**Name of Journal:** *World Journal of Gastroenterology*

**Manuscript NO:** 55188

**Manuscript Type:** OPINION REVIEW

**Management of nonalcoholic fatty liver disease in the Middle East**

Sanai FM *et al.* NAFLD in the Middle East

Faisal M Sanai, Faisal Abaalkhail, Fuad Hasan, Muhammad Hamed Farooqi, Nawal Al Nahdi, Zobair M Younossi

**Faisal M Sanai**, Gastroenterology Unit, Department of Medicine, King Abdulaziz Medical City, Jeddah 21423, Saudi Arabia

**Faisal Abaalkhail**, Department of Medicine, Alfaisal University, Riyadh 11533, Saudi Arabia

**Faisal Abaalkhail**, Department of Liver Transplant, King Fahad Specialist Hospital, Dammam 32253, Saudi Arabia

**Fuad Hasan**, Department of Internal Medicine, Faculty of Medicine, Kuwait University, Safat 13110, Kuwait

**Muhammad Hamed Farooqi**, Dubai Diabetes Center, Dubai Health Authority, Dubai 00000, United Arab Emirates

**Nawal Alnahdi**, Department of Gastroenterology and Hepatology, Dubai Health Authority, Rashid hospital, Dubai 00000, United Arab Emirates

**Zobair M Younossi**, Department of Medicine, Inova Fairfax Medical Campus, Falls Church, VA 22042, United States

**Author contributions:** All authors equally contributed to this paper in terms of conception, literature review, drafting, critical revision, editing, and final approval for submission.

**Corresponding author:** **Zobair M Younossi, FAASLD, AGAF, FACG, FACP, MD, Chairman, Professor,** Department of Medicine, Inova Fairfax Medical Campus, Betty and Guy Beatty Center for Integrated Research, Inova Health System, Claude Moore Health Education and Research Building 3300 Gallows Road, Falls Church, VA 22042, United States. zobair.younossi@inova.org

**Received:** March 5, 2020

**Revised:** May 15, 2020

**Accepted:** June 10, 2020

**Published online:**

**Abstract**

The prevalence of nonalcoholic fatty liver disease (NAFLD) in the Middle East is increasing in parallel to an increase in the prevalence of associated risk factors such as obesity, metabolic syndrome, and type 2 diabetes mellitus. About 20% to 30% of the patients progress to develop nonalcoholic steatohepatitis (NASH), a histological subtype of NAFLD, with features of hepatocyte injury such as hepatocyte ballooning. NASH can progress to fibrosis, cirrhosis, and even hepatocellular carcinoma. NAFLD thus causes a substantial burden on healthcare systems and it is imperative that appropriate strategies are discussed at a regional level to facilitate effective management tailored to the needs of the region. To fulfil this unmet need, expert gastroenterologists, hepatologists, and endocrinologists from the region came together in three advisory board meetings that were conducted in Saudi Arabia, United Arab Emirates, and Kuwait, to discuss current local challenges in NAFLD screening and diagnosis, and the different available management options. The experts discussed the disease burden of NAFLD/NASH in the Middle East; screening, diagnosis, and referral patterns in NAFLD; and available treatment options for NAFLD and NASH. This paper summarizes the discussions and opinion of the expert panel on the management of NAFLD/NASH and also presents an extensive literature review on the topic.

**Key words:** Nonalcoholic fatty liver disease; Nonalcoholic steatohepatitis; Middle East; Expert opinion

Sanai FM, Abaalkhail F, Hasan F, Farooqi MH, Nahdi NA, Younossi ZM. Management of nonalcoholic fatty liver disease in the Middle East. *World J Gastroenterol* 2020; In press

**Core tip:** With the rising prevalence of nonalcoholic fatty liver disease (NAFLD) in the Middle East, there is an unmet need of appropriate strategies to facilitate effective management at a regional level. Therefore, expert gastroenterologists, hepatologists, and endocrinologists from the region came together in three advisory board meetings that were conducted in Saudi Arabia, United Arab Emirates, and Kuwait. Current local challenges in NAFLD screening and diagnosis, and the different available management options were discussed. This paper summarizes the discussions of the expert panel on the management of NAFLD/nonalcoholic steatohepatitis and also presents an extensive literature review on the topic.

**INTRODUCTION**

Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver disease worldwide and is characterized by fatty infiltration of the liver in the absence of alcohol abuse or other causes of hepatic steatosis such as medications and viral or autoimmune hepatitis[[1](#_ENREF_1)]. It encompasses the entire spectrum of manifestations from steatosis, steatohepatitis, and fibrosis to cirrhosis[[1](#_ENREF_1)]. NAFLD can be categorized as nonalcoholic fatty liver (NAFL) and nonalcoholic steatohepatitis (NASH) based on histopathological criteria. NAFL is defined as the presence of more than 5% of hepatic steatosis without evidence of hepatocellular injury and is generally a nonprogressive condition. On the other hand, NASH implies the presence of hepatic steatosis (> 5%), in conjunction with features of hepatocyte injury (such as hepatocyte ballooning), and can progress to fibrosis, cirrhosis, and even hepatocellular carcinoma (HCC)[[1](#_ENREF_1),[2](#_ENREF_2)]. Although patients with only hepatic steatosis (NAFL) typically do not develop cirrhosis or liver-related complications, about 20% to 30% of NAFLD can be classified as NASH[[3](#_ENREF_3),[4](#_ENREF_4)]. It is important to distinguish between the different types of NAFLD as it has an impact on prognosis and management[[5](#_ENREF_5)].

The estimated prevalence of NAFLD varies worldwide, ranging from 6% to 35%[[6](#_ENREF_6),[7](#_ENREF_7)]. In a recent meta-analysis on the global epidemiology of NAFLD, Younossi *et al*[8] reported its prevalence to be highest (32%) in the Middle East. Also, with an increase in the risk factors of NAFLD and NASH such as obesity, metabolic syndrome (MetS), and type 2 diabetes mellitus (T2DM), the prevalence is estimated to grow further[[6](#_ENREF_6)]. Alswat *et al*[9] conducted an analysis to estimate the burden of NAFLD in Saudi Arabia and United Arab Emirates (UAE) by the year 2030[[9](#_ENREF_9)]. The analysis projected that by 2030 there will be over 12 million individuals (an increase by 48% from 2017) with NAFLD in Saudi Arabia and 372000 (an increase by 46% from 2017) in UAE[[9](#_ENREF_9)]. This projected NAFLD prevalence corresponds to predicted increase in the burden of obesity and T2DM. Furthermore, NASH prevalence, which was 4.2% and 4.1% of the total population in Saudi Arabia and UAE, respectively, in 2017, is expected to rise by 96% and 87%, respectively, by 2030. This model also predicts that the percentage of patients with F3/F4 fibrosis or advanced liver disease (decompensated cirrhosis or HCC) is anticipated to increase to 21.8% (13.5% in 2017) and 21.1% (13.6% in 2017) of the NASH cases in Saudi Arabia and UAE, respectively, by 2030. In Saudi Arabia, incident decompensated cirrhosis is expected to rise by 273% with almost seven thousand cases in 2030. In UAE, the incident decompensation is anticipated to rise by 241%. NAFLD related HCC cases are projected to increase by 209% (580 to 1790) in Saudi Arabia and by 181% (18 to 51) in UAE. By 2030, annual liver-related deaths are estimated to rise by 295% in Saudi Arabia and by 270% in UAE[[9](#_ENREF_9)].

It is important to note that the clinical outcomes of NAFLD can vary across the globe. In a recent study of the Global NASH Registry™, NAFLD subjects enrolled from 14 different countries showed some clinical similarities but also a number of differences[[10](#_ENREF_10)]. These data suggest that the epidemiology of NAFLD must be considered in the context of regional and country-specific factors that impact the incidence, prevalence, and natural history of NAFLD.

NAFLD and NASH pose major challenges in both diagnosis and treatment. There is an ongoing debate as to whether at-risk patients should be screened for NAFLD/NASH in the absence of effective, approved pharmacological treatment options[[2](#_ENREF_2),[11](#_ENREF_11)]. In such a scenario, screening of high-risk groups could be a more practical option. Also, there are uncertainties regarding appropriate referral, management, and follow-up of these patients. With the rising prevalence of NAFLD and NASH in the Middle East, it is imperative that these concerns are discussed at a regional level to facilitate effective strategies tailored to the needs of the region.

With this objective, advisory board meetings were conducted between May 2018 and February 2019 in Saudi Arabia, UAE, and Kuwait, to discuss current local challenges in NASH screening and diagnosis and the different available management options. These meetings were attended by expert gastroenterologists, hepatologists, and endocrinologists from the region. This paper summarizes the discussions in the meetings, along with a comprehensive literature review on the topic. For the review, PubMed and Google Scholar were searched employing the Boolean operators, “AND” and “OR”, and using the following search terms: “nonalcoholic fatty liver disease”, “NAFLD”, “nonalcoholic steatohepatitis”, “NASH”, “type 2 diabetes mellitus”, “T2DM”, “metabolic syndrome”, “obesity”, “guidelines”. The bibliographies of the key references were also searched manually for additional relevant references.

During the meetings, the experts discussed the following topics: (1) Disease burden of NAFLD/NASH in the Middle East; (2) Screening, diagnosis, and referral patterns in NAFLD; and (3) Available treatment options for NAFL and NASH.

