Non-alcoholic liver disease

Abstract

Nonalcoholic fatty liver disease (NAFLD) may becoming increasingly common. Whilst it can be a non-progressive disorder with minimal impact, for some people, it develops into a serious disorder with significant implications for life and health. This article outlines the disease pathology, epidemiology, progression and examines how people identified with this disorder can be advised.

In the 1980s and 1990s a new type of liver damage was noted, first in Japan and then elsewhere. It was like that seen in people with a history of alcohol abuse, yet these people claimed to never drink or only in modest quantities (no more than one standard drink per day or 70g of ethanol/week for women: and no more than two standard drinks per day or 140 g of ethanol/week for men). Ludwig et al (1980) explains some physicians believed clients were concealing their drinking habits, which may have delayed the formal recognition of this type of liver damage. However, as these problems were more widely discussed, it became apparent this type of liver disease could be a manifestation of metabolic disruption. The term non-alcoholic fatty liver disease (NAFLD) was coined as an umbrella term for a range of liver conditions affecting people who drink little or no alcohol.

NAFLD has become the most common form of liver disease in most developed countries (McPherson et al, 2015). It is increasingly recognised as the liver disease component of metabolic syndrome and type 2 diabetes mellitus (T2DM, Chalasani et al, 2012). As the name implies, the main characteristic of NAFLD is steatosis, or excessive lipid (fat) stored in the liver cells, in the absence of other known causes. As well as high alcohol consumption, these can include viral hepatitis or the use of drugs such as tamoxifen (Bellentani and Marino, 2009). In 2016 guidelines for the diagnosis and management of NAFLD were jointly released by the European Association for the Study of the Liver (EASL), the European Association for the Study of Diabetes (EASD), and the European Association for the Study of Obesity (EASO). In the UK, these have recently been updated by the British Society of Gastroenterology (2020).

NAFLD often causes no symptoms and so frequently comes to medical attention only when tests, done for other reasons, suggest the presence of liver problems. Indications can include a liver which looks unusual on ultrasound, or abnormal liver enzyme test. The actual rate of complications is difficult to estimate and may be as low as 0.2% mortality or may be as high as 1.6% (Stott and Dang, 2021).

Epidemiology

NAFLD is common around the world, especially in Western nations. It is increasing and may be under-reported (Farrel and McCollough, 2013). It appears people are developing NAFLD younger and so it can be assumed NASH rates will rise even faster than rates of NAFLD

(Farrel and McCollough, 2013). Due to the difficulties in diagnosing it, rates tend to be estimated. For example, ultrasound was used to diagnose NAFLD in 33% of men and 20% of women in Spain (Caballeria et al, 2010). A similar approach in Italy identified NAFDL in 24.5% of the general population (Bellentani and Marino, 2009). Both studies excluded individuals with known liver disease. Alarming though these figures are, for many this is a non-progressive condition. Nevertheless, a minority will go on to develop a more aggressive type of liver disease called non-alcoholic steatohepatitis (NASH). This is hepatic steatosis with the presence of damage to hepatocytes. These people are in danger of developing fibrosis and cirrhosis of the liver and may ultimately require liver transplantation (Chalasani et al, 2012). Little is known about why some people with fatty livers develop inflammation that progresses to cirrhosis, whilst others do not. Thus the disease progression cannot be predicted.

So, what is known about these diseases? NAFLD and NASH are both linked to the following:

- Overweight or obesity. NAFLD may be a feature of obesity because over 90% of clients undergoing bariatric surgery were found to have NAFLD (Portillo-Sanchez, 2015). Indeed, liver biopsies are becoming routine during bariatric procedures. Overweight individuals are at especially vulnerable if they have additional risk factors such as hyperlipidaemia (Bellentani et al, 2010), heavy drinking, or if they have central obesity (Caballería et al, 2010)

- Insulin resistance or diabetes. NAFLD has been reported in over 76% of people with T2DM (Portillo-Sanchez et al 2015). Further, this group may be at particular risk of disease progression. A different study (Prashanth et al, 2009) found nearly half of all people with T2DM had evidence of NAFLD and those with poorly controlled blood glucose were at increased risk of NASH, yet clients often reported no symptoms.

- Increased age. It is currently unknown whether age is, itself, a biological risk factor or whether older people are likely to have had NAFLD for longer and therefore have had longer time to develop the complications (Farrel and McCollough, 2013). This complicates management because increased age is also a risk factor for the comorbidities of hypertension, diabetes, hyperlipidaemia, and obesity (Frith et al, 2009). Older people with NAFLD are also more likely to progress to NASH (Adams et al, 2005) and other related problems such as hepatic fibrosis or hepatic cancer (Liew et al, 2008). That said, it is now being diagnosed in children, especially if they are obese (Bellentani and Marino, 2010).

