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Review paper

Epidemiology of non-alcoholic fatty liver disease and risk of hepatocellular carcinoma progression

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Abstract

Non-alcoholic fatty liver disease (NAFLD) has become the most common chronic liver disease worldwide. Its incidence has grown alongside the increasing global prevalence of type 2 diabetes, obesity, and metabolic syndrome. The risk of progression to hepatocellular carcinoma for nonalcoholic steatohepatitis patients over 5 years is 8%, and despite targeted and immunotherapy treatment advances, HCC maintains a bleak 5-year survival of 19%. NAFLD's primary risk factors are components of metabolic syndrome as well as possible sleep disturbances. NAFLD is most common among men 50-60 years of age, though incidence in women catches up after menopause. In the US, Hispanics are most likely to develop NAFLD and African Americans least likely, in part due to the prevalence of the *PNPLA3* gene variant. With NAFLD risk factors especially prevalent in underserved populations and developing nations, public health interventions, earlier diagnosis, and novel treatments could curb the growing disease burden.

Key words: risk factor, incidence, prevalence, etiology, mortality.

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Introduction

Non-alcoholic fatty liver disease (NAFLD) has grown in incidence to become the most common chronic liver disease worldwide [1] and is projected to surpass alcoholic liver disease as the leading cause of liver transplantation in the United States by 2030 [2]. NAFLD can be classified based on histological progression: non-alcoholic fatty liver (NAFL), non-alcoholic steatohepatitis (NASH), NASH cirrhosis, and NASH-related hepatocellular carcinoma (HCC) [2]. A better understanding of NAFLD epidemiology and risk factors may facilitate ongoing prevention efforts aimed at reducing the quality of life burden, demand for a liver transplant, and risk of HCC all posed by the global rise in NAFLD.

Diagnostic criteria

NAFLD is a diagnosis of exclusion – it is defined as hepatic fat accumulation of greater than 5% of total liver volume without a known secondary cause [3]. While it may histologically and clinically resemble alcohol-induced liver disease, patients with NAFLD do not have a significant history of alcohol consumption (typically considered > 30 g daily for over 10 years for men and 20 g daily for women). Physicians must also exclude infectious hepatitis (hepatitis B, C, and D patients can develop chronic infection, leading to cirrhosis) as well as hepatitis induced by medications (acetaminophen, aspirin, corticosteroids, amiodarone, isoniazid, cytotoxic chemotherapies, and more), endogenous toxic compounds (hemochromatosis, Wilson's disease), autoim-

mune disorders (autoimmune hepatitis, systemic lupus erythematosus, sarcoidosis) and ischemia (thromboses, Budd-Chiari syndrome) [3].

While the gold standard remains liver biopsy, new non-invasive modalities are being used to facilitate the diagnosis of NAFLD. Hepatic ultrasonography, magnetic resonance imaging (MRI), and computed tomography (CT) are all utilized in detecting fatty infiltration in the liver. Levels of aminotransferase enzymes (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) have also been used with varying degrees of success as a screening tool for liver disease. Ultrasonography has become the standard modality for screening for moderate to severe fatty liver disease. Nevertheless, a biopsy is essential to differentiate steatosis (fatty liver) from NASH, which has a higher risk of disease progression. Early diagnosis of NASH can have implications for management, allowing patients to try newly approved medications and off-label developmental therapies in the hopes of preventing progression to cirrhosis or HCC. A biopsy is indicated for all NAFLD patients (confirmed with chronically elevated aminotransferase levels and imaging) who are 65 years and older, have symptoms of metabolic syndrome, or as a means to rule out other causes of liver diseases after appropriate imaging/bloodwork has been exhausted.

Histological progression

The steatosis seen in NAFLD is "macro-steatosis", as opposed to micro-steatosis characteristic of Reye syndrome, which is fulminant hepatitis following aspirin administration in children with viral illness [4]. A diagnosis of NASH requires four components: steatosis, inflammation (steatohepatitis), fibrosis, and cellular ballooning [5]. Variability among pathologists in the identification of cellular ballooning (an indicator of hepatocyte apoptosis) may result in fewer patients meeting the criteria for NASH and receiving appropriate management or enrollment in clinical trials [6]. NASH may also present with Mallory-Denk bodies (eosinophilic inclusions indicative of apoptosis) or councilman bodies (remnants of hepatocytes undergoing apoptosis) [7, 8].

Non-invasive methods for the diagnosis of NASH are currently under development, including the biomarker cytokeratin 18 [9], as well as the predictive NAFLD fibrosis score and FIB-4, which are derived from clinical presentation (i.e. age, body mass index [BMI], hyperglycemia, platelet count, albumin and AST/ALT ratio) [10].

NASH can progress to "cryptogenic cirrhosis", which is defined as cirrhosis of an unclear origin. While progressing, NASH loses its prototypical inflammation and steatosis, leaving behind only the bridging fibrosis characteristic of cirrhosis [11]. Cirrhosis can result in jaundice, asterixis, portal hypertension (leading to portocaval anastomoses such as esophageal varices, which are the most common acute cause of death), encephalopathy, and thrombocytopenia [11]. End-stage cirrhosis requires liver transplantation for survival and also increases the risk of HCC development by 45-fold (discussed further under "risk of progression") [12].

Epidemiology

Incidence

Incidence rates reported are highly variable due to variable disease presentation, different screening standards across nations, and sensitivity discrepancies between diagnostic modalities. A retrospective study from England estimated the incidence at 29/100,000 [13], while a Japanese study based on aminotransferase levels found an incidence of 31/1,000 person-years [14], over a thousand-fold greater. A pooled meta-analysis among Asian nations estimated the incidence at 52/1,000 person-years [15]. These disparate estimates of NAFLD warrant further meta-analysis, with many studies suggesting that incidence rates are grossly underestimated due to limited diagnosis of early-stage disease [15].

