Updates in the Epidemiology of Fatty Liver and its Consequences in Saudi Arabia: Review Article

Abstract

For the reason that obesity epidemic, the occurrence of NAFLD have exponentially increased worldwide. A considerable majority of cases advance to NASH in the nonexistence of therapeutic measures, which increases morbidity and death. Because the initial phases of the illness are frequently clinically unapparent, the identification of NAFLD frequently rests on biochemical and radiographic studies. Concentrated life modifications that result in weight loss are the mainstay of the disease's management. Therapeutic treatments that could be additional to lifestyle changes once essential for case managing comprise insulin sensitizers, antioxidants, incretin-based pharmaceuticals, cholesterol depressing mediators, weight reduction therapies, bariatric surgery, and liver transplantation. For NAFLD to be managed more effectively and lessen its worldwide impact, research must be conducted continuously.

Key words: fatty liver, NAFLD, NASH, epidemiology.

Introduction:

The phrase "non-alcoholic fatty liver disease" (NAFLD) refers to a broad range of conditions, from basic adipose tissue deposition in the liver to more advanced steatosis with accompanying hepatitis, fibrosis, cirrhosis, and even hepatocellular cancer (HCC). (1) (NAFLD) or "Fatty Liver" refers to the presence of lobular inflammation without macrovesicular alterations (steatosis) and inflammation without considerable alcohol usage. It may be separated into two subgroups: NASH and NAFL (Non-Alcoholic Fatty Liver) (Non-Alcoholic Steatohepatitis). (2) Steatosis of the liver, involving more than 5% of the parenchyma, and the absence of hepatocyte damage are the hallmarks of NAFL. NASH, on the other hand, is described histologically as a necroinflammatory process in which the liver cells are harmed against a backdrop of steatosis. The onset and

progression of non-alcoholic fatty liver disease (NAFLD) are influenced by both environmental and genetic variables. Patients with NAFLD who have first-degree relatives are more at risk than the general public. (3)

Prevalence:

In wealthy countries, NAFLD has recently become the chronic liver disease that affects people the most frequently. In the United States, a population-based survey revealed that NAFLD was 30% common. (4) A meta-analysis using imaging reporting systems in several parts of the world discovered that roughly 25% of people had NAFLD. A research released in 2020 revealed a startling increase in the frequency of NAFLD worldwide. The prevalence of NAFLD increased with time, rising from 391.2 million in 1990 to 882.1 million in 2017, with a prevalence rate increase from 8.2 percent to 10.9 percent. In Saudi Arabia, the prevalence across all ages was calculated to be 24.8%. The frequency of NAFLD in various communities throughout the world is as follows: United States (30%), Middle East (32%), and South America 32% – 30%, Asia – 27%, Europe – 24% and Africa – 13%. Additionally, there are significant differences in frequency across these communities' various ethnic groupings. The rising frequency of NAFLD among paediatric age groups has been identified as another intriguing trend. After adjusting for age, sex, race, and ethnicity, autopsy-based data revealed a 9.6 percent prevalence of NAFLD in children aged 2 to 19 years, rising to up to 38 percent in obese children. (5) Understanding gender disparities as a hazard influence for NAFLD is currently lacking. The relationship between gender and NAFLD is controversial; some studies contend that numerous gender-specific processes, including the impact of sex hormones and variations in physiology and lifestyle, have an impact on the incidence of NAFLD. Additionally, according to a lot of studies, men are discovered with NAFLD more often than women. (6) There are, however, certain researches from Western and Asian nations that indicate the disease may typically affect women more frequently.

