Nonalcoholic fatty liver disease (NAFLD) refers to a group of liver disorders that occur in the absence of significant alcohol consumption and are characterized by accumulation of pathological amount of fat [1]. NAFLD comprises a histological spectrum ranging from simple steatosis or fatty liver, to steatohepatitis, fibrosis, and cirrhosis and can be categorized into two principal phenotypes: (1) nonalcoholic fatty liver (NAFL) and (2) nonalcoholic steatohepatitis (NASH) [2]. NAFL is defined by macrovesicular steatosis of more than 5% of hepatocytes in the absence of inflammation. In contrast, NASH is defined by the presence of hepatic steatosis, along with inflammation and hepatocyte ballooning injury. NASH is associated with varying degree of fibrosis and progresses to cirrhosis.

**Epidemiology**

Obtaining epidemiological data for NAFLD is difficult due to differences in diagnosis and reporting practices as well as lack of specific case defining criteria. Most of the studies in the general population are based on liver ultrasound or liver chemistries, with liver biopsy mostly restricted to subjects at high risk for more aggressive liver disease. At least one third of the U.S. population is believed to have NAFLD. It is estimated that about 6 million individuals in the US general population have progressed to NASH, and about 600,000 to NAFLD-related cirrhosis [3, 4]. Autopsy studies have found evidence of hepatic steatosis in up to 36% of lean and 72% of obese subjects [5]. A recent prospective cohort study using ultrasound and liver biopsy determined the prevalence of NAFLD in asymptomatic middle-aged patients to be 46.0% and the prevalence of NASH to be 12.2% [6].

NAFLD is common in Europe as well with prevalence rates reported to be anywhere between 2 - 44% in the general population and 42.6 - 69.5% in people with type 2 diabetes [7]. Recent surveys show that the prevalence of NAFLD across the Asia-Pacific region is at least 10%, and in some regions as many as one-third of individuals could be affected [8,9]. Likewise, the reported prevalence of NAFLD ranges from 16% in Mexico, 23% in Italy, 30% in Israel, and 9.3% in Japan, respectively [10].

There are no clear data in terms of the incidence of NAFLD and NASH. As the incidence of all of the predisposing factors (see below) is steadily increasing, the incidence of NAFLD and NASH is expected to increase rapidly worldwide. In the United States, for example, NASH is now believed as the most common cause of cirrhosis. Similar trends are reported for the rest of the Western World and even for developing countries.

**RISK FACTORS**

**Metabolic syndrome**

There is a very strong association between NAFLD and components of the metabolic syndrome. NAFLD in essence is now regarded as the hepatic manifestation of the metabolic syndrome. As there has been a rapid increase in the metabolic syndrome in the recent years, the global incidence of NAFLD is rapidly increasing [11].

**Obesity**

Obesity, most prevalent among African American males, is the most common condition associated with NAFLD worldwide. It is not surprising that the epidemiology of NAFLD parallels that of obesity. In the year 2009-2010, almost 90 million U.S. citizens were obese of which over 80% are believed to have NAFLD [12].

**Insulin resistance**

Insulin resistance seems to be the primary underlying etiology of NAFLD [13]. The degree of insulin resistance may be associated with the severity of hepatic steatosis with more advanced fibrosis and cirrhosis noted among patients with morbid obesity and severe diabetes. Similarly, NAFLD can lead to insulin resistance and represents a risk for diabetes and cardiovascular diseases [14].
**Gut microbiome**

Recent studies suggest a role of intestinal microbiome in the pathogenesis of NAFLD. It is known that small intestinal bacterial overgrowth is noted in NAFLD patients. Gut bacteria derived lipopolysaccharides and endotoxins may promote liver injury and fibrosis [15]. The role of gut microbiota in the pathogenesis of NAFLD and other liver disorders is rapidly evolving.

**Environmental factors**

Western diet and sedentary lifestyle lead to obesity, diabetes, and metabolic syndrome. These conditions predispose for NAFLD and are regarded as the major cause of NAFLD.

**Gender, genetics and ethnic factors**

Despite the fact that there is gender difference in the distribution of obesity and metabolic syndrome, both men and women appear to be afflicted by NAFLD at an equal rate. Race appears to be very closely associated with NAFLD. In the U.S., Hispanics and Asians, particularly from the Indian subcontinent, are more likely to develop insulin resistance and NAFLD. While obesity and insulin resistance is most prevalent among African Americans, the prevalence of NAFLD in this group is only 24%, strikingly lower compared to the 45% prevalence among the Hispanic Americans [16]. NAFLD prevalence among Caucasians is around 33% [17]. Also, clustering around families is noted which is in line with a genetic predisposition. Recently, two major genetic polymorphisms have identified to be associated with NAFLD: PNPLA3 (adiponutrin) and ApoC3 [18]. The PNPLA3 mutation is more commonly seen in Hispanics and has the lowest prevalence in African-Americans. ApoC3 gene mutations have been identified to correlate with hepatic triglyceride accumulation and fatty liver disease among Asians.

**Natural history**

NAFLD was long considered to be a benign condition. While simple hepatic steatosis can have a benign non-progressive course, about 40% of patients with NAFL progress to NASH. Approximately 30-40% of patients with NASH develop liver fibrosis of which up to 20% may progress to liver cirrhosis. Patients with NASH are at increased risk of hepatocellular carcinoma (HCC) even in the absence of cirrhosis [19].

With the increasing prevalence of obesity, diabetes mellitus and metabolic syndrome in conjunction with the advancement in the treatment of viral hepatitis, NASH is clearly going to be the most common cause of liver cirrhosis and liver cancer globally. Thus it is not surprising that NASH is evolving as the major indication for liver transplantation. What is not so well known is the fact that NASH represents an independent risk factor for cardiovascular events. This may be related to endothelial injury and insulin resistance [20]. Individuals with NASH have higher incidence of insulin resistance and diabetes mellitus, and have a significantly higher mortality from cardiovascular events when compared to viral or alcohol related cirrhosis [21]. NASH will mostly lead to increased overall mortality due to increase in cardiovascular mortality as well as liver related mortality.

**DIAGNOSIS**

The diagnosis of NAFLD can easily be missed as specific symptoms are usually absent and specific laboratory tests are lacking. However, abnormal ALT, or a fatty liver on liver imaging should alert the clinician to pursue further evaluation excluding other common causes of chronic liver diseases.

**TREATMENT**

The mainstay of therapy is to identify and aggressively treat the predisposing factors such as diabetes, dyslipidemia, and insulin resistance, respectively. Weight loss either by caloric restrictions, exercise, or bariatric surgery is critical. Lifestyle modification involving combined diet restriction and physical activity is proven to improve liver function tests and to ameliorate steatosis when a sustained reduction in the BMI of 6.5–10% is achieved [18,21,23].

Despite extensive research for the last two decades, no specific therapeutic agents are available for treatment or prevention of NASH at this point. Several agents have been found effective in the short term, but none have been proven to be beneficial in the long term [21]. Currently, vitamin E supplementation may be recommended in non-cirrhotic, non-diabetic subjects with NASH [24]. Obeticholic acid, a farsenoid X receptor (FXR) agonist, has recently been found to improve insulin resistance in patients with diabetes mellitus and fatty liver [25]. Results of ongoing studies with obeticholic acid in patients with NASH (FLINT trial) are expected for later this year. Although statins are of no direct liver-related benefit in NAFLD, being instrumental in reducing the cardiovascular risk among patients with hyperlipidemia, statins should be utilized in NAFLD patients whenever indicated and are proven to be safe [21,26].

**REFERENCES**


