CME

Evidence-based management of patients with nonalcoholic fatty liver disease

Minal Patel, MSc, PA-C

ABSTRACT

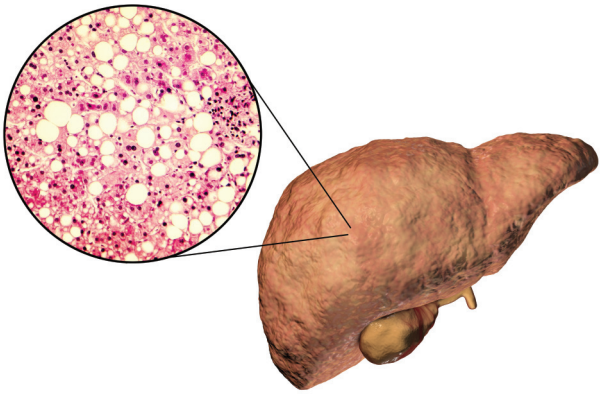
Over the past decade, fatty liver disease has become a forefront health issue. The clinical implication of this silent disease extends well beyond just the liver and is linked to a variety of health concerns, including cardiovascular disease, diabetes, and cancer. The prevalence of fatty liver disease in the United States is estimated to be 25% and increasing. This article reviews the pathophysiology of fatty liver disease, how clinicians can recognize contributing factors, and appropriate interventions based on the American Association for the Study of Liver Disease's guidelines.

Keywords: fatty liver disease, cirrhosis, American Association for the Study of Liver Disease, guidelines, diabetes, cancer

Learning objectives

- Describe the pathophysiology and spectrum of NAFLD.
- Describe the evaluation and diagnosis of NAFLD, nonalcoholic steatohepatitis, and cirrhosis.
- Outline management for the treatment of NAFLD.

Nonalcoholic fatty liver disease (NAFLD) is a spectrum of varying degrees of fatty infiltration, from hepatic steatosis without secondary causes for fat accumulation to cirrhosis (**Table 1**).[1] Studies show that patients with fatty liver disease have an overall poor quality of life and outcomes.[2] Nonalcoholic steatohepatitis (NASH), a subset of NAFLD, is an independent predictor for cardiovascular disease and is estimated to be associated with 38% of cardiovascular-related deaths and 17% of all cancers.[2] Patients with NASH are at increased risk for developing cirrhosis, liver failure, and hepatocellular carcinoma.[2] Because fatty liver disease is a slowly progressive condition, patients often do not seek medical care until they develop symptoms related to late-stage disease. Disease commonly is detected incidentally following routine blood work or on imaging.[3]



PATHOPHYSIOLOGY

Fatty deposition into the liver is influenced by many factors and generally occurs over a span of decades. Risk factors for fatty liver disease include any metabolic dysfunction, such as obesity, hyperlipidemia, diabetes, hypertension, sleep apnea, and polycystic ovary syndrome (PCOS).[1,4]

One of the crucial functions of a hepatocyte is to metabolize macronutrients. A normal healthy liver has the capacity to store some fat in the form of lipids. However, excess buildup of fat (hepatic steatosis) ultimately impairs liver function and cellular health. When cellular integrity is threatened, a cascade of reactive events occurs, including enzyme release followed by fibrotic collagen deposits, leading to fibrotic stranding throughout the liver parenchyma.[5]

The American Association for the Study of Liver Disease (AASLD) defines NAFLD as 5% or more hepatic steatosis on histology without evidence of hepatocellular injury.[1] NASH is defined as NAFLD with associated lobular inflammation and hepatocyte ballooning.[1] NASH-related cirrhosis is liver disease with features of NASH and evidence of advanced fibrosis.[1]

PREVALENCE

Fatty liver disease occurs at any stage of life. The prevalence of NAFLD in children is estimated to be 5% to 10%.[6] NAFLD appears more prevalent as people age, typically occurring in patients ages 30 to 50 years.[7] Although NASH is more common in men than women under age 50 years,

Minal Patel practices in gastroenterology/hepatology at Digestive Disease Associates in Wyomissing, Pa. The author has disclosed no potential conflicts of interest, financial or otherwise.