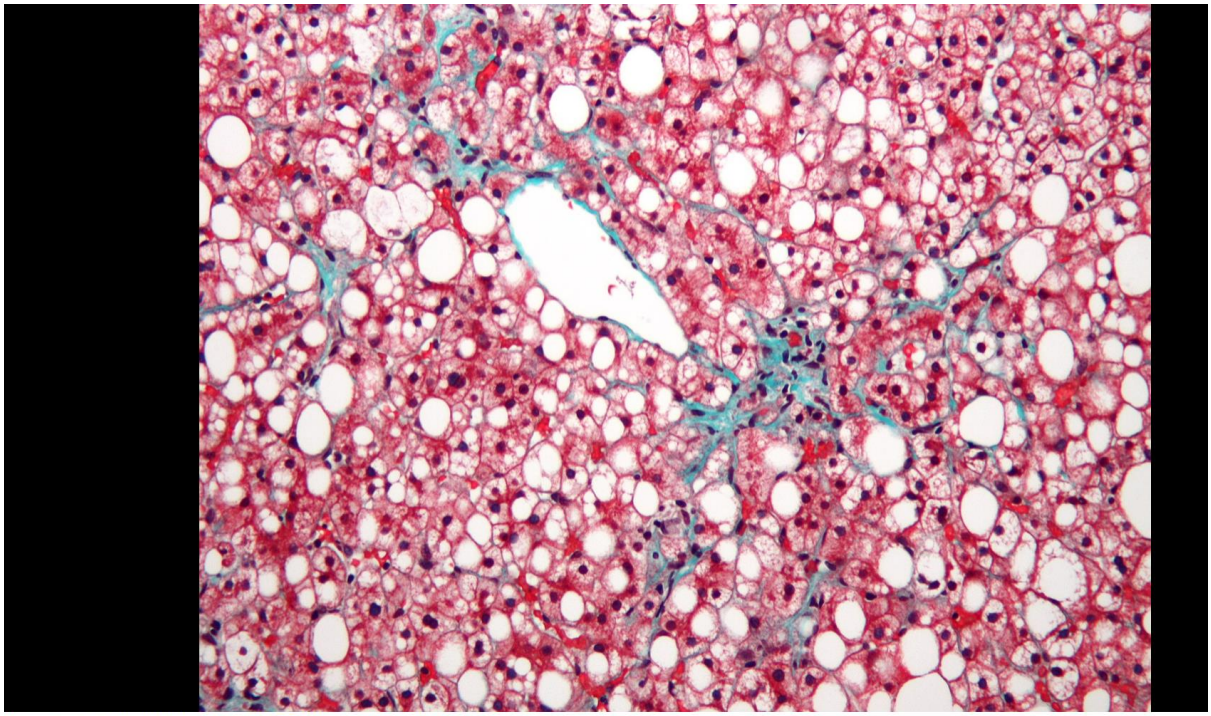
- Other metabolic conditions, such as polycystic ovary syndrome, underactive thyroid (hypothyroidism), and underactive pituitary gland (hypopituitarism) can all be diagnosed with NAFLD at higher-than-expected rates (Baranova et al, 2011).

- High levels of lipid, particularly triglycerides, in the blood.

- There may be some differences depending upon ethnicity. In America, Hispanics have the highest rates and African Americans the lowest (Wagenknecht et al, 2009). Although these differences are not understood, others have observed family clusters, suggesting a genetic link (Speliotes et al, 2011).

Pathology and Progression of the disease

The defining characteristic of NAFLD is steatosis, the accumulation of triglycerides in the cytoplasm of the hepatocytes, or liver cells. The triglycerides are present in clear vacuoles (droplets) in the cytoplasm. There can be several tiny vacuoles, which leave the nucleus of the hepatocyte undisturbed, and can make the cytoplasm appear foamy. Alternatively, there can be just one large vacuole, which can partially displace the nucleus (see figure 1). NAFLD is diagnosed when 5% or more of the cells are affected. Early in the disease, these are often clustered together. More advanced disease is often characterised by the affected cells spread throughout the liver acini (functional units) which can interrupt the blood supply (Farrel and McCollough, 2013).