Etiology and risk factors of NAFLD:

The liver develops fat deposits for a variety of causes. It most frequently entails increased transport of free fatty acids (FFAs) to the liver, increased fatty acid synthesis in the liver, reduced FFA oxidation, or decreased very-low-density lipoprotein production or secretion (VLDL). (7) People with NAFLD typically exhibit the traits of MS, along with the risk factors for cardiovascular disease that go along with it. Obesity, type 2 diabetes mellitus (T2DM), and dyslipidaemia are regarded as significant risk factors for NAFLD since they are strongly associated to metabolic syndrome. Studies have indicated that people with NAFLD, both with and without diabetes, have a higher frequency of cardiovascular disease (CVD). (8) As a result, NAFLD is typically linked to an unhealthy lifestyle, and there is evidence that making adjustments to an unhealthy lifestyle can lower transaminase levels and improve NAFLD. In a research of individuals with T2DM, it was shown that, in addition to the usual CVD risk factors, medication usage, and diabetes-related variables, there was a higher incidence of peripheral vascular, coronary, and cerebrovascular disorders in subjects with NAFLD than in those without this condition. According to Byrne et al., there have been over 20 research that have been published, both prospective and retrospective, examining the connection between NAFLD and cardiovascular disease. They came to the conclusion that CVD is a clear and present concern, which is being verified in ongoing investigations. (9)

It's debatable if smoking causes NAFLD or not. Generally, smoking is a significant contributor to the universal threat of developing chronic, non-transmissable diseases (NCD), comprising cancer, type 2 diabetes, respiratory, and cardiovascular problems. Cigarette smoke exacerbated the histopathological strictness of NAFLD, according to a research on obese mice. (10) In a cross-sectional research of NAFLD patients (both smokers and non-smokers), it was shown that smokers had much greater magnitudes of cases with severe liver fibrosis and unconventional hepatic fibrosis than non-smokers did. Smoking is strongly related with NAFLD, according to a systematic review and meta-analysis of 20 published studies. Further research is advised to understand the

underlying processes of this connection. Although smoking was considered an independent risk factor for the development of NAFLD, a cross-sectional study of 933 patients (368 smokers and 565 nonsmokers as controls) between the two groups There was no difference in the prevalence of NAFLD (22.2% vs. 29%). Heavy smoker (more than 20 packs of cigarettes per year). (11)

Diagnosis:

A considerable number of people with NAFLD still show fatty liver on biochemical or liver imaging tests (ultrasonic, computer tomography [CT], or magnetic resonance imaging of the liver [MRI]) When aberrant liver function is discovered, a diagnosis is frequently considered. shown by the liver. if you're running for another motive. (12) When more than 5% of hepatocytes exhibit steatosis and there is no underlying condition causing secondary steatosis, such as: B. Chronic liver disease accompanied by steatosis or excessive alcohol use (more than 20 grammes per day for women and 30 grammes per day for males) (viral, autoimmune, metabolic and toxic disorders). (13)

Biochemical markers:

Several NAFLD patients may have usual liver enzyme levels. For instance, alanine aminotransferase (ALT) levels might be standard in up to 60% of NASH cases, and in 53% of cases thru elevated ALT levels, there was no sign of severe fibrosis or NASH. Even though a number of biochemical indicators, comprising TNF-, IL-6, CRP, Pantraxin, Ferritin, serum prolidase enzyme action, solvable receptor for innovative glycation end product, and cytokeratin-18, have been suggested as helpful in predicting the severity of NAFLD/NASH in the past, none of these indicators have demonstrated appropriate compassion or specificity intended for tedious medical request for identification. (14)

The greatest reliable non-invasive technique to evaluate the illness is the NAFLD fibrosis score (NFS), which uses clinical and biochemical data to predict the degree of liver involvement. Age, BMI, AST, ALT, platelets, albumin, and the presence or absence of impaired fasting glucose are all factors that go into determining NFS. Progressive fibrosis

is excluded by a low cut-off score of 1.455, which has a negative predictive value (NPV) of 93%, while it is suggested by a high cut-off score of >0.676, which has a positive predictive value (PPV) of 90%. Even though NFS has strong specificity, its sensitivity has lately been revealed to be poor. (15)

Radiological diagnosis:

The usual imaging modalities for identifying NAFLD in medical practise are liver MRI, CT, and ultrasonography. For these methods to identify NAFLD, there typically has to be roughly 30% hepatic steatosis. Ultrasonography is affordable, widely accessible, and simple to use, even since the patient's bedside. As soon as hepatic steatosis is greater than 30%, the test's stated sensitivity is said to be > 90%, while the sensitivity is substantially lower at lower levels of steatosis. However, because ultrasonography is so operator- reliant on, different operators will produce different outcomes. (16)

cases with NAFLD and NASH could practice the ultrasound-based imaging procedure known as transient elastography (TE) to determine their level of fibrosis. According to reports, TE's sensitivity and specificity for diagnosing different phases of fibrosis are 79-92 percent and 75-92 percent, correspondingly. (17) The grade of steatosis in cases with NAFLD may be predicted using the ultrasound-based precise diminution limit price utilised in the TE approach, according to current research. (18)