DOI:10.1097/01.JAA.0000840492.53680.59

Key points

- NAFLD is defined as evidence of steatosis (either by imaging or histology) and lack of secondary causes for fat accumulation.
- Patients with incidental hepatic steatosis detected on imaging, who lack any liver-related symptoms or signs, and have normal biochemistries should be assessed for metabolic risk factors and alternate causes for hepatic steatosis, such as significant alcohol consumption or medication.
- Treatment focuses on managing the underlying metabolic conditions and helping patients lose weight through diet and moderate-intensity exercise.

TABLE 1. Common causes of secondary hepatic steatosis[1]

- Excessive alcohol consumption
- Hepatitis C
- Wilson disease
- Lipodystrophy
- Starvation
- Parenteral nutrition
- Abetalipoproteinemia
- Medications such as mipomersen, lomitapide, amiodarone, methotrexate, tamoxifen, corticosteroids, valproate, antiretroviral medicines
- Reye syndrome
- Acute fatty liver of pregnancy
- HELLP syndrome
- Inborn errors of metabolism such as lecithin-cholesterol acyltransferase deficiency, cholesterol ester storage disease, Wolman disease

the incidence increases in women after age 50 years, perhaps because of postmenopausal hormone changes.[8]

PRESENTATION

Most patients are asymptomatic at presentation, but some may complain of fatigue or right upper quadrant abdominal pain.[9] Obesity, specifically truncal adiposity, is the most common and often only physical sign of NAFLD.[9] Hepatomegaly occurs in about 10% of patients.[9] Patients who report symptoms of abdominal distension, pruritus, confusion, and prolonged bleeding may have advanced liver disease.[10]

Stigmata of chronic liver disease include jaundice, palmar erythema, spider angiomas, ascites, gynecomastia, encephalopathy, splenomegaly, caput medusa, and asterixis.[10]

EVALUATION

According to the AASLD, patients with incidental hepatic steatosis detected on imaging, who lack any liver-related symptoms and have normal biochemistries, should be assessed for metabolic risk factors and alternate causes for hepatic steatosis, such as significant alcohol consumption or medication effect (**Table 1**).[1] Patients with unsuspected hepatic steatosis detected on imaging who have symptoms or signs attributable to liver disease or have abnormal liver chemistries should be evaluated as though they have NAFLD and worked up accordingly.[1]

Biochemistries Liver chemistries often are normal in NAFLD.[9,11] Elevated liver function tests (LFTs) specifically AST and ALT are the most common enzyme abnormalities seen on laboratory tests.[9,11] Other serum markers associated with NAFLD include isolated alkaline phosphatase (10% of patients), positive ANA (33% of patients), and elevated ferritin levels (40% to 58% of patients).[9,12] Patients who present with elevated LFT results should undergo a comprehensive workup to exclude other causes of liver disease such as viral hepatitis, iron overload disorders, Wilson disease, autoimmune hepatitis, thyroid disease, drug-induced hepatitis, alpha-1 antitrypsin deficiency, and malignancy.[1] Patients presenting with incidental steatosis on imaging and normal LFT results also should have a serologic workup to rule out other infiltrative liver processes. Initial diagnostic tests should include hepatic function testing, ferritin, serum iron, iron saturation, hepatitis B and C serology, and autoimmune antibodies (ANA, AMA, and antiSMA).[4,9] Patients with NAFLD can have elevated ferritin acting as an acute phase reactant, but should still undergo further testing to rule out hereditary hemochromatosis.[9,12] Elevated ferritin may be an indicator of NASH and advanced fibrosis.[12]

