-Pediatrics - Non-medical treatment; 7-Pediatrics - Medical treatment; 8-Surgical treatment.
HEADINGS - Fatty liver, therapy. Non-alcoholic fatty liver disease, diagnosis. Consensus.

INTRODUCTION

The Brazilian Society of Hepatology (SBH) held an event with specialists' members from all over Brazil with the purpose of producing guideline for Nonalcoholic Fatty Liver Disease (NAFLD). The following categories were discussed:

1. Concepts and recommendations
2. Diagnosis
3. Non-medical treatment
4. Medical treatment
5. Pediatrics - Diagnosis
6. Pediatrics - Non-medical treatment
7. Pediatrics - Medical treatment
8. Surgical treatment

METHODS

The BASCE system⁽³⁾ used is an organizational method developed by the Axiabio consultancy that aims to minimize biases and misdirection in results, based on scientific criteria established in the literature.

The BASCE system proposes a systematic approach to adapting guidelines in different scenarios, taking into account answers to the relevant questions for Brazil and presenting the results in a clear and transparent methodology. The document has quality and local scientific validity. This system is composed of the following stages:

1) Ample and systematic search of the medical literature for guidelines and consensus referring to a specific disease.

In this first stage bibliographic research was carried out in databases of guidelines and consensus on NAFLD. The research was carried out on four databases:

- Pubmed Portal; through the following search protocol: "Non-alcoholic Fatty Liver Disease" [Mesh] OR ("non-alcoholic fatty liver disease" [MeSH Terms] OR ("non-alcoholic" [All Fields] AND "fatty" [All Fields] AND "liver" [All Fields] AND "disease" [AllFields]) OR "non-alcoholic fatty liver disease" [AllFields] OR ("non" [AllFields] AND "alcoholic" [AllFields] AND "fatty" [AllFields] AND "liver" [AllFields] AND "disease" [AllFields]) OR "non alcoholic fatty liver disease" [AllFields] AND (Practic eGuidelin e [ptyp] OR Guideline [ptyp])). Fifteen articles were recovered.
- Embase; portal: through the following search protocol: 'nonalcoholicfatty liver'/exp OR 'non-alcoholicfatty liver' AND ('practiceguideline'/exp OR 'practiceguideline') AND 'practiceguideline'/de. A total of 223 articles were recovered.
- NICE portal: through the following search term: Non-alcoholicFattyLiverDisease. Three results were recovered.
- National Guideline Clearing house: through the following search strategy: Non-alcoholicFattyLiverDisease. Thirty three studies were recovered.

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2) A total of 274 articles were found and 11 were chosen. The majority were guidelines^(2,4,6,7-14), that had the same objectives as the present study.

Following this, a structured evaluation of these guidelines, four or more local specialists selected the consensus or guidelines to be used, based on a validated score (AGREE II)⁽¹⁾.

3) A group of six specialists in hepatology, recognized scholars and researchers in NAFLD (Group I), recommended by the Brazilian Society of Hepatology, evaluated the guidelines obtained in the web searches using their own instrument for grading them.

The incorporation of the international guidelines in the local discussion was considered through the criteria established in AGREE II⁽¹⁾ (Appraisal of Guidelines Research and Evaluation). This tool evaluates and compares different guidelines, allowing the use of the best recommendations of each taking into account the local context. AGREE II⁽¹⁾ is a generic tool that can be applied to any diseases, including diagnostic aspects, health improvement, treatment and other interventions.

The AGREE II methodology⁽¹⁾ evaluates both the quality of the recommendation and the quality of some intrinsic aspects of them, divided into six domains:

- Domain 1: Scope and goal (overall goal of the orientation norms);
- Domain 2: Involvement of parties (representation of all stakeholders and potential users),
- Domain 3: Rigor of development (evidence collection process used, and formulation of recommendations);
- Domain 4: Clarity and presentation (language and formatting),
- Domain 5: Applicability (application of recommendations in organizational, behavioral and cost viability terms);
- Domain 6: Editorial independence (exemption of recommendations and recognition of conflicts of interest).

Based on this method of evaluation, guidelines that reached a score of equal to or greater than 51% on all categories were chosen (Table 1).

