What is non-alcoholic steatohepatitis (NASH)?

Non-alcoholic steatohepatitis (NASH) is a more severe, progressive form of non-alcoholic fatty liver disease (NAFLD)[1]. The prevalence of NAFLD in Western countries is 20-30%, and it is estimated that 2-3% of the population has NASH[2].

As fat builds up in the liver, it triggers a vicious cycle of chronic inflammation and fibrosis (scarring of the liver)[3]. If the liver damage continues long-term, it can result in advanced scarring of the liver, called cirrhosis[3]. Cirrhosis leads to an increased risk of developing a type of liver cancer called hepatocellular carcinoma (HCC), as well as liver failure and, barring a transplant, significant morbidity and death[2,3]. NASH is a major cause of liver disease worldwide and is now the leading cause of liver transplants for people under 50 in the US[4].

Most people who have NASH are aged 40 to 50[5], however increasing numbers of teenagers and young adults are being diagnosed[6]. Risk factors include[3]:

- **Obesity**, particularly if the individual has a large waist size
- **High levels of fats** (triglycerides) or abnormal levels of cholesterol in the blood
- **Having a metabolic syndrome** (group of traits linked to being overweight and obese, including large waist size, high levels of triglycerides in your blood, low levels of HDL cholesterol in your blood, high blood pressure and higher than normal blood glucose levels)
- **Type 2 diabetes**

NASH: a silent disease

NASH generally has no, or only a few, non-specific signs or symptoms on examination, although some people with the disease report feeling tired[3].

More than just a liver disease

Once the liver disease advances, or when cirrhosis develops, it is possible to experience symptoms such as fatigue, weight loss and weakness[5]. Cirrhosis has also been associated with a greater risk of developing HCC and can also lead to liver failure, requiring transplantation to avoid severe outcomes such as death[2,3]. Studies also suggest that people with NAFLD have a greater chance of developing cardiovascular disease and this is also one of the most common causes of death from NASH[3].

Reaching a diagnosis

A diagnosis can be achieved through physical exams, blood tests (to test for increased levels of specific liver enzymes, such as alanine aminotransferase - ALT, and aspartate aminotransferase - AST) imaging tests (e.g. an ultrasound), however for a definite diagnosis, liver biopsies are required[3].

Treatment goals

Currently no approved treatments for NASH exist. The current treatment is to manage the conditions that are associated with NASH, with the aim to reduce the liver inflammation. This can include treating obesity and Type 2 diabetes.

An urgent need for new treatment options for NASH patients

Currently no approved treatments for NASH exist, although studies have shown that Vitamin E and treatments for Type 2 diabetes may improve NASH[3]. There are recommendations to treat the conditions associated with NASH, including[3]:

- Diet and weight loss (if obese or overweight)
- Regular exercise
- Avoid significant alcohol

If cirrhosis develops and its complications develop, a liver transplant may be required[3].

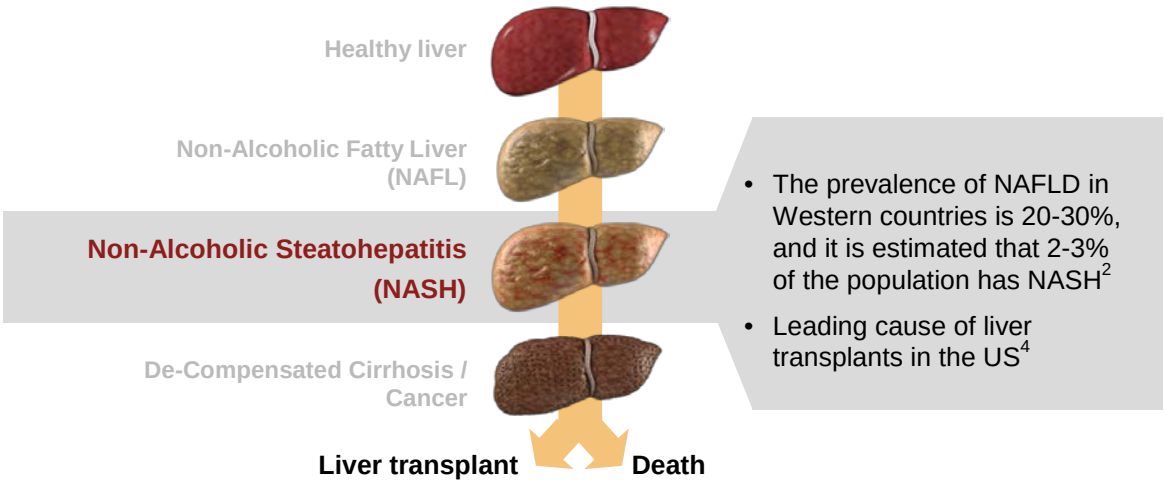
A NASH epidemic?