Imaging Hepatic steatosis most often is picked up by ultrasound, appearing as diffuse echogenicity of the liver parenchyma. When disease is advanced, ultrasound also may show hepatomegaly, cirrhosis, splenomegaly, or ascites. These features should alert clinicians to assess for contributing factors and refer patients to gastroenterology/hepatology for further evaluation. Liver CT or MRI rarely are necessary but can be considered if the presentation is unclear.[1]

Liver biopsy The most effective diagnostic tool in identifying fatty liver disease is liver biopsy; however, its use can be limited by cost, complication, and patient desire to avoid invasive testing. Liver biopsy is the standard of care to confirm diagnosis, rule out other causes of liver disease, delineate simple steatosis from steatohepatitis, and assess for advancing fibrosis. Distinguishing uncomplicated NAFLD from NASH is crucial because patients with NASH are at increased risk for developing cirrhosis and hepatocellular carcinoma, and requiring a liver transplant.[1]

The AASLD does not recommend liver biopsy for all patients with NAFLD.[1] However, consider liver biopsy for patients with risk factors for NASH or advanced fibrosis.[1] Substantial evidence supports metabolic syndrome as a strong predictor for NASH.[1] Consider metabolic syndrome in any patient with a large abdominal girth (greater than 102 cm [40 in] in men or 88 cm [34.6 in] in women), hypertriglyceridemia, hypertension, and diabetes.[1,13]

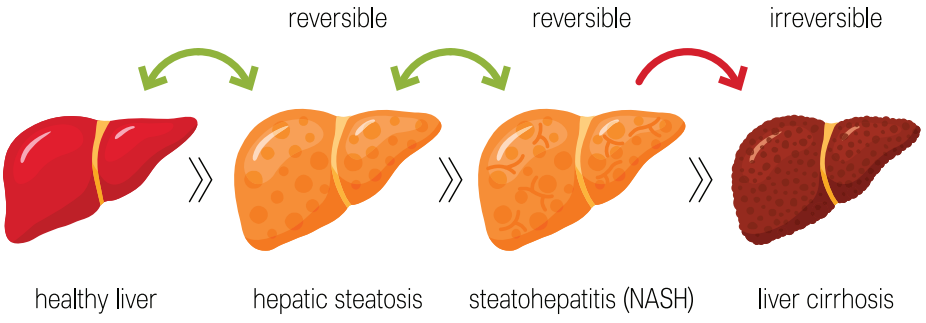


FIGURE 1. Stages of liver damage

Noninvasive tools for assessing advanced fibrosis Early identification of patients at risk for advanced disease results in early intervention and referral to a specialist.[1,11] The most readily available and useful tools for primary care clinicians include the NAFLD fibrosis score (NFS) and Fibrosis 4 score (Fib4), which are predictive calculators that use patient biomarkers to identify high-risk patients.[1,11] These calculators can be found online and used during a patient encounter. Fibrosis levels are based on the Metavir scoring system, which rates the level of damage as F0 (no fibrosis), F2 (mild to moderate fibrosis), F3 (advanced fibrosis), and F4 (cirrhosis).[14] The NFS factors are age, BMI, glucose impairment, platelet count, albumin, and AST/ALT ratio, and have a positive predictive value of 90% in determining the presence of advanced fibrosis.[1,11] A score lower than -1.455 excludes significant fibrosis with high accuracy; a score above 0.676 predicts a high probability for advanced fibrosis.[11] The FIB-4 is a simpler calculation that uses the patient's age, platelet count, and AST and ALT levels. Similar to NFS cutoffs, a value less than 1.45 or greater than 3.25 either rules in or rules out advanced fibrosis.[11,15] Clinicians can use these scores for baseline purposes as well as to monitor for disease progression.