These criteria were chosen for the American guidelines of 2012⁽¹²⁾. However, according decision of group 1, the European guidelines 2013⁽⁶⁾ and KASL 2013⁽⁹⁾, although have had a score lower than 51% in the second domain, both had merit to be included in the Brazilian consensus. This decision was based on the recommendations in the manual from the Brazilian Ministry of Health⁽⁵⁾ on tools to adapt clinical guidelines. It affirms that a set of guidelines having a score lower than the defined cut-off should not automatically be excluded. After this deliberation the group decided included those guidelines.

The chosen guidelines served as a base for drafting the initial document, which was composed of recommendations taken from them. The initial document was then evaluated by the members of group 1, who made their suggestions for additions to the recommendations.

4) The second stage of the methodology consisted in a Consensus Meeting with special guests of the Brazilian Society of Hepatology (Group II) with the aim of evaluating and deciding on the adoption or rejection of the preliminary recommendations made by group I. These decisions reflected the findings previously obtained and already cited.

The specialists were alerted to the fact that recommendations should be analyzed according to the degree of quality and applicability to the Brazilian context.

The selection of the drafted recommendations was done in person and electronically, the participants were not individually identified, they were presented as an aggregate of group II.

All recommendations were voted as YES or NO. According to the BASCE methodology, only those with a score of 70% or more as yes were considered part of the consensus. The affirmations not achieving consensus (less than 70%) on the first vote were subject to a debate between specialists, one arguing for and the other against. After the end of the debate, another vote was held. In cases where the recommendation did not reach 70% approval after the debate, they were not included in the Brazilian Consensus.

TABLE 1. Classification of domains according to the AGREE II methodology

Guidelines	RESULTS					
	Domain 1 (%)	Domain 2 (%)	Domain 3 (%)	Domain 4 (%)	Domain 5 (%)	Domain 6 (%)
WHO 2014	56	26	24	83	29	50
EASL 2013	93	48	76	91	61	83
KASL 2013	96	30	90	98	60	100
AASLD 2012	91	57	71	93	61	64
CASLD 2011	83	56	38	69	19	33
EASL 2010	39	15	17	61	17	17
AISF 2010	81	44	63	87	42	78
CASLD 2008	74	46	33	70	17	33
AMG 2008	24	2	24	59	22	17
APASL 2007	61	22	10	50	24	17
AGA 2002	50	20	44	52	21	36

5) In order to guarantee the credibility and integrity of the discussions and voting in group II, the process was recorded on video, and the voting itself recorded electronically.

RESULTS

1. Concepts and recommendations

- NAFLD is characterized by fatty infiltration of the liver (steatosis), which can be diagnosed by imaging methods. It may be related to necro-inflammatory changes and fibrosis (steatohepatitis) diagnosed using liver biopsy, and can progress into cirrhosis and hepatocellular carcinoma. It occurs in individuals with no significant history of alcohol abuse, who do not have other hepatic diseases that explain steatosis, and in the majority of cases is associated with the “metabolic syndrome”.
- The most frequent risk factors for NAFLD are obesity, type 2 diabetes and dyslipidemia. However, this condition can also be associated with the use of some medicines, anabolic steroids, environmental toxins and other diseases such as sleep apnea, hyperthyroidism, and polycystic ovary syndrome.
- The mortality rate in patients with steatohepatitis (NASH) are higher than those in the normal population. Cardiovascular diseases are the most common cause, followed by complications from cirrhosis and hepatocellular carcinoma.
- The following exclusion criteria should be considered when identifying NAFLD; significant consumption of alcohol (over 140g/week for men (± 21 units) and 70 g/week for women (± 14 units)).
- Some studies have suggested that moderate consumption of alcohol (< 20 g/day or < 140 g/week) could have a beneficial effect on the liver, for example, improving insulin resistance and necro-inflammatory changes in histology. However, in the absence of controlled clinical trials, in medical practice, alcohol consumption should not be recommended to patients with NAFLD.

2. Diagnosis

In patients with other chronic hepatic diseases showing concomitant NAFLD (steatosis or steatohepatitis) investigation of metabolic factors and diseases related to NAFLD is recommended.

- Patients with NAFLD should be evaluated for metabolic risk factors and factors for progression of liver dysfunction.
- Clinical, biochemical tests (enzymes, and liver function) and abdominal ultrasound are important for differential diagnosis of NAFLD from other conditions like alcoholic liver disease viral hepatitis, drug-induced hepatitis, autoimmune hepatitis and Wilson’s disease. However, in many cases liver biopsy and histological analyzes are necessary.