**DISEASE BURDEN OF NONALCOHOLIC FATTY LIVER DISEASE/NONALCOHOLIC STEATOHEPATITIS IN THE MIDDLE EAST**

***NAFLD/NASH burden in the Middle East countries is growing with the increase in the prevalence of risk factors such as obesity, MetS, and T2DM***

A population-wide screening program in UAE found that 35% of the population had obesity, 32% were overweight, 55% had central obesity, 18% had diabetes, 27% were prediabetic, and 44% had dyslipidemia[[12](#_ENREF_12)] (Table 1). Further, Radwan *et al*[13] reported a two to three-fold increase in the prevalence of obesity in the UAE between 1989 and 2017[[13](#_ENREF_13)]. In a survey conducted in 2013 in Saudi Arabia, 28.7% of the 10735 participants were obese (body mass index, ≥ 30 kg/m2)[[14](#_ENREF_14)]. Moreover, Al-Quwaidhi *et al*[15] projected an increase in the overall prevalence of obesity in Saudi Arabia to 41% in men, and 78% in women by 2022[[15](#_ENREF_15)]. Obesity has been strongly linked with NAFLD and is known to be associated with the entire histological spectrum from steatosis, hepatocellular injury, fibrosis, cirrhosis, and even HCC[[16](#_ENREF_16)]. In a study (*n* = 296), Alqahtani *et al*[17] found that 65% of severely obese young children in Saudi Arabia had NASH and 60% had clinically significant liver fibrosis[[17](#_ENREF_17)].

Similarly, regional disease burden from diabetes has been steadily increasing. As per the World Health Organization, in the Middle East and North Africa region, a 72% increase in the prevalence of diabetes from 39 million adults in 2017 to 85 million in 2045 is estimated[[18](#_ENREF_18)]. In Saudi Arabia, the prevalence of diabetes has risen almost 10 fold over the past three decades[[19](#_ENREF_19)]. There are several contributors to this, including rapid urbanization, unhealthy eating habits, and sedentary lifestyle[[18](#_ENREF_18" \o ",  #2)]. Patients with T2DM have a high prevalence of NAFLD and advanced fibrosis. In a meta-analysis of 24 studies, the pooled prevalence of NAFLD in T2DM patients was almost 60%[[20](#_ENREF_20" \o "Dai, 2017 #19)]. In another more recent (2019) meta-analysis, the global prevalence of NAFLD among T2DM patients was 55.5%[[21](#_ENREF_21)]. Similarly, a meta-analysis that included 17 studies with T2DM patients found the prevalence of NAFLD to be 54%[[22](#_ENREF_22)]. All these studies may have slightly different methodology but, as is evident, prevalence of NAFLD in individuals with T2DM was quite high. Moreover, presence of NAFLD has been reported to be associated with a twofold increased risk of incident diabetes[[23](#_ENREF_23)]. Further, the prevalence of NASH in diabetic patients with NAFLD has also been evaluated. In a recent meta-analysis by Younossi *et al*[21], while the global prevalence of NASH in patients with T2DM was found to be 37.3%, the prevalence of advanced fibrosis was 17%[[21](#_ENREF_21)]. In a study derived from the NASH Clinical Research Network, of 346 patients with diabetes and NAFLD, the prevalence of NASH and advanced fibrosis was 69.2% and 41%, respectively[[24](#_ENREF_24)].

Similar to T2DM, the prevalence of MetS (*i.e.*, abdominal obesity, hypertension, atherogenic dyslipidemia, and hyperglycemia) in the Middle East is also on the rise. A meta-analysis of cross-sectional studies from the Middle East countries reported the prevalence of MetS to be 16%-41% in Saudi-Arabia, 9%-36% in Kuwait, and 22%-50% in UAE[[25](#_ENREF_25)]. A recent study found the prevalence of MetS in Saudi Arabia to be about 40%[[26](#_ENREF_26)]. A strong association between MetS and NAFLD has been reported previously. In a study conducted on 304 patients with NAFLD without overt diabetes, 88% of patients who had NASH on liver biopsy had MetS. Further, the study showed that MetS was associated with a high risk of NASH among NAFLD patients [odds ratio (OR), 3.2; 95%CI: 1.2-8.9; *P* = 0.026][[27](#_ENREF_27)]. Furthermore, in the NASH Clinical Research Network data, presence of NASH was significantly associated with MetS (OR: 1.43; 95%CI: 1.09-1.98; *P* = 0.009)[[28](#_ENREF_28)]. In a regional study from Kuwait, T2DM (*P*= 0.02) and obesity (*P*< 0.004) were again significantly associated with NAFLD[[29](#_ENREF_29)].

In summary, obesity, MetS, T2DM, and NAFLD are all associated with each other. Emerging data also appears to show that the prevalence of NAFLD is growing in parallel with that of obesity, MetS, and T2DM, worldwide, with Middle East being no exception[[11](#_ENREF_11),[30](#_ENREF_30),[31](#_ENREF_31)].

**SCREENING, DIAGNOSIS, AND REFERRAL PATTERNS IN NONALCOHOLIC FATTY LIVER DISEASE**

***Patients with risk factors, namely obesity, MetS, and T2DM should be screened for NAFLD***

Given the high prevalence of NAFLD in high-risk groups, most international guidelines including European, Asia-Pacific, and National Institute for Health and Care Excellence recommend routine screening in these patients with liver enzymes, ultrasonography, and transient elastography, where available[[2](#_ENREF_2),[32](#_ENREF_32),[33](#_ENREF_33)]. European guidelines also recommend case finding of advanced disease (*i.e.* NASH with fibrosis) in high risk individuals (age > 50 years, T2DM, MetS)[[2](#_ENREF_2)]. However, the American Association for the Study of Liver Diseases (AASLD) guidelines currently do not recommend routine screening for NAFLD given the uncertainties regarding performance characteristics of diagnostic tests and available treatment options[[1](#_ENREF_1)]. Nevertheless, they urge clinicians to have a high index of suspicion for NAFLD and NASH in patients with diabetes even if liver enzymes are normal[[1](#_ENREF_1)]. European guideline also recommends that individuals with persistently abnormal liver enzymes be screened for NAFLD and all those with steatosis be screened for MetS independent of liver enzymes[[2](#_ENREF_2)]. Obtaining a random aspartate transaminase and alanine transaminase (ALT) level in individuals with obesity, MetS, and T2DM may be a reasonable approach[[34](#_ENREF_34)]. However, as it is known that liver enzymes may not always be elevated in NAFLD, an ultrasound can be done on patients suspected to have NAFLD. Other tests can be used for screening based on availability and feasibility.

***Definite diagnosis of NASH can only be made by liver biopsy. Candidates for liver biopsy should be chosen carefully based on the results of noninvasive tests.***

The diagnosis of NAFLD involves clinical history to rule out secondary causes of fatty liver and to obtain information on risk factors such as age (≥ 50 years) and the presence of T2DM and MetS[[35](#_ENREF_35)] (Figure 1). Further, biochemical investigations and radiological findings aid in making the diagnosis. Patients often do not experience overt symptoms but their quality of life is impaired[[36](#_ENREF_36" \o "Younossi, 2019 #85)]. In most cases, the diagnosis of NAFLD is made when elevated liver enzymes are found incidentally. Also, it is important to note that liver enzymes can be within the normal range in NASH and a definitive diagnosis can only be made by histology[[30](#_ENREF_30)].

Although liver biopsy is considered as the gold standard for establishing NASH and for staging of fibrosis, it is associated with the risk of complications such as pain, intraperitoneal bleeding, and pneumothorax[[35](#_ENREF_35)]. Noninvasive methods of diagnosis include serum biomarkers, routine radiologic tests such as ultrasound, computed tomography, magnetic resonance imaging, and assessment of liver stiffness by transient elastography (FibroScan®) and magnetic resonance elastography[[37](#_ENREF_37)]. Validated laboratory-based scoring systems for estimating the stage of hepatic fibrosis are also available, such as NAFLD fibrosis score, FibroMeter, and Fibrosis-4[[35](#_ENREF_35)]. The advantages and limitations of some of the available diagnostic modalities are listed in Table 2.

In addition to these tests, a number of serum fibrosis tests are being evaluated for risk-stratifying patients with NASH. Of these, Enhanced Liver Fibrosis (ELF™) is available in Europe and seems to be a promising non-invasive test for risk assessment in patients with NASH[[38](#_ENREF_38)].

Since none of the noninvasive tests can confirm a diagnosis of NASH, the only available option for definitive diagnosis is liver biopsy. However, it has been found that the combination or sequential use of different noninvasive methods or different scoring systems can increase overall diagnostic accuracy with consequent decrease in the need for liver biopsy[[39-41](#_ENREF_39)]. In summary, diagnosis of NASH is complex and needs careful consideration of available non-invasive diagnostic tools. It is advisable to use these various modalities based on availability and carefully select the subset of patients, who will benefit from liver biopsy, based on the results of the noninvasive methods.