The hepatic and instinctual fat may be quantified using a CT scan to determine the level of adiposity in people through metabolic syndrome and NAFLD. Conversely, the test is costly and linked to radiation danger, so it isn't typically advised in clinical settings. For both quantitative and qualitative evaluation of NAFLD, MRI is extremely sensitive and specific. In order to identify and evaluate the prediction of cases with NAFLD, more recent MRI methods, such as MR elastography, proton density fat fraction, and the Ferri Scan approach, can stage the degree of fibrosis non-invasively. However, these methods are pricey and only offered in specialist facilities. (19)

Liver biopsy and histology:

The gold standard for diagnosing NAFLD continues to be liver biopsy. In addition to providing information on the degree of fibrosis and steatosis, necro-inflammation, and architectural deformation, a biopsy not only verifies the diagnosis. The NASH Clinical Research Network histological scoring system, which is a validated scoring method that produces a NAFLD activity score, was previously the most extensively used histological scoring system (NAS). NASH is defined as a NAS score of 5 or above; a score of 3 does not qualify. (20)

Although it is helpful for the histological identification, current data shows that the NAS score can't be useful as a substitute for differentiating between NASH and NAFLD. (21) Because of this, the European Association for the Study of Liver suggests NAS for disease activity assessment rather than for diagnosis. The steatosis, inflammatory activity, and fibrosis (SAF) score, which was established in 2012, offers a valid and reproducible method for identifying NAFLD and grading disease with little inter-observer inconsistency. Conferring to the NASH Clinical Research Network, the SAF score evaluates the phase of fibrosis (F), the rating of steatosis (S), then the rating of activity (A). (22)

The main disadvantages of liver biopsy include its cost, procedure-related problems, and intra- and inter-observer discrepancies in commentary the histology; for these reasons, it is often not advised in clinical practise, unless in situations when additional differential diagnosis must be ruled out. (23)

Prevention and management:

The importance of avoiding the condition has gained attention because to the rising frequency and incidence of NAFLD worldwide. The pathophysiology of the illness is still poorly understood, making avoidance of NAFLD a challenging issue. The main method of preventing NAFLD is to alter the hazard influences for the condition. The three most significant risk factors for NAFLD that may be controlled are obesity, insulin resistance,

and metabolic syndrome. Consequently, the basis for the avoidance of NAFLD may be considered as universal training on lifestyle changes, such as diet and exercise, which can lower the hazard for the advance of insulin confrontation, weight advance, and metabolic syndrome. (24)

Lifestyle modifications:

Up until now, dietary and physical activity modifications have been the keystone of the therapy of steatosis and NASH. Although there isn't much study evidence available yet, diet and exercise have been suggested as a therapeutic option for steatosis and NASH. Lack of agreement over the methods to evaluate whether the illness worsened or improved has prevented studies from moving forward. (25) Although histologic comparison (the NAFLD Activity Score is a commonly used histologic grade for research) would be the ideal metric, getting biopsies is still challenging and fraught with danger. As a result, different studies examine steatohepatitis differently in their study participants. Other metrics employed include insulin confrontation and AST/ALT.

Dietary supplementation:

Since oxidative stress is a key factor in liver inflammation and destruction, antioxidant supplementation has been extensively speculated to offer advantages in NASH patients. Of all the potential antioxidants, vitamin E has perhaps received the most attention. Numerous studies have shown continuous reductions in ALT and improvements in liver histology, building on earlier work carried out as proof of concept in animal models. (26) There is enough proof to support giving non-diabetic individuals 800 IU of Vitamin E every day as an early NASH therapy. It is significant to note that studies have revealed a connection between vitamin E administration and an increase in prostate cancer risk as well as all-cause mortality (however contradicting information has since been published). Although these hazards are small, it is crucial that practitioners take them into account and discuss them with their patients before advising vitamin E. (27)

Consumption of caffeine and coffee was associated with reduced fibrosis, slowed development to steatohepatitis, and reduced prevalence of the illness in consumers.