The most recent addition to the diagnostic field is vibration-controlled transient elastography (VCTE). Using an ultrasound probe, elastography measures the shear wave velocity (or the amount of time it takes for a sound wave to flow through the liver) to predict underlying parenchymal stiffness. A literature review by Cheah and colleagues analyzing VCTE accuracy found that liver stiffness measurement corresponded to fibrosis levels to predict low risk versus high risk for advanced liver disease.[11] Using a cut-off liver stiffness measurement of 7.9 kPA ruled out advanced fibrosis; a measurement of 9.9 kPA or higher ruled in cirrhosis.[11] Values in between these cut-offs were less consistent in distinguishing intermediate fibrosis and should be assessed in combination with other clinical findings as discussed earlier.[11,16,17] Although transient elastography is useful, several factors may influence results. Marked steatosis, cellular inflammation, cholestasis, increased central venous pressure, obesity, food intake within 1 hour of testing, and operator handling can affect readings.[11] Elastography can be performed as a standalone test or in combination with an ultrasound but is not indicated in patients with ascites because of the difficulty in assessing a shear wave through fluid.[11] Magnetic resonance elastography (MRE) is more sensitive than ultrasound elastography and is unaffected by ascites or obesity, although it can be limited by motion artifact if the patient is unable to lie still.[11,16] Elastography does not replace liver biopsy and is not a confirmatory test for histology or definitive diagnosis. The AASLD recommends NFS or Fib4 index, or VCTE or MRE to identify patients at risk for advanced liver disease.[1] High-risk patients should be considered for liver biopsy, especially if they also have metabolic syndrome.[1]

TREATMENT

The primary goal in treating NAFLD is improving liver disease and managing associated metabolic contributors.[1] Despite lack of consensus in the guidelines on management, the AASLD, Asia-Pacific Working Party on Non-Alcoholic Fatty Liver Disease, European Association for the Study of the Liver (EASL), National Institute for Health and Care Excellence (NICE), and Italian Association for the Study of the Liver (AISF) agree that lifestyle modification and weight loss are essential to improving NAFLD and NASH histology.[14,17] A modest weight loss of 5% has been shown to reduce steatosis; a weight loss of 10% can improve necroinflammation that leads to fibrosis.[1] However, implementing and maintaining a weight loss strategy can be challenging; a multidisciplinary approach can help patients reach desired clinical endpoints. A team of experts in nutrition, behavior modification, and exercise led by a healthcare provider trained in managing NAFLD can provide comprehensive coordination of treatment.[4]

Diet and lifestyle modification The Mediterranean diet is a widely accepted way of eating to reduce inflammatory factors in cardiovascular disease and insulin-related metabolic disorders.[17,18] According to the AASLD, trials comparing the Mediterranean diet with a high-fat, low-carbohydrate diet found that patients had no change in weight loss but demonstrated significant improvement in steatosis after 6 weeks.[1] The Mediterranean diet is highly regarded for its antioxidant and anti-inflammatory benefits.[17,18] The plant-based diet consists of mainly fruits, vegetables, grains, nuts, and fish that are rich in polyunsaturated fats and various vitamins.[1,17,18] The diet reduces consumption of processed foods, specifically those containing high-fructose corn syrup, a common ingredient in the Western diet and a major contributor to *de novo* lipogen-

esis and hepatic fatty infiltration.[18,19] In addition to dietary modification, patients also may need to restrict calories and add exercise to achieve optimal weight loss. The ASIF endorses implantation of a very low calorie diet (1,200 to 1,600 kcal/day) composed of less than 10% saturated fat and carbohydrate intake less than 50% of total calories, in combination with a Mediterranean diet as an effective strategy to induce weight loss.[17] The AASLD recommends a calorie-deficit diet of 500 to 1,000 kcal/day along with moderate-intensity exercise as most likely to sustain weight loss over the long term.[1] The AASLD guidelines included data from a study in which a hypocaloric diet (750 kcal/day) in combination with 200 minutes of walking per week resulted in weight loss and improvements in biopsy-proven NASH histology.[1,20] Patients may find the need for diet and exercise overwhelming: most are not used to counting calories, monitoring food intake, or exercising regularly. Fortunately, many smart electronic devices and phone apps are available to help with such tasks as food journaling and tracking steps. Patients who do not have access to such technology may find that keeping a written journal can be just as effective and helpful.