Liver biopsy also plays an important role in staging and risk-stratification of the disease. NASH fibrosis is divided into four stages based on severity, ranging from the less severe stages (F1 and F2) to F3 and F4 (bridging fibrosis and cirrhosis, respectively)[[42](#_ENREF_42)]. The presence and degree of fibrosis has been shown to be the most important prognostic marker in NASH[[43-46](#_ENREF_43)]. In a study, during a follow-up of mean 20 years (range 0-40) equivalent to 139163 person-years, the risk of severe liver disease increased per stage of fibrosis (hazard ratio ranging from 1.9 in F0 to 104.9 in F4) compared to controls[[44](#_ENREF_44)]. In another study, features of liver biopsies significantly associated with death or liver transplantation included fibrosis stage 1 (HR: 1.88; 95%CI: 1.28-2.77), stage 2 (HR: 2.89; 95%CI: 1.93-4.33), stage 3 (HR: 3.76; 95%CI: 2.40-5.89), and stage 4 (HR: 10.9; 95%CI: 6.06-19.62) compared with stage 0[[43](#_ENREF_43)].

***Referral of patients should be done promptly once NASH is suspected and NASH should be managed by multidisciplinary teams***

Currently, NAFLD is underdiagnosed[[47](#_ENREF_47" \o "Alexander, 2018 #65)]. It is crucial to increase awareness regarding NAFLD and NASH *via* effective multi-disciplinary collaboration among healthcare professionals. Education of primary care physicians as well as diabetologists is important. Diabetologists and primary care physicians should be encouraged to screen at-risk patients for NAFLD, followed by time-sensitive referral, especially in patients with suspected NASH. In view of the co-morbid conditions often associated with NAFLD, a multidisciplinary management approach that includes primary care physicians, gastroenterologists, endocrinologists/diabetologists, cardiologists, and nutritionists is warranted.

**AVAILABLE TREATMENT OPTIONS FOR NONALCOHOLIC FATTY LIVER AND NONALCOHOLIC STEATOHEPATITIS**

***Patients with NAFL should be advised lifestyle modifications only. Patients with NASH should be considered for therapy based on the stage of the disease and the presence of comorbidities***

Once NAFLD/NASH is diagnosed, the next step is to consider appropriate therapeutic intervention. This is currently limited by lack of effective treatment options to prevent or reduce progression to cirrhosis and HCC. Although all patients with NAFLD are candidates for lifestyle intervention to optimize their cardiovascular risks, only patients with NASH are candidates for pharmacotherapy. Therefore, the current treatment options for NASH include lifestyle interventions, pharmacotherapy (mostly off-label), and consideration for bariatric surgery in the context of metabolic indication for weight loss surgery. Importantly, treatment should also involve the management of comorbidities[[1](#_ENREF_1),[2](#_ENREF_2)].

Patients with NAFL usually have a favorable liver-related prognosis and require management of their cardiovascular risks. In this context, NAFL patients do not require consideration of pharmacotherapy for liver disease and this treatment option should be reserved for patients diagnosed with NASH. Intervention in patients with NAFL should be limited to encouragement of appropriate lifestyle modifications[[1](#_ENREF_1),[2](#_ENREF_2)]. Lifestyle interventions, including diet and exercise, have been found to be effective when adequate weight loss is achieved. In a meta-analysis that included 20 studies and 1073 NAFLD patients, exercise significantly improved aspartate transaminase and ALT (*P*< 0.05). Additionally, combined exercise and diet decreased ALT (*P*< 0.01) and improved NAFLD activity score (standardized mean difference -0.61, 95%CI: -1.09 to -0.13)[[48](#_ENREF_48)]. Bradford *et al*[49] reviewed 30 studies that used diet and/or exercise as an intervention for patients with NAFLD[[49](#_ENREF_49)]. A total of 14 studies that included both diet and exercise showed improvement in the various outcome measures evaluated. Of the nine studies that included only exercise as an intervention, eight studies showed a positive outcome. Furthermore, all seven studies that used only diet as an intervention also showed improvement in markers of hepatic steatosis, leading the authors to conclude that lifestyle intervention is a critical component of management of patients with NAFLD[[49](#_ENREF_49)].

European Association for the Study of the Liver, European Association for the Study of Diabetes, and European Association for the Study of Obesity and AASLD guidelines recommend a combination of daily reduction in caloric intake by 500 to 1000 kcal and moderate-intensity exercise for sustaining weight loss over time[[1](#_ENREF_1),[2](#_ENREF_2)]. A systematic review and meta-analysis reported improved hepatic steatosis with ≥ 5% weight loss and improvement in NASH with a weight loss of ≥ 7%[[50](#_ENREF_50)]. As per the AASLD guidelines, weight loss of 3%-5% of total body weight is required to improve steatosis and weight loss of 7%-10% is necessary to improve histopathological features of NASH[[1](#_ENREF_1)]. It has also been suggested that weight loss of more than 10% may improve fibrosis[[51](#_ENREF_51),[52](#_ENREF_52)].

It is important to note that currently, there are no pharmacotherapies approved for the treatment of NASH. This underscores the need for clinicians to make treatment decisions based on individual patient circumstances, taking into account the stage of NASH and safety, expected benefit, pricing, and evidence base of available off-label pharmacological treatment options. Although metformin has been widely studied in patients with NASH, it was not found to have beneficial effects on liver histology[[53-55](#_ENREF_53)] and is therefore not recommended in patients with NASH[[1](#_ENREF_1),[2](#_ENREF_2),[32](#_ENREF_32)]. On the other hand, the thiazolidinedione, pioglitazone has been shown to be promising in improving liver histology in NASH patients with or without T2DM[[56-58](#_ENREF_56)]. Pioglitazone could be considered in these patients although currently AASLD guidelines recommend consideration of its use in biopsy-proven NASH only[[1](#_ENREF_1)]. Vitamin E has also been used in patients with NAFLD and NASH. In a meta-analysis, vitamin E supplementation was associated with significant (*P*< 0.05) improvement in all histological parameters including steatosis, ballooning, lobular inflammation, and fibrosis in nondiabetic individuals with NASH[[59](#_ENREF_59)]. Similar results were found in another meta-analysis, where vitamin E significantly reduced liver enzymes and improved liver histology[[60](#_ENREF_60)]. However, concerns have been raised about the safety of vitamin E supplementation, including increased all-cause mortality with dose of > 800 IU/d and an observed association with prostate cancer[[61](#_ENREF_61),[62](#_ENREF_62)]. Nevertheless, a large meta-analysis that included 57 studies including 246371 patients, who were followed for up to 10 years, did not show any association between vitamin E and all-cause mortality[[63](#_ENREF_63)]. Consequently, it is recommended that vitamin E at a dose of 800 IU/d be considered in nondiabetic adults with biopsy-proven NASH[[1](#_ENREF_1)]. A meta-analysis that included nine clinical trials (three with thiazolidinedione, three with metformin, two with vitamin E and one with both thiazolidinedione and vitamin E), found that thiazolidinedione and vitamin E improved liver histologic scores, but metformin did not. None of the agents improved fibrosis[[64](#_ENREF_64" \o "Said, 2017 #66)].

NAFLD has been shown to be associated with an increased risk of cardiovascular events, regardless of the presence of coexisting metabolic syndrome, mandating consideration of interventions to treat cardiovascular risk factors[[65](#_ENREF_65)]. Concerns persist amongst clinicians regarding statin use in patients with liver disease. However, statins can be used to treat dyslipidemia in patients with NAFLD and NASH without any concern regarding liver toxicity[[1](#_ENREF_1),[66](#_ENREF_66)]. Statins have also been studied for the treatment of NAFLD and NASH but their efficacy for this indication is debated due to inconsistent results in clinical trials[[66](#_ENREF_66)].

Sustained weight loss is indeed the most effective way to treat NAFLD and NASH. Unfortunately, this is difficult to achieve utilizing lifestyle modifications alone. Bariatric surgery, therefore, has an important role in the management of obese NASH patients. In one study, 85% of 109 morbidly obese patients with biopsy-proven NASH showed resolution of disease one year after bariatric surgery and the likelihood of improvement correlated with liver disease severity prior to surgery and degree of weight loss achieved[[67](#_ENREF_67)]. A third of patients were also observed to have improvement in hepatic fibrosis[[67](#_ENREF_67" \o "Lassailly, 2015 #52)]. In a systematic review and meta-analysis, bariatric surgery was associated with a significant reduction in the weighted incidence of a number of histological features of NAFLD including steatosis (50.2%), fibrosis (11.9%), hepatocyte ballooning (67.7%), and lobular inflammation (50.7%)[[68](#_ENREF_68)]. A study conducted in the United States found bariatric surgery to be not just effective but also cost-effective in the treatment of obese patients with NASH[[69](#_ENREF_69)].

In a study conducted in the UAE, 80 patients underwent bariatric surgery, either laparoscopic sleeve gastrectomy (*n* = 53) or mini-gastric bypass (*n* = 27). There was significant reduction in mean body weight at 3, 6, 12, and 24 mo (*P*< 0.001 for each time point). Of the 61.3% who had NAFLD, 22.4% showed improvement in sonographic features of hepatic steatosis with normalization of ALT[[70](#_ENREF_70)]. In another study (*n* = 27) conducted in Saudi Arabia, after 3 mo of bariatric surgery, 66.6% of the patients with preoperative steatosis (median score 2) had reduced steatosis scores postoperatively (*P*= 0.025) and 68% of the patients had reduced fibrosis (median score 1) (*P*= 0.012). Also, NAFLD activity score was decreased from 4 (3-5) to 2 (1-3) (*P*= 0.004)[[71](#_ENREF_71)]. However, it is also important to note that the use of bariatric surgery is limited by its cost and complications that are associated with any surgical procedure. As such, any advocacy for bariatric surgery must be tempered with a parallel education of its associated complications, which remains suboptimal in the region[[72](#_ENREF_72)].