Nonetheless, a similar benefit was not seen in individuals who consumed espresso, despite a previous study showing that coffee has protecting possessions in females diagnosed with NAFLD. Despite the fact this possibly will denote that coffee himself could provide more protection than just caffeine. Additional dietary complements were recommended as NAFLD therapy alternatives. (28)

Metformin:

Numerous research have looked at the use of oral insulin sensitising drugs to treat NAFLD because of the connection between insulin resistance and the condition. Metformin is one of the most researched insulin sensitising medications. (29) Several studies have shown a reduction in ALT and an increase in insulin sensitivity in individuals with fatty liver, but few have shown improvement in histology. In addition, a 2010 research found that metformin had just a modest benefit over diet alone. Another study found that metformin is less efficient than exercise alone at reducing liver enzymes and hepatic content. (30) Metformin was shown to have little to no histopathologic improvement when compared to controls in a research that solely examined people with insulin resistances, without diabetes, conversely, it must be emphasized that this trial had a sizable waster proportion and merely a slight numeral of cases. Regardless of ALT enhancement, a different trial relating metformin, vitamin E, and nutrition found no histopathological differences. (31) Although one small trial found histologic enhancement in NASH cases after a 48-week therapy period, the inconsistent and equivocal findings led researchers to the supposition that more research was required before advising metformin usage for NASH shorn of associated diabetes.

TZDs:

The TZDs, in particular pioglitazone and rosiglitazone, are additional insulin sensitising substance that is actively being researched for the treatment of NASH. (32) As previously mentioned, PPAR is activated by TZDs, and PPAR has been found to be downregulated in models of NAFLD. When compared to placebo, one of the early RCTs on rosiglitazone, the FLIRT study, conducted in 2008, showed a 31 percent reduction in

steatosis and transaminase levels, respectively. The FLIRT 2 trial, conducted in 2010, confirmed similar findings. In a different trial, non-diabetic individuals who received pioglitazone as opposed to a placebo showed a substantial reduction in transaminase levels and histopathologic damage. Cohort studies revealed that rosiglitazone unaided accomplished comparably to the adding, and pioglitazone lowered hepatic steatosis in diabetics with NASH once equated to metformin. (33)

Statins:

Cases of liver disease are substantially more likely to suffer from morbidity and death due to the circulatory symptoms of liver illnesses, comprising NAFLD, which are often observed. Cases with cardiovascular hazard influences and illness are frequently given statins as a prophylactic measure. (34) Statins could be administered to control cardiovascular disease in people who have liver disease, comprising NAFLD, and their usage has been proven to be safe. New research papers have suggested that the use of statins as a treatment especially for NASH is promising. There have been conflicting findings, with some trials indicating promise in addition to others display no change in serologic markers. (35)

Surgery:

Losing weight was proved to be a successful treatment for NAFLD patients. Therefore, it is fair to assume that people with NASH will benefit from bariatric surgery. Studies have shown that individuals who have undergone bariatric surgery see a considerable decline in steatohepatitis and that the presence of NASH does not raise the risks associated with the procedure. (36) NASH improves after bariatric surgery, according to practically all measured outcomes, according to two recent meta-analyses. Despite these findings, there is still insufficient controlled evidence and long-term data to support bariatric surgery just for NASH. Intragastric balloons are one less invasive alternative for bariatric therapy that has showed promise in improving liver function, insulin resistance, and histopathologic measurements in obese individuals with and without NASH. (37)

Cases of NAFLD may develop end-stage liver illness, in which case liver transplantation is the lone treatment decision. NAFLD-related cirrhosis has resulted in transplant outcomes that are on par with those of individuals without NAFLD. (38) Subsequently a transplant, NAFLD may return or appear suddenly. The greatest indicators of NAFLD post-transplantation are steroid treatment, obesity, hyperlipidemia, and diabetes. Inappropriately, one negative side effect of immunosuppressant medications is weight gain. Since studies on the use of vitamin E and insulin sensitizers in post-transplant patients are lacking, nutrition and exercise are still the lone guidance available at this time. (39)