Obesity is on the increase which is having a substantial impact on obesity-related diseases[2]. In children, obesity is the single biggest cause of NAFLD, with an estimated prevalence in overweight and obese children of 50-80% compared to 2-7% in children of normal weight[7]. Obesity also significantly increases the risk of developing NASH, of which 25% of children will progress to[7]. This increasing concern has led to a change in guidelines, which now recommends that all obese or overweight children, with additional risk factors, are screened for NAFLD[8].

This obesity epidemic has also impacted the prevalence of NAFLD across all ages globally. China has reported doubled figures of NAFLD in the past decade, with similar findings in the US and in Europe where NAFLD has become the most commonly diagnosed cause of chronic liver disease[9,10]. A recent publication evaluating the global prevalence of NASH, estimate it to be in the range of 1.5% to 6.5%[11].

Novartis: Growing liver portfolio to target multiple pathways involved in NASH progression

There are a number of new treatment options being investigated that are in clinical trials. Novartis currently has two FXR agonists in worldwide clinical studies with the aim of delivering new and much needed treatment options for people with NASH. Both FXR agonists recently received Fast Track designation from the US Food and Drug Administration (FDA). FXR agonists work by regulating the bile acid levels in the liver, reducing fat build up (steatosis), inflammation and thickening and scarring in the liver. The most advanced investigational compound is a potent, non-bile acid FXR agonist and is currently in a Phase II clinical trial.



Novartis recently announced a collaboration with Conatus Pharmaceuticals Inc. to jointly develop emricasan, an investigational, first-in-class, pan-caspase inhibitor which works by inhibiting pathways that result in cell death (apoptosis) and inflammation. As part of this collaboration, multiple Phase IIb clinical trials in NASH will be conducted investigating emricasan in NASH patients with fibrosis, cirrhosis, decompensated cirrhosis (the development of conditions such as jaundice) and those with clinically significant portal hypertension (increased blood pressure). If concluded positively, Novartis aims to conduct Phase III studies of emricasan with the view to develop a combination therapy with an FXR agonist.

Novartis also announced a clinical trial collaboration with Allergan to conduct a Phase IIb study, involving the combination of a Novartis FXR agonist and Allergan's cenicriviroc (CVC) for the treatment of NASH.

References

1. Vernon G, Baranova A, Younossi ZM. Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. *Aliment Pharmacol Ther. 2011;*34(3):274-85.
2. Wong RJ, Ahmed A. Obesity and non-alcoholic fatty liver disease: Disparate associations among Asian populations. *World J Hepatol. 2014*;6(5):263-273.
3. National Institute of Diabetes and Digestive and Kidney Diseases. Nonalcoholic Fatty Liver Disease (NAFLD) & Nonalcoholic Steatohepatitis (NASH). Available at: https://www.niddk.nih.gov/health-information/liver-disease/nafld-nash Last accessed: January 2017
4. Banini BA, *et al*. Nonalcoholic Steatohepatitis (NASH) Has Surpassed Hepatitis C as the Leading Etiology for Listing for Liver Transplant: Implications for NASH in Children and Young Adults. *ACG 2016.* Abstract 46. Available at: https://www.eventscribe.com/2016/ACG/QRcode.asp?Pres=199366 Last accessed: January 2017
5. WebMD. Nonalcoholic steatohepatitis (NASH) overview. Available at: http://www.webmd.com/digestive-disorders/tc/nonalcoholic-steatohepatitis-nash-overview#1 Last accessed: January 2017
6. Lerret SM, *et al*. Predictors of Nonalcoholic Steatohepatitis in Obese Children. *Gastroenterol Nurs. 2011*;34(6):434–437.
7. Temple JL, *et al*. A Guide to Non-Alcoholic Fatty Liver Disease in Childhood and Adolescence*. Int J Mol Sci. 2016*;17(6): 947.
8. Vos M, *et al*. NASPGHAN clinical practice guideline for the diagnosis and treatment of nonalcoholic fatty liver disease in children. *J Pediatr Gastroenterol Nutr. 2017*;64(2):319-334.
9. Weiß J, Rau M, Geier A. Non-Alcoholic Fatty Liver Disease. Epidemiology, Clinical Course, Investigation, and Treatment. Dtsch Arztebl Int. 2014;111(26):447-452.
10. Younossi ZM, *et al*. Changes in the prevalence of the most common causes of chronic liver diseases in the United States from 1988 to 2008. *Clin Gastroenterol Hepatol. 2011*;9:524-530.
11. Younossi ZM, *et al*. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes*. Hepatology. 2016*;64(1):73-84.