Micrograph of **non-alcoholic fatty liver disease (NAFLD)**. Masson's trichrome & Verhoeff stain. The liver has a prominent (centrilobular) macrovesicular steatosis (white/clear round/oval spaces) and mild fibrosis (green). The hepatocytes stain red. Macrovesicular steatosis is lipid accumulation that is so large it distorts the cell's nucleus. Differential diagnosis of centrilobular (zone III) macrovesicular hepatic steatosis: Diabetes. Obesity. Alcohol. See also ...

If NAFLD progresses, there is frequently inflammation. When this is present, lipogranulomas can be seen, which are clumps of liver tissue incorporating eosinophils and fibrotic material. Kupfer cells – cells of the immune system specific to the liver – and macrophages can also be present in higher-than-normal concentrations. If the disease continues to develop, steatohepatitis (or non-alcoholic steatohepatitis, NASH) is said to occur. The affected cells are larger than normal, described as ballooning. These hepatocytes do not function correctly and damage near-by cells. The affected parts of the liver develop cirrhosis. This is seen when the liver tries to halt inflammation, producing areas of scarring (fibrosis).

People with NAFLD experience an increased mortality, from all causes, of about 1.7% when compared to people of the same age and gender but no NAFLD (Adams et al, 2005). NAFLD has been compared to hypertension (Farrel and McCollough, 2013), because it is relatively common, with limited medical treatment, yet causes much morbidity and mortality. The biggest causes of death are cardiovascular disease and cancer, followed by liver disease and it can complicate the course of COVID-19. In clinical practice health professionals may need to manage multiple hazards (Herta and Berg, 2021).

Since most clients with NAFLD do not progress to more advanced disease and have a life expectancy similar to that of the general population (Portillo-Sanchez et al, 2015), it would be useful to identify those at risk of progressing to more advanced disease and NASH. Yet this is difficult to do because many of those with NAFLD have no symptoms and so are never identified. McPherson et al (2015) in Northern England, attempted to get around this difficulty by reviewing the results of 108 clients who had undergone more than one liver biopsy as part of their routine investigations and treatment. Those receiving treatment for liver disease were excluded from the analysis as was anyone known to take moderate amounts of alcohol. One quarter of the clients had NAFLD at the first biopsy and three-quarters had some degree of NASH. The second biopsy was, on average, five years later. Of the clients with NAFLD at the first biopsy, 40% were stable ('non-progressors'), 18% had improved, and 42% had deteriorated and were now showing results consistent with NASH ('progressors'), including 22% of clients who had advanced liver disease at the second biopsy. Of those clients with NASH at the first biopsy, 7% had improved and their results were now consistent with NAFLD. These results cannot be taken to show the typical course of the disease because all had health problems sufficiently severe to require two or more liver biopsies, so it is interesting the rates are like those discussed earlier in the general population (Caballeria, 2010). They also show two important features of the relationship between NAFLD and NASH. The first is that progression from NAFLD to NASH is not inevitable, even in those quite badly affected and second, it may even be possible for liver results to improve. Even more importantly McPherson et al (2015) hinted at the possibility of identifying those at risk of disease progression and possibly take action to avoid it. Those showing signs of NASH at the second biopsy were more likely to also have T2DM. 80% of progressors had T2DM compared to 25% of non-progressors. McPherson et al (2015) could only speculate on whether effective control of blood glucose through drugs could help prevent or delay progression. Progressors were also more likely to have a high BMI (average of 34.9 rather than 33.9 for the non-progressors). It was further noted they were more likely to have a low platelet count, which could have been caused by the liver disease. These combined health problems appear to promote the deposit of fat in the liver (McPherson et al, 2015). For some, this excess fat is hepatotoxic, causing liver inflammation and fibrosis, or NASH, which may lead to a build-up of scar tissue and liver cirrhosis.

NAFLD usually causes no signs and symptoms. When it does, they may include:

- Fatigue
- Pain or discomfort in the upper right abdomen

If the disease has progressed, possible signs and symptoms of NASH and advanced scarring (cirrhosis) include:

- Ascites
- Enlarged blood vessels just beneath the skin's surface and oesophageal varices, which can rupture and cause catastrophic bleeding
- Enlarged spleen
- Palmar erythema. The palms of the hands are red and blotchy. The client does not find them itchy or painful but may report extra warmth in their hands.
- Confusion, drowsiness, and slurred speech (hepatic encephalopathy)
- Liver cancer or end-stage liver failure