***NASH-related cirrhosis is growing as an indication for liver transplantation***

NASH is projected to become the most common indication for liver transplantation in near future[[73](#_ENREF_73" \o "Bzowej, 2018 #63)]. With the availability of highly effective treatment options for hepatitis C virus (HCV)-related cirrhosis, NASH-related cirrhosis is emerging as the leading indication for liver transplantation worldwide.

In a study conducted in Saudi Arabia, over the course of the time period from January 2001 to December 2006, 50%, 17%, and 12% of the patients underwent liver transplant for HCV-induced cirrhosis, HBV-induced cirrhosis, and NASH-related cirrhosis, respectively. On the other hand, from January 2007 to January 2012, 35%, 16%, and 20% of the patients underwent transplantation for HCV-, HBV-, and NASH-induced cirrhosis, respectively, underscoring the evolving trends in the indications for liver transplantation[[74](#_ENREF_74)].

Being a complex procedure, liver transplantation is associated with several limitations. Another important aspect to consider is that liver transplantation does not treat the comorbidities of NASH and therefore interventions to address the accompanying metabolic diseases is important, before and after transplantation[[73](#_ENREF_73)].

***Emerging therapies for NASH are awaited for more effective management of this disease***

Currently, many new drugs are being developed with varying mechanisms of action, with the goal of improving hepatic steatosis, inflammation, liver cell injury, and fibrosis in patients with NAFLD[[75](#_ENREF_75)]. Some of these include obeticholic acid (farnesoid X receptor agonist), elafibranor (a dual receptor peroxisome proliferator activated alpha/delta agonist), GS-9674 (farnesoid X receptor agonist), and GS-0976 (Acetyl-CoA carboxylase inhibitor). Future treatment options may also include combination therapies[[75](#_ENREF_75),[76](#_ENREF_76)].

**ADDRESSING NONALCOHOLIC FATTY LIVER DISEASE BURDEN IN THE MIDDLE EAST**

Despite the high burden of NAFLD, there are no proper epidemiological studies or regional clinical guidelines that are relevant to these countries. The lack of properly carried out community-based epidemiological studies is a particular concern, and has obvious fallouts on resource planning and allocation, and poses considerable difficulties to these countries’ healthcare systems. To some extent, regional prevalence numbers remain best guess estimates, based in part on modeling analyses or otherwise on indirect markers of NAFLD such as obesity and T2DM[9]. This stresses an immediate need for adequately sampled, large-scale, nationwide surveys for NAFLD, where the prevalence across all population sectors, age groups, and geographic distributions is properly estimated. The relevant health authorities and ministries of these countries would be best positioned to lead such an initiative, executing it jointly with regional scientists and public health experts. Part of the epidemiological equation entails understanding the demographics and evolution of the disease, and towards this an access to a national registry for NASH is crucial.

There must be an urgent commitment to address the factors contributing to obesity in the Middle East, including dietary factors and inactivity, with particular focus on childhood obesity[77]. Dietary and lifestyle changes have a substantial impact on the natural course of the disease. As such, from a public health perspective, one of the most crucial aspects to focus on is to modify risk factors that are geared towards reducing obesity rates and achieving better dietary habits. Targeted measures such as taxation of beverages, marketing regulation, improving nutritional labeling, conducting awareness campaigns, and allocating subsidies to improve healthy eating could be implemented[78].

The dearth of algorithms for primary care referral is worrisome in view of the high prevalence of NAFLD in the Middle East. Primary health care should play a key role in the management of NAFLD, not only because of its pivotal role in health promotion and community care but also because specialized liver care is generally not prepared to receive such a large number of patients. Simple and affordable algorithms to identify patients at high risk of complications could be implemented in primary care to determine patients needing specialized care. A broad availability of transient elastography in primary healthcare centers must be envisioned in any NAFLD national plan, since significant hepatic disease may exist in non-obese individuals, and in those with normal liver enzymes[79]. This approach would contribute substantially to managing the intricacies of NAFLD-related disease burden within a healthcare system that provides early detection while preserving economic sustainability and equity[78].

Therefore, continuing education programs and awareness campaigns are crucial, as well as development and adaptation of clinical guidelines to protocols that identify patients who need specialist referral. Potential factors that need to be assessed include the role of non-liver specialists, and the implementation of community-based initiatives and civil society involvement aimed at NAFLD education, prevention, detection, and care.

This huge challenge facing our medical community must be effectively tackled with comprehensive, widely adopted, national (or regional) NAFLD plans, that start from awareness and education, emphasize prevention, set up early detection programs, and provide the recommended algorithms of care in a cost-effective and evidence-based manner. Such efforts should be led by robust research machinery that is able to predict, rationalize, and assess the effectiveness of hereupon-adopted strategies. Alliances will require to be forged not just across different institutes and affiliations, but also involving patients and community partners. However, most importantly, such plans would demand unprecedented attention to public health and can only succeed if they are coupled with an enforcement power that can guarantee their implementation[80].

**CONCLUSION**

The prevalence of NAFLD in the Middle East is increasing, along with its known associations of obesity, MetS, and T2DM, thereby placing a substantial burden on healthcare systems in the region. Suggested interventions to mitigate this challenge include education and awareness of patients and primary care providers regarding NAFLD; management of the risk factors and comorbidities; appropriate screening, evaluation, and diagnosis; and timely referral to hepatologists. This calls for a multidisciplinary approach involving primary care providers, gastroenterologists, endocrinologists, diabetologists, cardiologists, and hepatologists. There remains a need for clinical care pathways to help guide clinicians involved in the care of these patients[81-86].

Many challenges and unmet needs remain in the diagnosis and management of NAFLD. There is a lack of reliable noninvasive tests for the accurate diagnosis of NASH. Also, there is no approved therapy for the treatment of NASH and current management is largely dependent on lifestyle modifications, which are challenging to initiate and sustain, resulting in inadequate weight reduction. Many therapies are currently under development and are keenly awaited. The availability of effective pharmacotherapy holds significant promise to improve the current landscape of available treatment options in NAFLD.

**REFERENCES**

1 **Chalasani N**, Younossi Z, Lavine JE, Charlton M, Cusi K, Rinella M, Harrison SA, Brunt EM, Sanyal AJ. The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. *Hepatology* 2018; **67**: 328-357 [PMID: 28714183 DOI: 10.1002/hep.29367]

2 **European Association for the Study of the Liver (EASL)**; European Association for the Study of Diabetes (EASD); European Association for the Study of Obesity (EASO). EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. *J Hepatol* 2016; **64**: 1388-1402 [PMID: 27062661 DOI: 10.1016/j.jhep.2015.11.004]

3 **Wong VW**, Wong GL, Choi PC, Chan AW, Li MK, Chan HY, Chim AM, Yu J, Sung JJ, Chan HL. Disease progression of non-alcoholic fatty liver disease: a prospective study with paired liver biopsies at 3 years. *Gut* 2010; **59**: 969-974 [PMID: 20581244 DOI: 10.1136/gut.2009.205088]

4 **Pais R**, Charlotte F, Fedchuk L, Bedossa P, Lebray P, Poynard T, Ratziu V; LIDO Study Group. A systematic review of follow-up biopsies reveals disease progression in patients with non-alcoholic fatty liver. *J Hepatol* 2013; **59**: 550-556 [PMID: 23665288 DOI: 10.1016/j.jhep.2013.04.027]

5 **Vuppalanchi R**, Chalasani N. Screening Strategies for Nonalcoholic Steatohepatitis in High-Risk Individuals: Trimming Away the Fat. *Dig Dis Sci* 2016; **61**: 1790-1792 [PMID: 27010545 DOI: 10.1007/s10620-016-4134-1]

6 **Sayiner M**, Koenig A, Henry L, Younossi ZM. Epidemiology of Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis in the United States and the Rest of the World. *Clin Liver Dis* 2016; **20**: 205-214 [PMID: 27063264 DOI: 10.1016/j.cld.2015.10.001]

7 **Bellentani S**. The epidemiology of non-alcoholic fatty liver disease. *Liver Int* 2017; **37 Suppl 1**: 81-84 [PMID: 28052624 DOI: 10.1111/liv.13299]

8 **Younossi ZM**, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology* 2016; **64**: 73-84 [PMID: 26707365 DOI: 10.1002/hep.28431]

9 **Alswat K**, Aljumah AA, Sanai FM, Abaalkhail F, Alghamdi M, Al Hamoudi WK, Al Khathlan A, Al Quraishi H, Al Rifai A, Al Zaabi M, Babatin MA, Estes C, Hashim A, Razavi H. Nonalcoholic fatty liver disease burden - Saudi Arabia and United Arab Emirates, 2017-2030. *Saudi J Gastroenterol* 2018; **24**: 211-219 [PMID: 29956688 DOI: 10.4103/sjg.SJG\_122\_18]