- In the diagnosis of NAFLD, ultrasound, computerized tomography, magnetic resonance imaging and magnetic resonance spectroscopy can help the assessment of steatosis, although these tests cannot distinguish steatosis from steatohepatitis.
- NAFLD Fibrosis Score (NFS), APRI, FIB-4 and transient elastography can also aid the diagnosis of hepatic fibrosis and staging of patients with NAFLD.
- Hepatic biopsy should be recommended in the following situations:
 - Patients with suspected steatohepatitis and differential diagnosis from other chronic liver disease.
 - Patients with NAFLD and high risk of steatohepatitis and/or advanced fibrosis suggested by serological markers and/or hepatic elastography.
 - Patients with high levels of hepatic enzymes (ALT/AST) for over 3 months.
 - Patients with metabolic syndrome not controlled with behavioral changes after 6 months.
- Current evidence does not support the use of hepatic biopsy as a sequential part of routine clinical practice in patients with steatosis or steatohepatitis.
- Liver biopsy also can be recommended in patients with persistent high serum ferritin levels and increase in iron saturation, especially for homozygous genotypes or heterozygous for C282Y mutations on the HFE gene.
- Hepatic biopsy is not recommended for patients with asymptomatic hepatic steatosis detected in imaging but showing normal levels of hepatic enzymes (ALT and AST).
- Systematic tracking of NAFLD in family members of NAFLD patients is not recommended.
- There is no policy definition for tracking patients at high risk of developing NAFLD.
- Patients with cirrhosis or steatohepatitis and a degree of fibrosis ≥ 3 should be monitored for gastroesophageal varices.
- There is still insufficient scientific evidence to screen for hepatocellular carcinoma (HCC) in patients with a diagnosis of NASH. Patients with cirrhosis and NASH should be included in the same protocols for screening HCC as patients with other hepatic diseases.
- In patients with a diagnosis of hepatic steatosis shown by imaging examinations, but who display symptoms or signals attributable to hepatic illness, investigation of NAFLD and follow-up is recommended.
- In asymptomatic patients with a diagnosis of hepatic steatosis in imaging exams and who present altered hepatic profile, metabolic risk factors (obesity, glucose intolerance, dyslipidemia), alcohol-related liver disease and other causes of NAFLD should be investigated.

- In patient who present characteristics suggestive of autoimmune liver disease (high aminotransferases, gamma globulin levels and serum antibody levels) or/ and autoimmune disease clinical profile, a more complete assessment is recommended.

3. Non-medical treatment

- For overweight or obese patients, weight loss through a controlled, balanced diet guided by the patients clinical condition associated with physical exercises are recommended to control NAFLD.
- The diet of patients with NAFLD should have a low carbohydrate and fructose content, but should avoid extreme restriction of carbohydrates. It should be remembered that it is not fructose from fruit or industrialized sources that is a risk factor for steatosis, but the excess of calories consumed.
- Exercise should be undertaken for at least 150 minutes per week. This activity can reduce the amount of fat in the liver. Although the exercises included in the main published studies are aerobic, resistance training might also be beneficial. However, there is still no consensus on the type, duration or intensity of physical activity as a treatment of NAFLD.
- The loss of at least 3%-5% of body mass in 6 months seems to be necessary to improve steatosis, but more weight loss (up to 10%) may be necessary before improvement in steatohepatitis.
- Healthy lifestyle and control of metabolic risk factors should be recommended for all patients with NAFLD.

4. Medical treatment

- Vitamin E (800IU/day) is recommended for patients with a histological diagnosis of NASH. However, collateral side effects should be monitored.
- There is no evidence to recommend use of vitamin E (800 IU/day) for diabetic patients or for those without hepatic biopsy and cirrhosis.
- Pioglitazone can be used to treat steatohepatitis diagnosed through biopsy. Improvement in the levels of ALT, steatosis and hepatic inflammation are observed. It should be noted however, that the patients with NAFLD who participated in the clinical trials for pioglitazone were not diabetic, and so the safety and long term efficacy of this drug for patients with NAFLD and diabetes is not established.
- Metformin is not recommended as a specific treatment for NASH, because no study has demonstrated a significant histological improvement. However, in patients with NASH, metformin can improve insulin resistance, hepatic enzyme levels and help with weight control.
- Statin administration can be considered as a treatment option for dyslipidemia and reduction of frequency of cardiovascular dysfunction in patients with NAFLD. However, it is not recommended for specific treatment of NASH.

