South African Journal of Gastroenterology and Hepatology. 2024;01(2):55-57
https://doi.org/10.36303/SAJGH.0934

SAJGH
ISSN 3078-1779

REVIEW

A discourse of non-alcoholic steatohepatitis

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Keywords: non-alcoholic fatty liver disease, hepatocellular carcinoma, cirrhosis, NASH, treatment

Introduction

Non-alcoholic fatty liver disease (NAFLD) is a major cause of chronic liver disease and a worldwide public health concern with a prevalence of 25%.[1] The highest recorded prevalence (32%) is found in the Middle East, followed by South America (31%), Asia (27%), the United States of America (USA) (24%), Europe (23%) and Africa (14%).[2] By 2030, 400 million people worldwide will be affected by NAFLD in Europe, the USA, and Asia. The incidence of the disease in China has recently exceeded that of the USA and Europe.[3] China will have the greatest growth in NAFLD patients worldwide by 2030, with 314.58 million individuals affected.[4] A term recently developed, metabolic dysfunction-associated fatty liver disease (MAFLD), highlights diagnostic characteristics, such as obesity, type II diabetes, and insulin resistance, which are favourable for the development of this disease.

Non-alcoholic fatty liver disease

NAFLD is mostly indicated by excessive fat deposition in hepatocytes without excessive alcohol use. NAFLD is diagnosed using a variety of clinical and pathological signs. By using imaging or histology, steatosis in NAFLD can be distinguished as 5% of liver fat.[5,6] From simple steatosis to steatohepatitis (NASH), a group of illnesses known as NAFLD combines fatty liver with parenchymal damage (apoptosis and ballooning, localised necrosis, lobular/portal inflammation, and varying degrees of fibrosis).[4,5,7] When NAFLD progresses from simple steatosis to non-alcoholic steatosis (NASH), a complex interplay of factors, including metabolic anomalies, lipo-toxicity, intestinal dysbiosis, oxidative stress, and hepatic necrosis, comes into play. These factors together encourage the growth of chronic inflammation, which maintains tissue damage and parenchyma cell.[7]

NASH is currently the primary cause of liver cirrhosis and the second most common indication for liver transplantation in the USA due to the exponential rise in global obesity.[4] It is not surprising that NAFLD is the fastest-growing cause of hepatocellular carcinoma (HCC) globally. Over 50% of cases are detected in individuals between the ages of 50 and 70. Men are more likely than women to have NASH, and those with diabetes, obesity, dyslipidaemia, etc. and hypertension are also more likely to have NASH. The frequency of NASH has grown by around 100%. It is believed that 2–3% of adult Americans suffer from NASH.[8,9]

Hepatocellular carcinoma (HCC)

Currently, HCC accounts for most of the primary liver cancers (PLC), accounting for approximately 75% of total cases,[10] and is the third leading cause of cancer-related mortality worldwide, being responsible for more than 800 000 deaths annually.[11] Incidence rates have been rising in many countries globally, but particularly rapidly in Western Europe, Australasia, and North America. In the United Kingdom (UK), PLC has been amongst the cancers with the most rapid rate of growth in both incidence and mortality in recent decades and is projected to be the important driver of future liver cancer trends worldwide.[12] Survival is poor for HCC with five-year relative survival estimates below 10%.[13] Most HCC cases arise in the setting of chronic liver disease, such as chronic hepatitis B virus (HBV) infection, chronic hepatitis C virus (HCV) infection, alcoholic steatohepatitis (ASH), and now more with NASH. With the current obesity pandemic, and the introduction of direct-acting antivirals for the treatment of HCV, NASH is becoming the leading cause of HCC.[14]

The poor prognoses observed in HCC associated with NASH may be attributed to patients at risk of HCC not receiving a complete diagnosis. Tissue histology indicates that 25% of NASH-related HCCs have no underlying cirrhosis; this has also been referred to in other studies as the development of HCC in non-cirrhotic NASH.[8] Individuals with NASH, even those with screening-detected HCC, have a poorer survival rate than individuals with other underlying liver disorders. This might be due to the high prevalence of extrahepatic metabolic problems that render surgical intervention unfeasible, such as chronic renal disease and cardiovascular disease.[15]

Diagnosis and surveillance

The development of reliable and practical diagnostic tools is critical to the early detection and effective treatment of NAFLD. Blood biomarkers that can accurately diagnose and stage NAFLD at any stage of the illness are still unknown. Combining prognostic and diagnostic biomarkers would be ideal for identifying high-risk situations and therapeutic benefits.[6]

The most reliable method for diagnosing NASH is still liver biopsy, but this is limited by cost, procedure morbidity, and inaccurate sampling. Non-invasive tests like magnetic resonance elastography (MRE), ultrasound-based transient elastography (FibroScan), and marker-based predictive assessment panels like the Fibrosis-4 Index (FIB-4)[16] and the NAFLD fibrosis score

(NFS) have contributed to the improvement of the diagnostic approach for NAFLD.