Liver transplantation:

According to contemporary research, NASH-related end-stage liver disease is the third most prevalent reason for liver transplants in the United States and is predicted to overtake other causes in the next 20 to 30 years as a result of the obesity pandemic. with the nearby impending, it is anticipated that most other parts of the biosphere will experience the similar health burden due to the rising global trend in the incidence of obesity. As a result, liver transplantation would become a common form of therapy for a sizable fraction of individuals having unconventional NAFLD. (40)

Conclusion:

The occurrence of NAFLD is rising globally, and a sizable fraction of cases advance to NASH. Inquiries using biochemical and radiological methods are frequently used to diagnose NAFLD. Forceful lifestyle modifications that result in weight loss are the mainstay of the disease's management. Therapies include liver transplantation. For NAFLD to be managed more effectively and lessen its worldwide impact, study must be conducted continuously.

References:

1. Younossi ZM, Otgonsuren M, Henry L, Venkatesan C, Mishra A, Erario M, et al. Association of nonalcoholic fatty liver disease (NAFLD) with hepatocellular carcinoma (HCC) in the United States from 2004 to 2009. *Hepatology.* 2015;62:1723–30. [PubMed] [Google Scholar]
2. Sanyal A, Poklepovic A, Moyneur E, Barghout V. Population-based risk factors and resource utilization for HCC: US perspective. *Curr Med Res Opin.* 2010;26:2183–91. [PubMed] [Google Scholar]
3. Alswat K., Aljumah A., Sanai F., Abaalkhail F., Alghamdi M., Al Hamoudi W., Razavi H. Nonalcoholic fatty liver disease burden & #8211; Saudi Arabia and United Arab Emirates, 2017–2030. Saudi J. Gastroenterol. 2018;24(4):211–219. doi: 10.4103/sjg.SJG_122_18. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
4. Bellentani S, Scaglioni F, Marino M, Bedogni G. Epidemiology of non-alcoholic fatty liver disease. *Dig Dis.* 2010;28:155–161. 10.1159/000282080. [PubMed] [Google Scholar]
5. Jimba S, Nakagami T, Takahashi M, Wakamatsu T, Hirota Y, Iwamoto Y, et al. Prevalence of non-alcoholic fatty liver disease and its association with impaired glucose metabolism in Japanese adults. Diabet Med. 2005;22:1141–1145. 10.1111/j.1464-5491.2005.01582.x. [PubMed] [Google Scholar]
6. López-Velázquez JA, Silva-Vidal KV, Ponciano-Rodríguez G, Chávez-Tapia NC, Arrese M, Uribe M, et al. The prevalence of nonalcoholic fatty liver disease in the Americas. *Ann Hepatol.* 2014;13:166–178. [PubMed] [Google Scholar]
7. Browning JD, Szczepaniak LS, Dobbins R, Nuremberg P, Horton JD, Cohen JC, et al. Prevalence of hepatic steatosis in an urban population in the United States: impact of ethnicity. *Hepatology.* 2004;40:1387–1395. 10.1002/hep.20466. [PubMed] [Google Scholar]
8. Calzadilla Bertot L, Adams LA. The Natural Course of Non-Alcoholic Fatty Liver Disease. *Int J Mol Sci.* 2016;17:pii: E774. [PMC free article] [PubMed] [Google Scholar]