Pharmacotherapy No medications are FDA-approved to treat NAFLD. However, several are in trial phases of investigation but are not yet commercially available.

According to the AASLD, NASH clinical trial endpoints for conditional approval must demonstrate improvement of the necro-inflammatory and fibrotic effects of NAFLD.[1,21] Several available medications have been considered for treating NAFLD. Insulin sensitizers such as metformin and pioglitazone were studied for their therapeutic benefits.[1,22-24] Although metformin improved insulin resistance, it failed to show improvement in liver histology and is not recommended for treating NAFLD, but may be considered for off-label use in patients with evidence of insulin resistance.[1,17] The PIVENS trial was a large randomized study that compared pioglitazone (300 mg/day) with placebo and vitamin E (800 international units [IU]/day) with placebo in patients without diabetes.[1,25] Both pioglitazone and vitamin E demonstrated improvement in hepatocellular ballooning, inflammation, and no worsening of fibrosis compared with placebo; however, vitamin E had better results than pioglitazone.[1] Because of concerns over potential adverse reactions (weight gain, osteoporosis, and bladder cancer), the AASLD does not recommend the use of pioglitazone to treat patients with NAFLD without biopsy-proven NASH until more data are available to support its safety and efficacy.[1] FDA-approved weight loss medications such as orlistat, lorcaserin, and glucagon-like peptide-1 analogs (GLP-1) are indicated for obesity treatment but are not endorsed by any of the guidelines for NAFLD because vigorous testing is needed to establish their exact role in the management of NAFLD.[1,17] Statins may be used as part of treatment for cardiovascular risk factors in patients with NAFLD but data on NASH resolution have been inconsistent and these drugs are not recommended for NAFLD itself. The AASLD recommends avoiding statins in patients with decompensated liver disease.[1]

Supplements Oxidative stress has been identified as a significant factor in the development of hepatic inflammation.[1,19] Additionally, hypovitaminosis may have a role in disease states and supplements may have a protective effect against inflammation.[19,26] Vitamin D might have a protective effect against inflammation. In a study by Nelson and colleagues as part of an ancillary trial by the NASH clinical network research, 55% of patients with biopsy-proven NAFLD were deficient in vitamin D.[26] Although the relationship between vitamin D deficiency and NAFLD is not well understood, patients with NAFLD should be screened and treated accordingly.[26,27] Vitamin E, a potent antioxidant, showed promise in the PIVENS trial; however, the long-term safety of vitamin E remains unclear.[1,25] One meta-analysis found that vitamin E in doses greater than 800 IU/day was linked with increased all-cause mortality and a modest increase in prostate cancer.[1,28] However, these studies were criticized for not taking into consideration concomitant factors such as other medications, smoking history, and gender.[1] The AASLD recommends the use of vitamin E at a dose of 800 IU/day only in patients with biopsy-proven NASH who do not have diabetes until further supporting data regarding efficacy are established.[1]

Omega-3 fatty acids, although a core staple of the Mediterranean Diet, and polyunsaturated fatty acid supplements are not recommended for NAFLD treatment because of insufficient supporting data.[1] However, they may be considered for lipid management in patients with fatty liver disease.[1,29,30]

Bariatric surgery For patients unable to lose sufficient weight, bariatric surgery may be an option. Bariatric surgery is positively correlated with lower incidence of cardiovascular events, diabetes, malignancies, and overall mortality in obese adults.[1,31,32] Several studies investigating histologic changes in patients with probable or definite NASH found that the benefits of bariatric surgery at 1 year were sustained for up to 5 years postoperatively.[1,33] Histologic steatosis, ballooning, and fibrosis all improved in patients who underwent bariatric weight loss surgery.[34] The AASLD recommends considering bariatric surgery in eligible patients with NAFLD or NASH who have difficulty resolving their obesity.[1]