Screening and diagnosing NAFLD and NASH

A liver biopsy followed by microscopy and staining of the liver cells remains the 'gold standard' for diagnosing NAFLD and NASH (Vali et al, 2020) but this invasive procedure can lead to haemorrhage which can even be fatal. It is therefore not a procedure to be undertaken lightly. Further, liver biopsy itself may be subject to sampling errors and interobserver variation (Patel and Wilder, 2014) and other tests can be useful. Vibration-controlled transient elastography (VCTE, often referred to as FibroScan), uses an ultrasound probe to generate waves to assess the stiffness of the liver. It can be useful in assessing clients with NAFLD but is less accurate in children or in the presence of ascites or obesity (Patel and Wilder, 2014). The enhanced liver fibrosis (ELF) test can help identify clients with NAFLD who are progressing onto NASH. The test has a high negative predictive value, especially in populations with low disease prevalence, so can exclude advanced fibrosis in patients with NAFLD. However, the positive predictive value of the ELF test is low and Vali et al (2020), suggest additional strategies may be needed to make a positive diagnosis. In view of the risk for clients with diabetes mellites also being affected by NAFLD, Byrne and Targher (2016) recommend clients newly diagnosed with T2DM be screened for NAFLD using ultrasound and an ELF test. If NAFLD is suspected, clients should undergo a comprehensive assessment including assessment of dietary and lifestyle factors, alcohol intake, metabolic risk factors and secondary causes of liver steatosis and, if present, causes for elevated liver enzymes (EASL–EASD–EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease, 2016). If NAFLD is identified, they should also be assessed for insulin resistance and T2DM. Such clients should also be assessed for hypertension and cardiovascular disease.

Management

There is currently no single, proven therapy for the management of NAFLD and only those with NASH require active treatment (Younossi, 2008). Nevertheless, according to the guidelines, clients with NAFLD are likely to benefit from lifestyle changes including weight loss and exercise. People who are pre-obese (overweight) or obese, should reduce the amount of energy in their diet and aim to lose 7-10% weight loss (British Society of Gastroenterology, 2020). Even those with a healthy weight should choose a healthy diet. This means a plant-based diet rich in fruits, vegetables, whole grains, and healthy (unsaturated) lipids, sometimes referred to as the Mediterranean diet. They should exclude NAFLD-promoting components (processed foods, and foods and beverages high in added fructose). The rationale is that loss of white adipose tissue protects the liver. Even quite modest weight reduction of 7% demonstrated improvement in NASH (Angulo, 2013). This should be achieved through supportive strategies including cognitive-behavioural therapies to help clients achieve healthier diets and increased physical activity. Neither aerobic exercise nor resistance training on their own are likely to lead to weight loss but are effective to reduce liver fat and improve insulin sensitivity. The choice of training can be tailored to the clients' preferences because enjoyable activities are more likely to be maintained in the long term.

Younossi (2008) adopted a range of measures designed to help clients with NAFLD. They found some evidence that prescribing *Orlistat* (a drug which impedes the absorption of lipid from the gut) improves short-term liver function, but the long-term effects are currently unknown (Younossi, 2008). It is likely that drugs which reduce insulin resistance can help prevent progression in NAFLD. However, the benefits of improving insulin resistance may be offset by clients gaining weight due to the drugs, which happened to two-thirds of their clients (Younossi, 2008). A further problem is much of the improvement appears short-lived. For example, a small study (Nair et al, 2004) of metformin given to clients with NASH showed early improvement in liver enzymes, but this was reversed after only 12 months. Younossi (2008) discusses other options, such as lipid lowering drugs or drugs to reduce oxidative stress. Neither showed significant, long-term benefit. It is possible bariatric surgery can help liver function in the longer-term and even to NASH resolving (Dixon et al, 2004). Theoretically, vitamin E may reduce oxidative stress (which can trigger inflammation) and has no unwanted effects at therapeutic doses. However, high doses should be avoided (Mayo clinic, 2020). There is also some evidence coffee may provide some protective effect (Mayo clinic, 2020). These are examples of some simple strategies which could be useful in NAFLD and NASH, but much more evidence is required.