9. Browning JD, Szczepaniak LS, Dobbins R, Nuremberg P, Horton JD, Cohen JC, et al. Prevalence of hepatic steatosis in an urban population in the United States: impact of ethnicity. *Hepatology (Baltimore, Md)* 2004;**40**(6):1387–1395. [PubMed] [Google Scholar]
10. Younossi Z, Anstee QM, Marietti M, Hardy T, Henry L, Eslam M, et al. Global burden of NAFLD and NASH: trends, predictions, risk factors and prevention. Nat Rev Gastroenterol Hepatol. 2018;15(1):11–20. [PubMed] [Google Scholar]
11. Kabbany MN, Conjeevaram Selvakumar PK, Watt K, Lopez R, Akras Z, Zein N, et al. Prevalence of nonalcoholic steatohepatitis-associated cirrhosis in the United States: an analysis of national health and nutrition examination survey data. *Am J Gastroenterol.* 2017;112:581–587. 10.1038/ajg.2017.5. [PubMed] [Google Scholar]
12. Machado MV, Diehl AM. Pathogenesis of nonalcoholic Steatohepatitis. *Gastroenterology.* 2016;**150**(8):1769–1777. [PMC free article] [PubMed] [Google Scholar]
13. Camhi S.M., Bray G.A., Bouchard C., Greenway F.L., Johnson W.D., Newton R.L., Katzmarzyk P.T. The relationship of waist circumference and BMI to visceral, subcutaneous, and total body fat: sex and race differences. Obesity. 2011;19(2):402–408. doi: 10.1038/oby.2010.248. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
14. Pan JJ, Fallon MB: Gender and racial differences in nonalcoholic fatty liver disease. *World J Hepatol.* 2014;6(5):274–83. 10.4254/wjh.v6.i5.274 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
15. Dahshan A., Chalmers L.J., Tolia V. Nonalcoholic fatty liver disease in children. Therapy. 2009;6(1):83–91. [Google Scholar]
16. Kanwar P, Kowdley KV. The Metabolic Syndrome and Its Influence on Nonalcoholic Steatohepatitis. *Clin Liver Dis.* 2016;20:225–243. [PubMed] [Google Scholar]

17. Federico A, Dallio M, Masarone M, Persico M, Loguercio C. The epidemiology of non-alcoholic fatty liver disease and its connection with cardiovascular disease: role of endothelial dysfunction. Eur Rev Med Pharmacol Sci. 2016;20:4731–4741. [PubMed] [Google Scholar]
18. Goyal NP, Schwimmer JB. The Progression and Natural History of Pediatric Nonalcoholic Fatty Liver Disease. *Clin Liver Dis.* 2016;20:325–338. [PMC free article] [PubMed] [Google Scholar]
19. Khov N, Sharma A, Riley TR. Bedside ultrasound in the diagnosis of nonalcoholic fatty liver disease. *World J Gastroenterol.* 2014;20:6821–6825. 10.3748/wjg.v20.i22.6821. [PMC free article] [PubMed] [Google Scholar]
20. Kahn SE, Hull RL, Utzschneider KM: Mechanisms linking obesity to insulin resistance and type 2 diabetes. *Nature.* 2006;444(7121):840–6. 10.1038/nature05482 [PubMed] [CrossRef] [Google Scholar]
21. Brea A, Puzo J. Non-alcoholic fatty liver disease and cardiovascular risk. *Int J Cardiol.* 2013;167:1109–1117. [PubMed] [Google Scholar]
22. Carr RM, Oranu A, Khungar V. Nonalcoholic fatty liver disease: pathophysiology and management. *Gastroenterol Clin North Am.* 2016;45:639–652. 10.1016/j.gtc.2016.07.003. [PMC free article] [PubMed] [Google Scholar]
23. Schwimmer JB, Behling C, Newbury R, Deutsch R, Nievergelt C, Schork NJ, et al. Histopathology of pediatric nonalcoholic fatty liver disease. *Hepatology.* 2005;42:641–649. 10.1002/hep.20842. [PubMed] [Google Scholar]
24. Polyzos SA, Aronis KN, Kountouras J, Raptis DD, Vasiloglou MF, Mantzoros CS. Circulating leptin in non-alcoholic fatty liver disease: a systematic review and meta-analysis. *Diabetologia.* 2016;59:30–43. 10.1007/s00125-015-3769-3. [PubMed] [Google Scholar]
25. Bugianesi E, Pagotto U, Manini R, Vanni E, Gastaldelli A, de Iasio R, et al. Plasma adiponectin in nonalcoholic fatty liver is related to hepatic insulin resistance and

hepatic fat content, not to liver disease severity. *J Clin Endocrinol Metab.* 2005;90:3498–3504. 10.1210/jc.2004-2240. [PubMed] [Google Scholar]