CONCLUSION

Fatty liver disease is a growing epidemic. Given its close association with other metabolic diseases, patients should have a comprehensive evaluation and risk stratification to distinguish mild steatosis from advanced disease. Diet, lifestyle modification, and weight loss are essential elements of treatment. Because treatment adherence and lack of guidance remain obstacles for many patients,

clinicians must clearly outline patient goals and follow up with them regularly to help them stay on track. Practices with limited resources should refer patients to a facility that can provide support. Many tertiary centers and gastroenterology/hepatology practices have fatty liver disease clinics whose sole focus is managing this condition. With individualized care and motivation, patients can reduce their risk for a cascade of chronic and often debilitating conditions. **JAAPA**

Earn Category I CME Credit by reading both CME articles in this issue, reviewing the post-test, then taking the online test at http://cme.aapa.org. Successful completion is defined as a cumulative score of at least 70% correct. This material has been reviewed and is approved for 1 hour of clinical Category I (Preapproved) CME credit by the AAPA. The term of approval is for 1 year from the publication date of August 2022.

REFERENCES

1. Chalasani N, Younossi Z, Lavine JE, 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):328-357.
2. Kim G-A, Lee HC, Choe J, et al. Association between non-alcoholic fatty liver disease and cancer incidence rate. *J Hepatol*. [e-pub Nov. 2, 2017]
3. Hassan K, Bhalla V, El Regal ME, A-Kader HH. Nonalcoholic fatty liver disease: a comprehensive review of a growing epidemic. *World J Gastroenterol*. 2014;20(34):12082-12101.
4. Puri P, Fuchs M. Population management of nonalcoholic fatty liver disease. *Fed Pract*. 2019;36(2):72-82.
5. Heyens LJM, Busschots D, Koek GH, et al. Liver fibrosis in non-alcoholic fatty liver disease: from liver biopsy to non-invasive biomarkers in diagnosis and treatment. *Front Med (Lausanne)*. 2021;8:615978.
6. Schwimmer JB, Deutsch R, Kahen T, et al. Prevalence of fatty liver in children and adolescents. *Pediatrics*. 2006;118(4):1388-1393.
7. Koehler EM, Schouten JNL, Hansen BE, et al. Prevalence and risk factors of non-alcoholic fatty liver disease in the elderly: results from the Rotterdam study. *J Hepatol*. 2012;57(6):1305-1311.
8. Lonardo A, Nascimbeni F, Ballestri S, et al. Sex differences in nonalcoholic fatty liver disease: state of the art and identification of research gaps. *Hepatology*. 2019;70(4):1457-1469.
9. Stengel JZ, Harrison SA. Nonalcoholic steatohepatitis: clinical presentation, diagnosis, and treatment. *Gastroenterol Hepatol (N Y)*. 2006;2(6):440-449.
10. Arroyo V, Moreau R. Diagnosis and prognosis of acute on chronic liver failure (ACLF) in cirrhosis. *J Hepatol*. 2017;66(2):451-453.
11. Cheah MC, McCullough AJ, Goh GB. Current modalities of fibrosis assessment in non-alcoholic fatty liver disease. *J Clin Transl Hepatol*. 2017;5(3):261-271.
12. Kowdley KV, Belt P, Wilson LA, et al. Serum ferritin is an independent predictor of histologic severity and advanced fibrosis in patients with nonalcoholic fatty liver disease. *Hepatology*. 2012;55(1):77-85.
13. Grundy SM, Cleeman JI, Daniels SR, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation*. 2005;112(17):2735-2752.
14. Pandyarajan V, Gish RG, Alkhouri N, Noureddin M. Screening for nonalcoholic fatty liver disease in the primary care clinic. *Gastroenterol Hepatol (N Y)*. 2019;15(7):357-365.