Nursing role

This article has shown it is difficult to know who may have NAFLD, but it should be considered in clients who are obese, take a diet high in lipid and sugar, or have T2DM. Such clients should be supported in choosing a plant-based, reduced lipid, and low sugar diet. Clients in this situation may require significant support since the presence of NAFLD rarely causes symptoms or make the person feel unwell, yet the foods they are being asked to forgo are popular. However, the nurse can point out the recommended diet is not specific to liver disease and the NHS encourages most adults to adopt it (National Health Service,

2019). This means it may be appropriate for the client to adopt a new diet along with their families or partners. They should further be encouraged to review other aspects of their lifestyle and identify opportunities to increase their physical activity in ways they find acceptable. Some of these clients may be in poor physical condition, remembering they are at high risk of concurrent cardiovascular disease, and unused to vigorous exercise. They may require help in choosing appropriate activities. This need not be a formal exercise or sports programme, but could include housework, gardening, and walking. They may require encouragement to continue with them after any initial enthusiasm has worn off. The risk of developing NAFLD and NASH provide further incentives for clients with T2DM to achieve good glycaemic control. Whilst not wishing to frighten clients into taking action to protect their liver, nurses may need to remind them liver disease is a serious condition which greatly impacts quality of life. If end-stage liver failure is reached, they may need a liver transplant. If this is not possible or unsuccessful, the prognosis for the client is poor. On the other hand, it appears possible for most clients to halt, or even reverse modest liver damage and to achieve a near-normal life expectancy.

Conclusion

This review has shown some degree of liver damage is quite common in the population and should be considered in those who are overweight / obese, have T2DM or other metabolic disruption. For many people, the disease will not progress or cause significant health problems. For some, however, it can do. This progression is not inevitable and adopting a healthy lifestyle could protect the client's liver from further damage and even reverse that which has occurred.

References

Adams LA, Lymp JF, St Sauver J, Sanderson SO, Lindor KD, Feldstein A, Angulo P 2005. The natural history of nonalcoholic fatty liver disease: a population-based cohort study. *Gastroenterology*. 2005 Jul;129(1):113-21.

Angulo, P. (2013). The natural history of NAFLD. In: Farrell, G.C.; McCullough, A.J.; Day, C.P. *Non-Alcoholic Fatty Liver Disease: A Practical Guide.* Wiley , pp. 37-45.

Baranova A, Tran TP, Birerdinc A, Younossi ZM. 2011 Systematic review: association of polycystic ovary syndrome with metabolic syndrome and non-alcoholic fatty liver disease. *Aliment Pharmacol Ther*. 33(7):801-14.

Bellentani S, Marino M: 2009 Epidemiology and natural history of non-alcoholic fatty liver disease (NAFLD). *Ann Hepatol*; 8(suppl 1):S4–S8.

British Society of Gastroenterology 2020 *NAFLD – diagnosis, assessment and management* https://www.bsg.org.uk/clinical-articles-list/nafld-diagnosis-assessment-and-management/ accessed August 2021

Byrne, C.D. & Targher, G. 2016, EASL–EASD–EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease: is universal screening appropriate?, *Diabetologia*, vol. 59, no. 6, pp. 1141-1144.

Caballería L, Pera G, Auladell MA, Torán P, Muñoz L, Miranda D, Alumà A, Casas JD, Sánchez C, Gil D, Aubà J, Tibau A, Canut S, Bernad J, Aizpurua MM. 2010 Prevalence and factors associated with the

presence of nonalcoholic fatty liver disease in an adult population in Spain. *Eur J Gastroenterol Hepatol*. 22(1):24-32.

Chalasani N, Younossi Z, Lavine JE, Diehl AM, Brunt EM, Cusi K, Charlton M, Sanyal AJ. 2012 The diagnosis and management of non-alcoholic fatty liver disease: practice Guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association. *Hepatology*. 55(6)

European Association for the Study of Diabetes (EASD), European Association for the Study of Obesity (EASO) & European Association for the Study of the Liver (EASL) 2016, EASL–EASD–EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease, *Diabetologia*, vol. 59, no. 6, pp. 1121-1140.

Dixon JB, Bhathal PS, Hughes NR, O'Brien PE. 2004 Nonalcoholic fatty liver disease: improvement in liver histological analysis with weight loss. *Hepatology*; 39: 1647–54

Farrel, G. and McCullough, A. D. C., (2013). What is NAFLD and why is it important. In: G. Farrel & A. D. C. McCullough, eds. *Non-alcoholic fatty liver disease, a practical guide*. s.l.:s.n.

Frith J, Day CP, Henderson E, Burt AD, Newton JL. (2009) Non-alcoholic fatty liver disease in older people. *Gerontology*. 2009;55(6):607-13.