10 **Younossi ZM,** Yu ML, El Kassas M, Esmat G, Yilmaz Y, Fernandez MC, Duseja AK, Isakov VA, Buti M, Mendez‐Sanchez N, Papatheodoridis GV, Chan WK, George J, Bugianesi E, Romero‐Gomez M, Roberts SK, Younes Z, Wai‐Sun Wong V, Fan JG, Eguchi Y, Gordon SC, Ahmed A, Ong J, Jacobson IM, Rinella ME, Hamid SS, Ziayee M, Younossi I, Lam BP, Arrese M, Nader F, Racila A, Henry L, Stepanova M on behalf of the Global NASH Council. Clinical and Patient‐Reported Outcomes Data for Patients with Non‐Alcoholic Fatty Liver Disease (NAFLD) and Non‐Alcoholic Steatohepatitis (NASH) Across the World: Data from the Global NASH Registry. *Hepatology* 2019; **70(S1)**: i-ii, 1-1476 Available from: <https://aasldpubs.onlinelibrary.wiley.com/doi/10.1002/hep.30941>

11 **Lonardo A**, Nascimbeni F, Maurantonio M, Marrazzo A, Rinaldi L, Adinolfi LE. Nonalcoholic fatty liver disease: Evolving paradigms. *World J Gastroenterol* 2017; **23**: 6571-6592 [PMID: 29085206 DOI: 10.3748/wjg.v23.i36.6571]

12 **Hajat C**, Harrison O, Al Siksek Z. Weqaya: a population-wide cardiovascular screening program in Abu Dhabi, United Arab Emirates. *Am J Public Health* 2012; **102**: 909-914 [PMID: 21940918 DOI: 10.2105/AJPH.2011.300290]

13 **Radwan H**, Ballout RA, Hasan H, Lessan N, Karavetian M, Rizk R. The Epidemiology and Economic Burden of Obesity and Related Cardiometabolic Disorders in the United Arab Emirates: A Systematic Review and Qualitative Synthesis. *J Obes* 2018; **2018**: 2185942 [PMID: 30652030 DOI: 10.1155/2018/2185942]

14 **Memish ZA**, El Bcheraoui C, Tuffaha M, Robinson M, Daoud F, Jaber S, Mikhitarian S, Al Saeedi M, AlMazroa MA, Mokdad AH, Al Rabeeah AA. Obesity and associated factors--Kingdom of Saudi Arabia, 2013. *Prev Chronic Dis* 2014; **11**: E174 [PMID: 25299980 DOI: 10.5888/pcd11.140236]

15 **Al-Quwaidhi AJ**, Pearce MS, Critchley JA, Sobngwi E, O'Flaherty M. Trends and future projections of the prevalence of adult obesity in Saudi Arabia, 1992-2022. *East Mediterr Health J* 2014; **20**: 589-595 [PMID: 25356689 DOI: 10.26719/2014.20.10.589]

16 **Polyzos SA**, Kountouras J, Mantzoros CS. Obesity and nonalcoholic fatty liver disease: From pathophysiology to therapeutics. *Metabolism* 2019; **92**: 82-97 [PMID: 30502373 DOI: 10.1016/j.metabol.2018.11.014]

17 **Alqahtani A**, Elahmedi M, Alswat K, Arafah M, Fagih M, Lee J. Features of nonalcoholic steatohepatitis in severely obese children and adolescents undergoing sleeve gastrectomy. *Surg Obes Relat Dis* 2017; **13**: 1599-1609 [PMID: 28600116 DOI: 10.1016/j.soard.2017.04.005]

18 **International Diabetes Federation,** Diabetes Atlas. Eighth Edition 2017. [accessed 2019 Nov 07]. In: idf.org [Internet]. Available from: https://www.idf.org/our-network/regions-members/middle-east-and-north-africa/diabetes-in-mena.html

19 **Alzaid A.** Diabetes: A tale of two cultures. 2012; **12**: 57-59 [DOI: 10.1177/1474651412444143]

20 **Dai W**, Ye L, Liu A, Wen SW, Deng J, Wu X, Lai Z. Prevalence of nonalcoholic fatty liver disease in patients with type 2 diabetes mellitus: A meta-analysis. *Medicine (Baltimore)* 2017; **96**: e8179 [PMID: 28953675 DOI: 10.1097/MD.0000000000008179]

21 **Younossi ZM**, Golabi P, de Avila L, Paik JM, Srishord M, Fukui N, Qiu Y, Burns L, Afendy A, Nader F. The global epidemiology of NAFLD and NASH in patients with type 2 diabetes: A systematic review and meta-analysis. *J Hepatol* 2019; **71**: 793-801 [PMID: 31279902 DOI: 10.1016/j.jhep.2019.06.021]

22 **Amiri Dash Atan N**, Koushki M, Motedayen M, Dousti M, Sayehmiri F, Vafaee R, Norouzinia M, Gholami R. Type 2 diabetes mellitus and non-alcoholic fatty liver disease: a systematic review and meta-analysis. *Gastroenterol Hepatol Bed Bench* 2017; **10**: S1-S7 [PMID: 29511464]

23 **Mantovani A**, Byrne CD, Bonora E, Targher G. Nonalcoholic Fatty Liver Disease and Risk of Incident Type 2 Diabetes: A Meta-analysis. *Diabetes Care* 2018; **41**: 372-382 [PMID: 29358469 DOI: 10.2337/dc17-1902]

24 **Bazick J**, Donithan M, Neuschwander-Tetri BA, Kleiner D, Brunt EM, Wilson L, Doo E, Lavine J, Tonascia J, Loomba R. Clinical Model for NASH and Advanced Fibrosis in Adult Patients With Diabetes and NAFLD: Guidelines for Referral in NAFLD. *Diabetes Care* 2015; **38**: 1347-1355 [PMID: 25887357 DOI: 10.2337/dc14-1239]

25 **Ansarimoghaddam A**, Adineh HA, Zareban I, Iranpour S, HosseinZadeh A, Kh F. Prevalence of metabolic syndrome in Middle-East countries: Meta-analysis of cross-sectional studies. *Diabetes Metab Syndr* 2018; **12**: 195-201 [PMID: 29203060 DOI: 10.1016/j.dsx.2017.11.004]

26 **Al-Rubeaan K**, Bawazeer N, Al Farsi Y, Youssef AM, Al-Yahya AA, AlQumaidi H, Al-Malki BM, Naji KA, Al-Shehri K, Al Rumaih FI. Prevalence of metabolic syndrome in Saudi Arabia - a cross sectional study. *BMC Endocr Disord* 2018; **18**: 16 [PMID: 29506520 DOI: 10.1186/s12902-018-0244-4]

27 **Marchesini G**, Bugianesi E, Forlani G, Cerrelli F, Lenzi M, Manini R, Natale S, Vanni E, Villanova N, Melchionda N, Rizzetto M. Nonalcoholic fatty liver, steatohepatitis, and the metabolic syndrome. *Hepatology* 2003; **37**: 917-923 [PMID: 12668987 DOI: 10.1053/jhep.2003.50161]

28 **Brunt EM**, Kleiner DE, Wilson LA, Belt P, Neuschwander-Tetri BA; NASH Clinical Research Network (CRN). Nonalcoholic fatty liver disease (NAFLD) activity score and the histopathologic diagnosis in NAFLD: distinct clinicopathologic meanings. *Hepatology* 2011; **53**: 810-820 [PMID: 21319198 DOI: 10.1002/hep.24127]

29 **Babusik P**, Bilal M, Duris I. Nonalcoholic fatty liver disease of two ethnic groups in Kuwait: comparison of prevalence and risk factors. *Med Princ Pract* 2012; **21**: 56-62 [PMID: 22024606 DOI: 10.1159/000331591]

30 **Iqbal U**, Perumpail BJ, Akhtar D, Kim D, Ahmed A. The Epidemiology, Risk Profiling and Diagnostic Challenges of Nonalcoholic Fatty Liver Disease. *Medicines (Basel)* 2019; **6** [PMID: 30889791 DOI: 10.3390/medicines6010041]

31 **Tesfay M**, Goldkamp WJ, Neuschwander-Tetri BA. NASH: The Emerging Most Common Form of Chronic Liver Disease. *Mo Med* 2018; **115**: 225-229 [PMID: 30228727]

32 **National Guideline Centre (UK)**. 2016 [PMID: 27441333]

33 **Wong VW**, Chan WK, Chitturi S, Chawla Y, Dan YY, Duseja A, Fan J, Goh KL, Hamaguchi M, Hashimoto E, Kim SU, Lesmana LA, Lin YC, Liu CJ, Ni YH, Sollano J, Wong SK, Wong GL, Chan HL, Farrell G. Asia-Pacific Working Party on Non-alcoholic Fatty Liver Disease guidelines 2017-Part 1: Definition, risk factors and assessment. *J Gastroenterol Hepatol* 2018; **33**: 70-85 [PMID: 28670712 DOI: 10.1111/jgh.13857]

34 **Spengler EK**, Loomba R. Recommendations for Diagnosis, Referral for Liver Biopsy, and Treatment of Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis. *Mayo Clin Proc* 2015; **90**: 1233-1246 [PMID: 26219858 DOI: 10.1016/j.mayocp.2015.06.013]

35 **Tsai E**, Lee TP. Diagnosis and Evaluation of Nonalcoholic Fatty Liver Disease/Nonalcoholic Steatohepatitis, Including Noninvasive Biomarkers and Transient Elastography. *Clin Liver Dis* 2018; **22**: 73-92 [PMID: 29128062 DOI: 10.1016/j.cld.2017.08.004]