- Statins can be used to treat dyslipidemia in patients with steatosis and NASH, because there is no evidence to show that statins cause an elevated risk of drug-induced liver damage for these patients.
- It is still premature to recommend treatment with omega-3 fatty acids for steatosis or NASH, but they can be considered as treatment for patients with NAFLD and hypertriglyceridemia.
- Ursodeoxycholic acid is not recommended as a specific monotherapy for treatment of NAFLD/NASH because there is no scientific evidence that it improves the condition.
- Metabolic risk factors should be treated according to the clinical needs of each patient, and medication should be administered when necessary.
- The use of pioglitazone and vitamin E, especially in conjunction with a modified lifestyle, is cost effective in individuals with NASH and advanced fibrosis. However, pioglitazone and vitamin E are not without collateral side effects.
- There are no data to support the use of vitamin E or pioglitazone to improve other hepatic diseases coexisting with NAFLD and NASH.
- The use of medications described as hepatoprotectors, such as silymarin, methionine, betaine, metadoxine and other drugs, do not present scientific data that allow their prescription in treatment of NAFLD.
- The use of prebiotics, probiotics and nutritional supplements still do not show scientific data strong enough to support their recommendation in NAFLD treatment.

5. Pediatrics - Diagnosis

- Very young children (first decade), or those without excess weight but who have a fatty liver, should be evaluated for monogenic causes of chronic liver disease like dysfunction in the oxidization of fatty acids, lysosomal storage diseases and peroxisome dysfunctions, as well as the usual causes for adults.
- Early diagnosis is important for all age groups, because the noted rise in the frequency of NAFLD in children and adolescents correlates with the rising number of cases of childhood obesity.
- Consider hepatic biopsy in children with suspected NAFLD whose diagnosis was not clarified by clinical and laboratory exams, when there is the possibility of differential diagnosis and before beginning therapy with medication to treat NAFLD.
- During the interpretation of hepatic biopsies in children and adolescents, the characteristics of NASH for this population should be considered, to avoid confusing NASH with other hepatic diseases that store fat.
- Pathologists should recognize the standard most frequently found in children and adolescents in interpreting biopsies for NAFLD, to not erroneously categorize it as pediatric NAFLD.

6. Pediatrics - Non-medical treatment

- Lifestyle change is recommended as primary treatment, combined with diet therapy and exercise in both children and adolescents with NAFLD.

7. Pediatrics - Medical treatment

- Vitamin E can be administered to children and adolescents with NASH confirmed by biopsy.
- The administration of Metformin (500 mg) twice daily does not offer any benefit to children with NAFLD, and therefore should not be prescribed. Metformin side effects, when prescribed in higher doses, are unknown.

8. Surgical treatment

- Bariatric surgery is not considered a specific treatment for NAFLD, however, it can be recommended for patients eligible for surgical treatment for severe obesity.
- Patients with cirrhosis diagnosis the bariatric surgery should be recommended only for patients with preserved hepatic function and without portal hypertension.
- Liver transplantation for obese patients with NAFLD/NASH the same criteria for other liver disease should be used.

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RESUMO - A prevalência de obesidade relacionada à síndrome metabólica tem crescido no Brasil, que implicou em uma maior frequência de doença hepática gordurosa não alcoólica, não havia recebido muita atenção no passado. Contudo, essa atenção tem merecido interesse cada vez maior desde que se observou o elevado potencial de progressão para formas mais graves dessa doença como cirrose e carcinoma hepatocelular. No Brasil ainda não havia sido proposta nenhuma diretriz para orientar o diagnóstico e tratamento da doença hepática gordurosa não alcoólica. A Sociedade Brasileira de Hepatologia realizou então um evento que reuniu especialistas de todo o Brasil com o objetivo de propor uma diretriz para a doença hepática gordurosa não alcoólica baseada em evidências científicas e opiniões de especialistas nesse tema. A diretriz final é composta dos seguintes temas: 1-Conceitos e recomendações; 2-Diagnóstico; 3-Tratamento não medicamentoso; 4-Tratamento medicamentoso; 5-Diagnóstico em Pediatria; 6-Tratamento não medicamentoso em Pediatria; 7-Tratamento medicamentoso em Pediatria; 8-Tratamento cirúrgico.