Herta, T.; Berg, T. (2021) COVID-19 and the liver – Lessons learned. *Liver Int*.; 41: 1– 8

Kral JG, Thung SN, Biron S, *et al*. 2004 Effects of surgical treatment of the metabolic syndrome on liver fibrosis and cirrhosis. *Surgery*; 135: 48–58

Liew PL, Lee WJ, Wang W, Lee YC, Chen WY, Fang CL, Huang MT. 2008 Fatty liver disease: predictors of nonalcoholic steatohepatitis and gallbladder disease in morbid obesity. *Obes Surg*.18(7):847-53.

Ludwig, J.; Viggiano, T.R.; McGill, D.B.; Oh, B.J. 1980 Nonalcoholic steatohepatitis: Mayo Clinic experiences with a hitherto unnamed disease *Mayo Clin Proc* 55(7)434-8

Mayo Clinic (2020) Nonalcoholic fatty liver disease https://www.mayoclinic.org/diseases-conditions/nonalcoholic-fatty-liver-disease/diagnosis-treatment/drc-20354573 accessed August 2021

McPherson S, Hardy T, Henderson E, Burt AD, Day CP, Anstee QM. 2015 Evidence of NAFLD progression from steatosis to fibrosing-steatohepatitis using paired biopsies: implications for prognosis and clinical management. *J Hepatol*. 62(5):1148-55.

Nair S, Diehl Am, Wiseman M, Farr, G.H. Perrillo, R.P. 2004 Metformin in the treatment of non-alcoholic steatohepatitis: a pilot open label trial. *Aliment Pharmacol Ther*; 20: 23–8

National Health Service (NHS) The eatwell guide 2019 available at https://www.nhs.uk/live-well/eat-well/the-eatwell-guide / accessed July 2021

Patel, K. & Wilder, J. 2014, Fibroscan, *Clinical liver disease* (Malden, Mass.), vol. 4, no. 5, pp. 97-101

Portillo-Sanchez P, Bril F, Maximos M, Lomonaco R, Biernacki D, Orsak B, Subbarayan S, Webb A, Hecht J, Cusi K. 2015 High Prevalence of Nonalcoholic Fatty Liver Disease in Patients With Type 2 Diabetes Mellitus and Normal Plasma Aminotransferase Levels. *J Clin Endocrinol Metab*. Jun;100(6):2231-8.

Prashanth, M.; Ganesh H.K.; Vimal, M.V.; John, M.; Bandgar, T.; Joshi, S.R.; Shah, S.R.; Rathi, P.M.; Joshi, A.S.; Thakkar. H.; Menon, P.S.; Shah, N.S. 2009 Prevalence of Nonalcoholic Fatty Liver Disease in Patients with Type 2 Diabetes Mellitus *J Assoc Physicians India* 57 205-210

Portillo-Sanchez, P.; Bril, F.; Maximos, M.; Lomonaco, R.; Biernacki, D.; Orsak, B.; Subbarayan, S.; Webb, A.; Hecht, J.; Cusi, K. 2015 High Prevalence of Nonalcoholic Fatty Liver Disease in Patients with Type 2 Diabetes Mellitus and Normal Plasma Aminotransferase Levels. *J Clin Endocrinol Metab*. 100(6):2231-8.

Speliotes EK, Yerges-Armstrong LM, Wu J, Hernaez R, Kim LJ, Palmer CD, et al. 2011 Genome-Wide Association Analysis Identifies Variants Associated with Nonalcoholic Fatty Liver Disease That Have Distinct Effects on Metabolic Traits. *PLoS Genet* 7(3): e1001324.

Stott, B. & Dang, J.C. 2021, Updated Statistics for Liver Biopsy Risk, *American family physician*, 103, 8, 453-453

Vali, Y.; Lee, J.; Boursier, J.; Spijker, R.; Löffler, J.; Verheij, J.; Brosnan, M.J.; Böcskei, Z.; Anstee, Q.M.; Bossuyt, P.M.; Zafarmand, M.H. (2020) Enhanced liver fibrosis test for the non-invasive diagnosis of fibrosis in patients with NAFLD *J of hepatology* 73[2] 252-262

Wagenknecht, L. E., Scherzinger, A. L., Stamm, E. R., Hanley, A. J., Norris, J. M., Chen, Y. D., Bryer-Ash, M., Haffner, S. M., & Rotter, J. I. 2009. Correlates and heritability of nonalcoholic fatty liver disease in a minority cohort. *Obesity (Silver Spring, Md.)*, *17*(6), 1240–1246.

Younossi, Z.M. 2008 Review article: current management of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis. *Aliment Pharmacol Ther*.