26. Patel V, Sanyal AJ, Sterling R. Clinical Presentation and Patient Evaluation in Nonalcoholic Fatty Liver Disease. *Clin Liver Dis.* 2016;20:277–292. [PubMed] [Google Scholar]
27. Mittendorfer B, Yoshino M, Patterson BW, Klein S. VLDL triglyceride kinetics in lean, overweight, and obese men and women. *J Clin Endocrinol Metab.* 2016;101:4151–4160. 10.1210/jc.2016-1500. [PMC free article] [PubMed] [Google Scholar]
28. Sun DQ, Liu WY, Wu SJ, Zhu GQ, Braddock M, Zhang DC, et al. Increased levels of low-density lipoprotein cholesterol within the normal range as a risk factor for nonalcoholic fatty liver disease. *Oncotarget.* 2016;7:5728–5737. 10.18632/oncotarget.6799. [PMC free article] [PubMed] [Google Scholar]
29. Bataller R, Rombouts K, Altamirano J, Marra F. Fibrosis in alcoholic and nonalcoholic steatohepatitis. *Best Pract Res Clin Gastroenterol.* 2011;25:231–244. 10.1016/j.bpg.2011.02.010. [PubMed] [Google Scholar]
30. Adams L. Transient elastography in nonalcoholic fatty liver disease: making sense of echoes. *Hepatology.* 2010;51:370–372. 10.1002/hep.23422. [PubMed] [Google Scholar]
31. Dixon JB, Bhathal PS, O'Brien PE. Nonalcoholic fatty liver disease: predictors of nonalcoholic steatohepatitis and liver fibrosis in the severely obese. *Gastroenterology.* 2001;**121**(1):91–100. [PubMed] [Google Scholar]
32. Ahmed A, Wong RJ, Harrison SA. Nonalcoholic fatty liver disease review: diagnosis, treatment, and outcomes. *Clin Gastroenterol Hepatol.* 2015;**13**(12):2062–2070. [PubMed] [Google Scholar]
33. Leoni S, Tovoli F, Napoli L, Serio I, Ferri S, Bolondi L. Current guidelines for the management of non-alcoholic fatty liver disease: A systematic review with comparative analysis. World J Gastroenterol. 2018 Aug 14;24(30):3361-3373. [PMC free article] [PubMed]

34. Chalasani N, Younossi Z, Lavine JE, Diehl AM, Brunt EM, Cusi K, et al. The diagnosis and management of non-alcoholic fatty liver disease: practice guideline by the American Gastroenterological Association, American Association for the Study of Liver Diseases, and American College of Gastroenterology. *Gastroenterology.* 2012;**142**(7):1592–1609. [PubMed] [Google Scholar]
35. Oh H, Jun DW, Saeed WK, Nguyen MH. Non-alcoholic fatty liver diseases: update on the challenge of diagnosis and treatment. *Clin Mol Hepatol.* 2016;22:327–335. 10.3350/cmh.2016.0049. [PMC free article] [PubMed] [Google Scholar]
36. Golabi P, Locklear CT, Austin P, Afdhal S, Byrns M, Gerber L, et al. Effectiveness of exercise in hepatic fat mobilization in non-alcoholic fatty liver disease: Systematic review. *World J Gastroenterol.* 2016;22:6318–6327. 10.3748/wjg.v22.i27.6318. [PMC free article] [PubMed] [Google Scholar]
37. 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. 10.1016/j.metabol.2016.12.006. [PubMed] [Google Scholar]
38. Nseir W, Hellou E, Assy N. Role of diet and lifestyle changes in nonalcoholic fatty liver disease. *World J Gastroenterol.* 2014;20:9338–9344. 10.3748/wjg.v20.i28.9338. [PMC free article] [PubMed] [Google Scholar]
39. Li Y, Liu L, Wang B, Wang J, Chen D. Metformin in non-alcoholic fatty liver disease: A systematic review and meta-analysis. *Biomed Rep.* 2013;1:57–64. 10.3892/br.2012.18. [PMC free article] [PubMed] [Google Scholar]
40. Bhat A, Sebastiani G, Bhat M. Systematic review: Preventive and therapeutic applications of metformin in liver disease. *World J Hepatol.* 2015;7:1652–1659. 10.4254/wjh.v7.i12.1652. [PMC free article] [PubMed] [Google Scholar]