15. Sterling RK, Lissen E, Clumeck N, et al. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. *Hepatology*. 2006;43(6):1317-1325.
16. Eddowes PJ, Sasso M, Allison M, et al. Accuracy of FibroScan controlled attenuation parameter and liver stiffness measurement in assessing steatosis and fibrosis in patients with nonalcoholic fatty liver disease. *Gastroenterology*. 2019;156(6):1717-1730.
17. Leoni S, Tovoli F, Napoli L, et al. Current guidelines for the management of non-alcoholic fatty liver disease: a systematic review with comparative analysis. *World J Gastroenterol*. 2018;24(30):3361-3373.
18. Miller JB, Henry Z. Diet in non-alcoholic fatty liver disease. *Pract Gastroenterol*. 2019;43(10):24-29.
19. García-Ruiz C, Fernández-Checa JC. Mitochondrial oxidative stress and antioxidants balance in fatty liver disease. *Hepatol Commun*. 2018;2(12):1425-1439.
20. Vilar-Gomez E, Martinez-Perez Y, Calzadilla-Bertot L, et al. Weight loss through lifestyle modification significantly reduces features of nonalcoholic steatohepatitis. *Gastroenterology*. 2015;149(2):367-378.
21. Rinella ME, Tacke F, Sanyal AJ, et al. Report on the AASLD/EASL joint workshop on clinical trial endpoints in NAFLD. *J Hepatol*. 2019;71(4):823-833.
22. Li Y, Liu L, Wang B, et al. Metformin in non-alcoholic fatty liver disease: a systematic review and meta-analysis. *Biomed Rep*. 2013;1(1):57-64.
23. Musso G, Gambino R, Cassader M, Pagano G. A meta-analysis of randomized trials for the treatment of nonalcoholic fatty liver disease. *Hepatology*. 2010;52(1):79-104.
24. Cusi K. Role of obesity and lipotoxicity in the development of nonalcoholic steatohepatitis: pathophysiology and clinical implications. *Gastroenterology*. 2012;142(4):711-725.e6.
25. Sanyal AJ, Chalasani N, Kowdley KV, et al. Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis. *N Engl J Med*. 2010;362(18):1675-1685.
26. Nelson JE, Roth CL, Wilson LA, et al. Vitamin D deficiency is associated with increased risk of non-alcoholic steatohepatitis in adults with non-alcoholic fatty liver disease: possible role for MAPK and NF-κB? *Am J Gastroenterol*. 2016;111(6):852-863.
27. Hariri M, Zohdi S. Effect of vitamin D on non-alcoholic fatty liver disease: a systematic review of randomized controlled clinical trials. *Int J Prev Med*. 2019;10:14.
28. Klein EA, Thompson IM Jr, Tangen CM, et al. Vitamin E and the risk of prostate cancer: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). *JAMA*. 2011;306(14):1549-1556.
29. Capanni M, Calella F, Biagini MR, et al. Prolonged n-3 polyunsaturated fatty acid supplementation ameliorates hepatic steatosis in patients with non-alcoholic fatty liver disease: a pilot study. *Aliment Pharmacol Ther*. 2006;23(8):1143-1151.
30. Lee C-H, Fu Y, Yang S-J, Chi C-C. Effects of omega-3 polyunsaturated fatty acid supplementation on non-alcoholic fatty liver: a systematic review and meta-analysis. *Nutrients*. 2020;12(9):2769.
31. Sjöström L, Peltonen M, Jacobson P, et al. Bariatric surgery and long-term cardiovascular events. *JAMA*. 2012;307(1):56-65.
32. Pontiroli AE, Morabito A. Long-term prevention of mortality in morbid obesity through bariatric surgery. A systematic review and meta-analysis of trials performed with gastric banding and gastric bypass. *Ann Surg*. 2011;253(3):484-487.
33. Mathurin P, Hollebecque A, Arnalsteen L, et al. Prospective study of the long-term effects of bariatric surgery on liver injury in patients without advanced disease. *Gastroenterology*. 2009;137(2):532-540.
34. Lassailly G, Caiazzo R, Buob D, et al. Bariatric surgery reduces features of nonalcoholic steatohepatitis in morbidly obese patients. *Gastroenterology*. 2015;149(2):379-388.