Random liver biopsy of patients with NAFLD revealed NASH in 6.67% of cases. 59.10% of NAFLD patients with a clinical justification for a liver biopsy had NASH.[9] Additionally, as they have a significantly higher risk of developing cirrhosis and HCC, patients with NAFLD and elevated liver enzymes should be constantly monitored.[17]

The HCC surveillance technique includes testing for tumour markers (alpha-fetoprotein, or AFP) and abdominal ultrasonography (US) every three to six months. Intervals of three to four months are recommended for monitoring the extreme-risk group. This routine monitoring strategy could be used with dynamic computed tomography (CT) or magnetic resonance imaging (MRI) for patients who are especially high-risk. New nodular lesions are differentially diagnosed by US using dynamic CT and dynamic MRI with contrast. If there is a prolonged rise of ≥ 200 ng/mL AFP or ≥ 15% of the AFP-L3 fraction, dynamic CT/MRI should be studied even if no tumour is seen in the US.[16]

Treatment

According to the European Association for the Study of the Liver guidelines,[18] pharmacological therapy should be commenced in patients with either:

- Progressive NASH (bridging fibrosis and cirrhosis).
- Early-stage NASH with high risk for disease progression (increased serum ALT, presence of metabolic syndrome and diabetes mellitus, age > 50 years), or
- Active NASH with high necro-inflammatory activities.

Although a single drug therapy is not currently accessible, there are several different approaches to address the disease, including weight loss, lifestyle changes, and surgical and pharmacological therapy. Reversing alcohol and/or tobacco usage, increasing physical activity, and changing lifestyle are examples of combination therapy that may be beneficial. Those individuals who lost at least 5% of their body weight showed some improvement.[6] International standards have strongly advocated aiming for a weight loss of at least 10% to achieve optimum benefits.

The most recent American Association for Study of Liver Diseases guidelines recommend vitamin E therapy for patients without diabetes mellitus and pioglitazone medication for individuals with diabetes and NASH. This pharmaceutical treatment includes pioglitazone, peroxisome proliferator-activated receptor γ (PPARγ), vitamin E, and semaglutide. Among the approved medications are ertugliflozin, dapagliflozin, empagliflozin, and canagliflozin. Clinical trials with pioglitazone and empagliflozin combination therapy (in process) and evoglipin monotherapy (completed) have produced encouraging findings. A recent meta-analysis found that the combination of pioglitazone with Roux-en-Y gastric bypass surgery has a stronger positive effect on NAFLD activity.[6]

The role of metabolic surgery for NAFLD and NASH is still being defined. The two most commonly performed procedures include a laparoscopic Roux-en-Y gastric bypass (RYGB) and a laparoscopic sleeve gastrectomy (LSG), both of which have been shown to have an impact on NAFLD. RYGB has been shown to significantly reduce NAFLD activity scores, steatosis, inflammation and liver ballooning during a one-year postoperative observation period;[19] and LSG reduces activation of hepatic progenitor cells, hepatic stellated cells and macrophages thereby improving the NAFLD activity score and decreasing liver fibrosis.[20] Of note, a minority of studies have shown worsening NAFLD following bariatric procedure, the mechanism for this having not been identified.[21,22]

Conclusion

NAFLD is likely to surpass all other causes of end-stage liver disease in the coming decades. Since there aren't any particular, non-invasive markers for NAFLD, liver biopsy is now the gold standard for diagnosing and staging the condition. Although a number of drugs are in the early stages of development, there is currently no approved pharmacological therapy specifically for

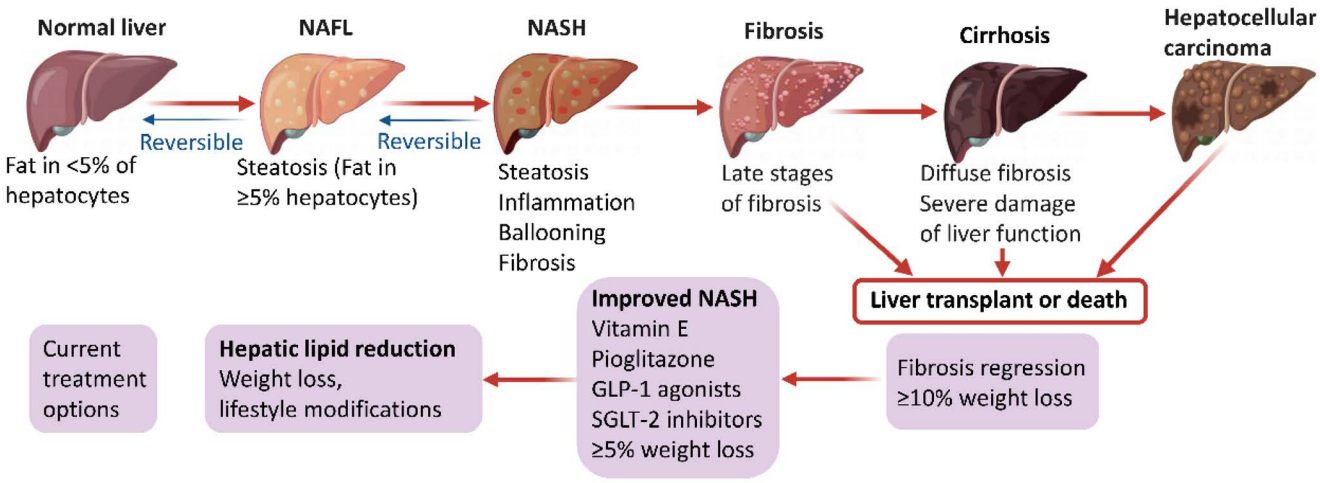

Figure 1: Pathophysiology and management options in NAFLD
Int J Mol Sci. 2023 Feb; 24(3):2844.
Published online 2023 Feb2. https://doi.org/10.3390/ijms24032844[6]

non-alcoholic fast-fat liver disease. Metabolic surgery is proving to be an effective treatment option and may soon feature more prominently in guidelines.

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