36 **Younossi ZM**, Stepanova M, Lawitz EJ, Reddy KR, Wai-Sun Wong V, Mangia A, Muir AJ, Jacobson I, Djedjos CS, Gaggar A, Myers RP, Younossi I, Nader F, Racila A. Patients With Nonalcoholic Steatohepatitis Experience Severe Impairment of Health-Related Quality of Life. *Am J Gastroenterol* 2019; **114**: 1636-1641 [PMID: 31464743 DOI: 10.14309/ajg.0000000000000375]

37 **Neuschwander-Tetri BA**. Non-alcoholic fatty liver disease. *BMC Med* 2017; **15**: 45 [PMID: 28241825 DOI: 10.1186/s12916-017-0806-8]

38 **Day J**, Patel P, Parkes J, Rosenberg W. Derivation and Performance of Standardized Enhanced Liver Fibrosis (ELF) Test Thresholds for the Detection and Prognosis of Liver Fibrosis. *J Appl Lab Med* 2019; **3**: 815-826 [PMID: 31639756 DOI: 10.1373/jalm.2018.027359]

39 **Festi D**, Schiumerini R, Marzi L, Di Biase AR, Mandolesi D, Montrone L, Scaioli E, Bonato G, Marchesini-Reggiani G, Colecchia A. Review article: the diagnosis of non-alcoholic fatty liver disease -- availability and accuracy of non-invasive methods. *Aliment Pharmacol Ther* 2013; **37**: 392-400 [PMID: 23278163 DOI: 10.1111/apt.12186]

40 **Demir M**, Lang S, Nierhoff D, Drebber U, Hardt A, Wedemeyer I, Schulte S, Quasdorff M, Goeser T, Töx U, Steffen HM. Stepwise combination of simple noninvasive fibrosis scoring systems increases diagnostic accuracy in nonalcoholic fatty liver disease. *J Clin Gastroenterol* 2013; **47**: 719-726 [PMID: 23442837 DOI: 10.1097/MCG.0b013e3182819a89]

41 **Petta S**, Vanni E, Bugianesi E, Di Marco V, Cammà C, Cabibi D, Mezzabotta L, Craxì A. The combination of liver stiffness measurement and NAFLD fibrosis score improves the noninvasive diagnostic accuracy for severe liver fibrosis in patients with nonalcoholic fatty liver disease. *Liver Int* 2015; **35**: 1566-1573 [PMID: 24798049 DOI: 10.1111/liv.12584]

42 **Benedict M**, Zhang X. Non-alcoholic fatty liver disease: An expanded review. *World J Hepatol* 2017; **9**: 715-732 [PMID: 28652891 DOI: 10.4254/wjh.v9.i16.715]

43 **Angulo P**, Kleiner DE, Dam-Larsen S, Adams LA, Bjornsson ES, Charatcharoenwitthaya P, Mills PR, Keach JC, Lafferty HD, Stahler A, Haflidadottir S, Bendtsen F. Liver Fibrosis, but No Other Histologic Features, Is Associated With Long-term Outcomes of Patients With Nonalcoholic Fatty Liver Disease. *Gastroenterology* 2015; **149**: 389-397.e10 [PMID: 25935633 DOI: 10.1053/j.gastro.2015.04.043]

44 **Hagström H**, Nasr P, Ekstedt M, Hammar U, Stål P, Hultcrantz R, Kechagias S. Fibrosis stage but not NASH predicts mortality and time to development of severe liver disease in biopsy-proven NAFLD. *J Hepatol* 2017; **67**: 1265-1273 [PMID: 28803953 DOI: 10.1016/j.jhep.2017.07.027]

45 **Younossi ZM**, Stepanova M, Rafiq N, Makhlouf H, Younoszai Z, Agrawal R, Goodman Z. Pathologic criteria for nonalcoholic steatohepatitis: interprotocol agreement and ability to predict liver-related mortality. *Hepatology* 2011; **53**: 1874-1882 [PMID: 21360720 DOI: 10.1002/hep.24268]

46 **Dulai PS**, Singh S, Patel J, Soni M, Prokop LJ, Younossi Z, Sebastiani G, Ekstedt M, Hagstrom H, Nasr P, Stal P, Wong VW, Kechagias S, Hultcrantz R, Loomba R. Increased risk of mortality by fibrosis stage in nonalcoholic fatty liver disease: Systematic review and meta-analysis. *Hepatology* 2017; **65**: 1557-1565 [PMID: 28130788 DOI: 10.1002/hep.29085]

47 **Alexander M**, Loomis AK, Fairburn-Beech J, van der Lei J, Duarte-Salles T, Prieto-Alhambra D, Ansell D, Pasqua A, Lapi F, Rijnbeek P, Mosseveld M, Avillach P, Egger P, Kendrick S, Waterworth DM, Sattar N, Alazawi W. Real-world data reveal a diagnostic gap in non-alcoholic fatty liver disease. *BMC Med* 2018; **16**: 130 [PMID: 30099968 DOI: 10.1186/s12916-018-1103-x]

48 **Katsagoni CN**, Georgoulis M, Papatheodoridis GV, Panagiotakos DB, Kontogianni MD. Effects of lifestyle interventions on clinical characteristics of patients with non-alcoholic fatty liver disease: A meta-analysis. *Metabolism* 2017; **68**: 119-132 [PMID: 28183444 DOI: 10.1016/j.metabol.2016.12.006]

49 **Bradford V**, Dillon J, Miller M. Lifestyle interventions for the treatment of non-alcoholic fatty liver disease. *Hepat Med* 2014; **6**: 1-10 [PMID: 24826079 DOI: 10.2147/HMER.S34472]

50 **Musso G**, Cassader M, Rosina F, Gambino R. Impact of current treatments on liver disease, glucose metabolism and cardiovascular risk in non-alcoholic fatty liver disease (NAFLD): a systematic review and meta-analysis of randomised trials. *Diabetologia* 2012; **55**: 885-904 [PMID: 22278337 DOI: 10.1007/s00125-011-2446-4]

51 **Hannah WN Jr**, Harrison SA. Lifestyle and Dietary Interventions in the Management of Nonalcoholic Fatty Liver Disease. *Dig Dis Sci* 2016; **61**: 1365-1374 [PMID: 27052013 DOI: 10.1007/s10620-016-4153-y]

52 **Glass LM**, Dickson RC, Anderson JC, Suriawinata AA, Putra J, Berk BS, Toor A. Total body weight loss of ≥ 10 % is associated with improved hepatic fibrosis in patients with nonalcoholic steatohepatitis. *Dig Dis Sci* 2015; **60**: 1024-1030 [PMID: 25354830 DOI: 10.1007/s10620-014-3380-3]

53 **Haukeland JW**, Konopski Z, Eggesbø HB, von Volkmann HL, Raschpichler G, Bjøro K, Haaland T, Løberg EM, Birkeland K. Metformin in patients with non-alcoholic fatty liver disease: a randomized, controlled trial. *Scand J Gastroenterol* 2009; **44**: 853-860 [PMID: 19811343 DOI: 10.1080/00365520902845268]

54 **Shields WW**, Thompson KE, Grice GA, Harrison SA, Coyle WJ. The Effect of Metformin and Standard Therapy versus Standard Therapy alone in Nondiabetic Patients with Insulin Resistance and Nonalcoholic Steatohepatitis (NASH): A Pilot Trial. *Therap Adv Gastroenterol* 2009; **2**: 157-163 [PMID: 21180541 DOI: 10.1177/1756283X09105462]

55 **Nair S**, Diehl AM, Wiseman M, Farr GH Jr, Perrillo RP. Metformin in the treatment of non-alcoholic steatohepatitis: a pilot open label trial. *Aliment Pharmacol Ther* 2004; **20**: 23-28 [PMID: 15225167 DOI: 10.1111/j.1365-2036.2004.02025.x]

56 **Belfort R**, Harrison SA, Brown K, Darland C, Finch J, Hardies J, Balas B, Gastaldelli A, Tio F, Pulcini J, Berria R, Ma JZ, Dwivedi S, Havranek R, Fincke C, DeFronzo R, Bannayan GA, Schenker S, Cusi K. A placebo-controlled trial of pioglitazone in subjects with nonalcoholic steatohepatitis. *N Engl J Med* 2006; **355**: 2297-2307 [PMID: 17135584 DOI: 10.1056/NEJMoa060326]

57 **Cusi K**, Orsak B, Bril F, Lomonaco R, Hecht J, Ortiz-Lopez C, Tio F, Hardies J, Darland C, Musi N, Webb A, Portillo-Sanchez P. Long-Term Pioglitazone Treatment for Patients With Nonalcoholic Steatohepatitis and Prediabetes or Type 2 Diabetes Mellitus: A Randomized Trial. *Ann Intern Med* 2016; **165**: 305-315 [PMID: 27322798 DOI: 10.7326/M15-1774]

58 **Aithal GP**, Thomas JA, Kaye PV, Lawson A, Ryder SD, Spendlove I, Austin AS, Freeman JG, Morgan L, Webber J. Randomized, placebo-controlled trial of pioglitazone in nondiabetic subjects with nonalcoholic steatohepatitis. *Gastroenterology* 2008; **135**: 1176-1184 [PMID: 18718471 DOI: 10.1053/j.gastro.2008.06.047]

59 **Xu R**, Tao A, Zhang S, Deng Y, Chen G. Association between vitamin E and non-alcoholic steatohepatitis: a meta-analysis. *Int J Clin Exp Med* 2015; **8**: 3924-3934 [PMID: 26064294]