DESCRITORES - Fígado gorduroso, terapia. Hepatopatia gordurosa não alcoólica, diagnóstico. Consenso.

REFERENCES

1. Agree. Instrumento para Avaliação de Diretrizes Clínicas. Appraisal of guidelines research & evaluation: AGREE II 2009. [Internet]. Available from: http://www.agreetrust.org/wp-content/uploads/2013/06/AGREE_II_Brazilian_Portuguese.pdf
2. American Gastroenterological Association. American Gastroenterological Association medical position statement: nonalcoholic fatty liver disease. *Gastroenterology.* 2002;123:1702-4.
3. Axia.Bio Farmacoeconomia e pesquisa em saúde. Available from: www.axiabio.brazil.com
4. Bosques-Padilla F, Aguirre García J, Kershenobich SD, Tamayo de la Cuesta JL, Stoopen RM, Kettenhofen EW, et al. [Gastroenterology diagnosis and treatment guidelines of not alcoholic hepatic disease. Diagnosis]. *Rev Gastroenterol Mex.* 2008;73:129-33.
5. Brasil. Ministério da Saúde. Secretaria de Ciência, Tecnologia e Insumos Estratégicos. Departamento de Ciência e Tecnologia. Diretrizes metodológicas: Sistema GRADE – Manual de graduação da qualidade da evidência e força de recomendação para tomada de decisão em saúde. 2014.
6. Chalasani N, Younossi Z, Lavine JE, Diehl AM, Brunt EM, Cusi K, et al. The diagnosis and management of non-alcoholic fatty liver disease: practice guideline by the American Gastroenterological Association, American Association for the Study of Liver Diseases, and American College of Gastroenterology. *Gastroenterology.* 2012;142:1592-609.
7. Fan JG, Jia JD, Li YM, Wang BY, Lu LG, Shi JP, Chan LY; Chinese Association for the Study of Liver Disease. Guidelines for the diagnosis and management of nonalcoholic fatty liver disease: update 2010: (published in Chinese on Chinese Journal of Hepatology. 2010;18:163-6). *J Dig Dis.* 2011;12:38-44.
8. Farrell GC, Chitturi S, Lau GK, Sollano JD; Asia-Pacific Working Party on NAFLD. Guidelines for the assessment and management of non-alcoholic fatty liver disease in the Asia-Pacific region: executive summary. *J Gastroenterol Hepatol.* 2007;22:775-7.
9. Korean Association for the Study of the Liver (KASL). KASL clinical practice guidelines: management of nonalcoholic fatty liver disease. *ClinMolHepatol.* 2013;19:325-48.
10. LaBrecque DR, Abbas Z, Anania F, Ferenci P, Khan AG, Goh KL, et al. World Gastroenterology Organisation. World Gastroenterology Organisation global guidelines: Nonalcoholic fatty liver disease and nonalcoholic steatohepatitis. *J Clin Gastroenterol.* 2014;48:467-73.
11. Loria P, Adinolfi LE, Bellentani S, Bugianesi E, Grieco A, Fargion S, et al. Practice guidelines for the diagnosis and management of non-alcoholic fatty liver disease. A decalogue from the Italian Association for the Study of the Liver (AISF) Expert Committee. *Dig Liver Dis.* 2010;42:272-82.
12. Nascimbeni F, Pais R, Bellentani S, Day CP, Ratziu V, Loria P, Lonardo A. From NAFLD in clinical practice to answers from guidelines. *J Hepatol.* 2013;59:859-71.
13. Ratziu V, Bellentani S, Cortez-Pinto H, Day C, Marchesini G. A position statement on NAFLD/NASH based on the EASL 2009 special conference. *J Hepatol.* 2010;53:372-84.
14. Zeng MD, Fan JG, Lu LG, Li YM, Chen CW, Wang BY, Mao YM; Chinese National Consensus Workshop on Nonalcoholic Fatty Liver Disease. Guidelines for the diagnosis and treatment of nonalcoholic fatty liver diseases. *J Dig Dis.* 2008;9:108-12.