60 **Sato K**, Gosho M, Yamamoto T, Kobayashi Y, Ishii N, Ohashi T, Nakade Y, Ito K, Fukuzawa Y, Yoneda M. Vitamin E has a beneficial effect on nonalcoholic fatty liver disease: a meta-analysis of randomized controlled trials. *Nutrition* 2015; **31**: 923-930 [PMID: 26059365 DOI: 10.1016/j.nut.2014.11.018]

61 **Miller ER 3rd**, Pastor-Barriuso R, Dalal D, Riemersma RA, Appel LJ, Guallar E. Meta-analysis: high-dosage vitamin E supplementation may increase all-cause mortality. *Ann Intern Med* 2005; **142**: 37-46 [PMID: 15537682 DOI: 10.7326/0003-4819-142-1-200501040-00110]

62 **Klein EA**, Thompson IM Jr, Tangen CM, Crowley JJ, Lucia MS, Goodman PJ, Minasian LM, Ford LG, Parnes HL, Gaziano JM, Karp DD, Lieber MM, Walther PJ, Klotz L, Parsons JK, Chin JL, Darke AK, Lippman SM, Goodman GE, Meyskens FL Jr, Baker LH. Vitamin E and the risk of prostate cancer: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). *JAMA* 2011; **306**: 1549-1556 [PMID: 21990298 DOI: 10.1001/jama.2011.1437]

63 **Abner EL**, Schmitt FA, Mendiondo MS, Marcum JL, Kryscio RJ. Vitamin E and all-cause mortality: a meta-analysis. *Curr Aging Sci* 2011; **4**: 158-170 [PMID: 21235492 DOI: 10.2174/1874609811104020158]

64 **Said A**, Akhter A. Meta-Analysis of Randomized Controlled Trials of Pharmacologic Agents in Non-alcoholic Steatohepatitis. *Ann Hepatol* 2017; **16**: 538-547 [PMID: 28611274 DOI: 10.5604/01.3001.0010.0284]

65 **Patil R**, Sood GK. Non-alcoholic fatty liver disease and cardiovascular risk. *World J Gastrointest Pathophysiol* 2017; **8**: 51-58 [PMID: 28573067 DOI: 10.4291/wjgp.v8.i2.51]

66 **Pastori D**, Polimeni L, Baratta F, Pani A, Del Ben M, Angelico F. The efficacy and safety of statins for the treatment of non-alcoholic fatty liver disease. *Dig Liver Dis* 2015; **47**: 4-11 [PMID: 25224698 DOI: 10.1016/j.dld.2014.07.170]

67 **Lassailly G**, Caiazzo R, Buob D, Pigeyre M, Verkindt H, Labreuche J, Raverdy V, Leteurtre E, Dharancy S, Louvet A, Romon M, Duhamel A, Pattou F, Mathurin P. Bariatric Surgery Reduces Features of Nonalcoholic Steatohepatitis in Morbidly Obese Patients. *Gastroenterology* 2015; **149**: 379-88; quiz e15-6 [PMID: 25917783 DOI: 10.1053/j.gastro.2015.04.014]

68 **Bower G**, Toma T, Harling L, Jiao LR, Efthimiou E, Darzi A, Athanasiou T, Ashrafian H. Bariatric Surgery and Non-Alcoholic Fatty Liver Disease: a Systematic Review of Liver Biochemistry and Histology. *Obes Surg* 2015; **25**: 2280-2289 [PMID: 25917981 DOI: 10.1007/s11695-015-1691-x]

69 **Klebanoff MJ**, Corey KE, Chhatwal J, Kaplan LM, Chung RT, Hur C. Bariatric surgery for nonalcoholic steatohepatitis: A clinical and cost-effectiveness analysis. *Hepatology* 2017; **65**: 1156-1164 [PMID: 27880977 DOI: 10.1002/hep.28958]

70 **Alnageeb H**, Abdelgadir E, Khalifa A, Suliman M, Gautam SC, Layani L, Subramaniam S, Bashier A. Efficacy of bariatric surgery in improving metabolic outcomes in patients with diabetes. A 24-month follow-up study from a single center in the UAE. *Diabetes Metab Syndr Obes* 2018; **11**: 459-467 [PMID: 30214265 DOI: 10.2147/DMSO.S176761]

71 **Aldoheyan T**, Hassanain M, Al-Mulhim A, Al-Sabhan A, Al-Amro S, Bamehriz F, Al-Khalidi H. The effects of bariatric surgeries on nonalcoholic fatty liver disease. *Surg Endosc* 2017; **31**: 1142-1147 [PMID: 27405478 DOI: 10.1007/s00464-016-5082-8]

72 **Alamri AA**, Alsadiqi AI, Dahlawi A, Alghamdi A, Alnefaie M, Alhazmi M, Tewfik O, Almaymuni A, Al-Abbadi H, Mosli M. Are patients aware of potential risks of weight reduction surgery? An internet based survey. *Saudi J Gastroenterol* 2019; **25**: 97-100 [PMID: 30479318 DOI: 10.4103/sjg.SJG\_232\_18]

73 **Bzowej NH**. Nonalcoholic steatohepatitis: the new frontier for liver transplantation. *Curr Opin Organ Transplant* 2018; **23**: 169-174 [PMID: 29356708 DOI: 10.1097/MOT.0000000000000502]

74 **Al-Hamoudi W**, Elsiesy H, Bendahmash A, Al-Masri N, Ali S, Allam N, Al Sofayan M, Al Bahili H, Al Sebayel M, Broering D, Saab S, Abaalkhail F. Liver transplantation for hepatitis B virus: Decreasing indication and changing trends. *World J Gastroenterol* 2015; **21**: 8140-8147 [PMID: 26185387 DOI: 10.3748/wjg.v21.i26.8140]

75 **Younossi ZM**, Loomba R, Rinella ME, Bugianesi E, Marchesini G, Neuschwander-Tetri BA, Serfaty L, Negro F, Caldwell SH, Ratziu V, Corey KE, Friedman SL, Abdelmalek MF, Harrison SA, Sanyal AJ, Lavine JE, Mathurin P, Charlton MR, Chalasani NP, Anstee QM, Kowdley KV, George J, Goodman ZD, Lindor K. Current and future therapeutic regimens for nonalcoholic fatty liver disease and nonalcoholic steatohepatitis. *Hepatology* 2018; **68**: 361-371 [PMID: 29222911 DOI: 10.1002/hep.29724]

76 **Connolly JJ**, Ooka K, Lim JK. Future Pharmacotherapy for Non-alcoholic Steatohepatitis (NASH): Review of Phase 2 and 3 Trials. *J Clin Transl Hepatol* 2018; **6**: 264-275 [PMID: 30271738 DOI: 10.14218/JCTH.2017.00056]

77 **Al-Hussaini A**, Bashir MS, Khormi M, AlTuraiki M, Alkhamis W, Alrajhi M, Halal T. Overweight and obesity among Saudi children and adolescents: Where do we stand today? *Saudi J Gastroenterol* 2019; **25**: 229-235 [PMID: 31187784 DOI: 10.4103/sjg.SJG\_617\_18]

78 **Lazarus JV**, Ekstedt M, Marchesini G, Mullen J, Novak K, Pericàs JM, Roel E, Romero-Gómez M, Ratziu V, Tacke F, Cortez-Pinto H, Anstee QM; EASL International Liver Foundation NAFLD Policy Review Collaborators. A cross-sectional study of the public health response to non-alcoholic fatty liver disease in Europe. *J Hepatol* 2020; **72**: 14-24 [PMID: 31518646 DOI: 10.1016/j.jhep.2019.08.027]

79 **Alsaif FA**, Alqahtani SH, Alsadoon AM, Alswat KA, Abdo AA, Hassanain MM, Alsharabi AB, Aljuhani GR, Alkhalidi HM, Elsharkawy MS, Alotaibi MA, Sanai FM, Al-Hamoudi WK. Prevalence of biopsy-proven nonalcoholic fatty liver among patients with gallstone disease. *Saudi J Gastroenterol* 2020 [PMID: 32341228 DOI: 10.4103/sjg.SJG\_29\_20]

80 **Alaama T**. Nonalcoholic fatty liver disease: One more reason to strengthen public health. *Saudi J Gastroenterol* 2018; **24**: 199-200 [PMID: 30052238 DOI: 10.4103/sjg.SJG\_266\_18]

81 **Haroun D**, Mechli R, Sahuri R, AlKhatib S, Obeid O, El Mallah C, Wood L, AlSuwaidi K. Metabolic syndrome among adolescents in Dubai, United Arab Emirates, is attributable to the high prevalence of low HDL levels: a cross-sectional study. *BMC Public Health* 2018; **18**: 1284 [PMID: 30463538 DOI: 10.1186/s12889-018-6215-x]

82 **Al Zenki S**, Al Omirah H, Al Hooti S, Al Hamad N, Jackson RT, Rao A, Al Jahmah N, Al Obaid I, Al Ghanim J, Al Somaie M, Zaghloul S, Al Othman A. High prevalence of metabolic syndrome among Kuwaiti adults--a wake-up call for public health intervention. *Int J Environ Res Public Health* 2012; **9**: 1984-1996 [PMID: 22754486 DOI: 10.3390/ijerph9051984]

83 **Weiderpass E**, Botteri E, Longenecker JC, Alkandari A, Al-Wotayan R, Al Duwairi Q, Tuomilehto J. The Prevalence of Overweight and Obesity in an Adult Kuwaiti Population in 2014. *Front Endocrinol (Lausanne)* 2019; **10**: 449 [PMID: 31338067 DOI: 10.3389/fendo.2019.00449]

84 **Awad AI**, Alsaleh FM. 10-year risk estimation for type 2 diabetes mellitus and coronary heart disease in Kuwait: a cross-sectional population-based study. *PLoS One* 2015; **10**: e0116742 [PMID: 25629920 DOI: 10.1371/journal.pone.0116742]

85 **Cobbina E**, Akhlaghi F. Non-alcoholic fatty liver disease (NAFLD) - pathogenesis, classification, and effect on drug metabolizing enzymes and transporters. *Drug Metab Rev* 2017; **49**: 197-211 [PMID: 28303724 DOI: 10.1080/03602532.2017.1293683]

86 **Leung JC**, Loong TC, Pang J, Wei JL, Wong VW. Invasive and non-invasive assessment of portal hypertension. *Hepatol Int* 2018; **12**: 44-55 [PMID: 28361299 DOI: 10.1007/s12072-017-9795-0]

**Footnotes**

**Conflict-of-interest statement:** SanaiFMhas been a speaker and advisor for Gilead Sciences, Intercept pharmaceuticals, and an advisor for Pfizer. Younossi ZM has received research funds and/or is consultant to BMS, Gilead Sciences, Intercept pharmaceuticals, Novo Nordisk, Siemens and Terns pharmaceuticals. Other authors do not have anything to declare.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

**Manuscript source:** Unsolicited manuscript

**Peer-review started:** March 5, 2020

**First decision:** April 8, 2020

**Article in press:**

**Specialty type:** Gastroenterology and hepatology

**Country/Territory of origin:** United States

**Peer-review report’s scientific quality classification**

Grade A (Excellent): A

Grade B (Very good): 0

Grade C (Good): C

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** Baffy G, Thompson RR **S-Editor:** Zhang L **L-Editor:** **E-Editor:**

**Figure Legends**

****

**Figure 1 Basic algorithm for diagnosis and treatment of nonalcoholic fatty liver disease/nonalcoholic steatohepatitis.** MetS: Metabolic syndrome; NAFL: Nonalcoholic fatty liver; NAFLD: Nonalcoholic fatty liver disease; NASH: Nonalcoholic steatohepatitis; T2DM: Type 2 diabetes mellitus.

**Table 1 Prevalence and Estimation Studies of Risk Factors of nonalcoholic fatty liver disease in United Arab Emirates, Kingdom of Saudi Arabia, and Kuwait**

|  |  |  |  |
| --- | --- | --- | --- |
| **Place of study** | **Study** | **Main findings** | **Ref.** |
| Dubai, UAE | Cross-sectional study to access prevalence of MetS and its associated risk factors among children and adolescents (596 students) | Prevalence of MetS was 3.7%; was more common among boys than girls (12 boys versus 10 girls); 18.6% were overweight; 21.2% were obese; MetS was more commonly found in obese (16%) compared to overweight students (2%) | Haroun *et al*[81], 2018 |
| Abu Dhabi, UAE | Multicenter cohort study to determine cardiovascular risk factor prevalence rates (50138 participants) | 35% were obese, 32% were overweight, 55% had central obesity, 18% were diabetic, 27% were prediabetic; Age-standardized diabetes and prediabetes rates were 25% and 30%, respectively; Age-standardized obesity and overweight rates were 41% and 34%, respectively | Hajat *et al*[[12](#_ENREF_12)],2012 |
| UAE | Systematic review and qualitative synthesis of prevalence, incidence rates, trends, and Economic Burden of Obesity and cardiometabolic disorder (36 studies) | All studies reported high prevalence rates for obesity, diabetes, hypertension, and MetS; Obesity and related cardiometabolic disorders seem highly prevalent in the UAE but estimating an accurate occurrence is challenging due to methodological heterogeneity of the epidemiological studies addressing them; Frequency of overweight and obesity was reported to increase by 2-3-fold between 1989 and 2017 | Radwan *et al*[13]*,*2018 |
| Saudi Arabia | Survey to determine obesity prevalence and associated factors (*n* = 10293) | 28.7% of the population evaluated were obese; Obesity prevalence was higher among women (33.5%) than men (24.1%) | Memish *et al*[[14](#_ENREF_14)], 2014 |
| Saudi Arabia | Secondary analysis to estimate the trends in the prevalenceof adult obesity over the period 1992–2022 (5 studies) | Obesity trend from 1992-2005: In men, the prevalence increased from (1) 10.1% to 27.1% in age-group 25-34 yr; and (2) 12.9% to 31.0% in age group 55-64 yr. In women, obesity prevalence was higher; increased from (1) 16.1% to 39.5% in age group 25-34 yr; and (2) 22.8% to 53.2% in age group 55-64 yr. Obesity projection from 1992-2022: The future obesity prevalence was estimated to increase from (1) 12% to 41% in men; and (2) 21% to 78% in women | Al-Quwaidhi *et al*[[15](#_ENREF_15)], 2014 |
| Saudi Arabia | Cross sectional study to evaluate the prevalence of MetS | The prevalence of MetS in Saudi Arabia was found to be 39.8% (34.4% in men and 29.2% in women) as per the NCEP ATP III and 31.6% (45.0% in men and 35.4% in women) as per IDF criteria | Al-Rubeaan *et al*[[26](#_ENREF_26)], 2018 |
| Kuwait | Observational study (multicenter) to examine the prevalence of MetS and its components (992 adults ≥ 20 yr) | Obesity percentage was significantly greater in females (54.7%) compared to males (32.3%); Abdominal obesity was the most predominant MetS abnormality; Prevalence of MetS increased with age and was higher in females than males | Al Zenki *et al*[82], 2012 |
| Kuwait | Cross-sectional survey to estimate prevalence of overweight, obesity, and various types of adiposity (3589 adults, 18-69 yr) | Overall obesity prevalence was 40.3% (men, 36.5%; women, 44.0%); The prevalence of Class I, Class II, and Class III obesity was 24.9%, 9.9%, and 5.5%, respectively | Weiderpass *et al*[83], 2019 |
| Kuwait | Descriptive, cross-sectional survey (multicenter) to understand the prevalence of MetS, and estimation of the 10-year risk for developing T2DM and CHD (*n* = 1610) | 4% subjects were found to have screen detected T2DM. A history of high blood glucose levels was reported by 18.0% subjects; 35.5% of the participants were obese; MetS was present in about 32% of the participants; Almost 30% of participants were found to be at moderate/high/very high risk of developing T2DM within the next 10 yr; 8.45% were found to be at moderate/high/very high risk of developing both T2DM/CHD within the next 10 yr | Awad *et al*[84], 2014 |

IDF: International Diabetes Federation; MetS: Metabolic syndrome; NCEP ATP III: National Cholesterol Education Program and Adult Treatment Panel III; T2DM: Type 2 diabetes mellitus; UAE: United Arab Emirates.

**Table 2 Key diagnostic modalities for nonalcoholic fatty liver disease and nonalcoholic steatohepatitis[**[**11**](#_ENREF_11)**,**[**35**](#_ENREF_35)**,**[**8**](#_ENREF_81)**5,**[**8**](#_ENREF_82)**6]**

|  |  |  |
| --- | --- | --- |
| **Diagnostic Tests** | **Advantages** | **Limitations** |
| Liver enzymes and other blood tests for fibrosis |
| Platelet count; APRI; AST; ALT; AST/ALT ratio; Hyaluronic acid; ELF; Hepascore; FibroSpect; FibroTest/FibroSure | Simple and easy; AST/ALT of > 1 is predictive of fibrosis; ELF can predict stage of fibrosis and outcomes | AST and ALT can be normal in some patients with NAFLD; ELF is not widely available; Some tests initially developed for HCV; Limited published data on external validation |
| Radiology |
| Ultrasonography | Easily available; Safe; Overall scanning of abdominal organs | Cannot detect mild degree of steatosis (< 30% of hepatocytes); Does not distinguish between steatosis and NASH; Operator dependent |
| MRI | More sensitive than ultrasonography | Cost and availability; Does not distinguish between steatosis and NASH |
| Transient; Elastography | Can detect fibrosis | Cost and availability |
| MRE | Can detect fibrosis and MRI-PDFF can quantify steatosis | Cost and availability |
| Fibrosis scoring systems |
| NAFLD fibrosis score (NFS), Fibro Meter Fibrosis-4 (FIB-4) | Allow a more targeted use of liver biopsy by reliably excluding advanced fibrosis in a high proportion of NAFLD patients; Potentially predict liver-related and cardiovascular complications and death  | Significant number with indeterminate scores; Limited external validation in NASH |
| Liver biopsy | Gold standard for diagnosis of NAFLD and NASH; Allows staging of the disease | Invasive; Associated with complications – pain, intraperitoneal bleeding; Cost |

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; APRI: AST-to-platelet ratio index; CT: Computerized tomographic; ELF: Enhanced liver fibrosis; MRE: Magnetic resonance elastography; MRI: Magnetic resonance imaging; MRI-PDFF: MRI-based proton density fat fraction; NAFLD: Nonalcoholic fatty liver disease; NASH: Nonalcoholic steatohepatitis.