Prevalence

The global prevalence of NAFLD is estimated at 25.2% (over 2 billion people worldwide), though studies suggest that statistics may be underreported due to lack of access to healthcare and variable clinical presentation [15, 16]. Estimates for prevalence can also vary based on diagnostic methods. In the US, from 1988 to 1992, 7.9% of the general population tested with elevated aminotransferases, and 69% of these had unexplained liver disease (i.e. NAFLD) [17]. Meanwhile, the prevalence of signs of fatty liver infiltration on ultrasound ranged from 22% in the Netherlands [18] to 33% in Bangladesh [19] and 46% in the United States [20]. Magnetic resonance spectroscopy (MRS) is likewise highly sensitive for fatty infiltrates, with one study from the US reporting a prevalence of 33.6% [21].

The prevalence of NAFLD is rising in developing nations, likely due to the adoption of the "Western" diet and lifestyle and consequent rise in metabolic syndrome. Meta-regression of global epidemiological studies estimates that NAFLD prevalence has increased globally from 15% in 2005 to 25% in 2015, and is projected to continue growing [15]. The highest prevalence has been

recorded in the Middle East and South America, while South and East Africa have the lowest [15].

One-quarter of patients with NAFLD in the US are estimated to progress to NASH [22]. The prevalence of NASH, which carries a greater risk of progression (cirrhosis and HCC) and mortality, is estimated at 1.5-6.5% worldwide [15, 16]. The prevalence of NASH in the US is predicted to increase by 55% by the year 2030, thus becoming the leading cause of liver transplant [2].

Risk of progression to cirrhosis, HCC, and mortality

Out of the NAFLD spectrum, only NASH has been shown to progress to cirrhosis and HCC [23]. Of the estimated 25% of NAFLD patients who progress to NASH, 21-26% are at risk of progression to cirrhosis over 8 years [24]. Cirrhosis further increases the risk of progression to HCC and/or hepatic failure leading to the need for a transplant, with the stage of fibrosis being a reliable prognosticator of progression, though cirrhosis in not necessary for HCC.

The incidence of HCC has increased in parallel with NAFLD globally. Since 1973, HCC incidence has grown 4-fold worldwide [25]. In the US, the incidence of HCC has more than tripled from 2.6/100,000 in 1975 to 8.9/100,000 in 2017 [26]. Advanced fibrosis, as seen in NASH, carries an 8% 5-year cumulative incidence rate for HCC, almost one thousand times greater than the risk for the general population [27]. While the risk of NAFLD-related HCC is low, the risk of NASH-related HCC is 5.29 cases per 1,000 person-years [15]. This reflects a 9% annual increase in HCC caused by NAFLD and NASH from 2004 to 2009 [15]. NAFLD accounts for approximately 8% of HCC diagnoses [28].

While cirrhosis is a significant risk factor for the development of HCC, studies suggest that 35-50% of NAFLD patients who progress to HCC never develop cirrhosis [29]. Among patients with NAFLD, liver-related mortality was the third-leading cause of death following cardiovascular disease and malignancy. In contrast, among the general population, liver-related mortality is the 12th leading cause of death [30]. Mortality from NAFLD is increasing in the United States. The average life expectancy among NAFLD patients is estimated at 64.4 years, more than 10 years less than the general population life expectancy of 78.6 years [31].

HCC is among the most fatal malignancies, with a 5-year survival rate of 19.6% in the US. Patients presenting with localized disease have a survival of 34.2%, while patients diagnosed with distant metastases (most commonly the lungs) have a 5-year survival of only 2.5%. HCC accounted for approximately 30,000 deaths in 2020 (5% of all cancer deaths), of which an estimated 2,500 were likely caused by NAFLD [26].

Advances in early detection and treatment modalities have increased survival from 1.9% in 1975 [26]. First-line treatment options as recommended by the NCCN guidelines include small molecule vascular endothelial growth factor (VEGF) inhibitors such as sorafenib, which interfere with tumor angiogenesis, and since approval in 2017, PD-1 inhibitors (checkpoint inhibitors) such as nivolumab and pembrolizumab, which inhibit tumor immunosuppression and activate CD8 T-cells targeting the tumor [32].

Active surveillance of those with risk factors such as NAFLD, a history of alcoholism or chronic hepatitis infection (HBV, HCV, HDV) can facilitate earlier detection of HCC and improved survival rates. Primary prevention by reducing rates of obesity, diabetes, and other metabolic syndromes could curb the disease burden of HCC, with NAFLD projected to become the leading contributor [33].

Non-modifiable risk factors

Genetic predisposition

The variability in NAFLD development among those with predisposing lifestyle risk factors suggests a genetic, heritable component. Genetic variants in or near several identified loci (*TM6SF2*, *NCAN*, *PNPLA3*, and *PPP1R3B*) have been shown to account for 27% of disease heritability within families [34]. Many of these variants have been found to increase disease risk independently of the primary contributing lifestyle factors, such as obesity and diabetes [35, 36].

Gender and age

Men are at greater risk of NAFLD and NASH, at least until after menopause when women lose the apparent protective effect of estrogen and their risk becomes comparable to that of men. The peak incidence of NAFLD is noted in the 50-60 age range in men and the 60-70 age range in women due to later disease development following the loss of the protective effects of estrogen.

Race/ethnicity

Among US ethnic groups, Hispanics have been found to incur the greatest risk of NAFLD, while African Americans have the lowest risk. Some studies find that Hispanics have almost double the prevalence as compared to African Americans (45-58% vs. 24-35%), with those of Mexican origin have the highest preva-

lence among Hispanics [20, 31, 37]. Specifically, variants of the predisposing *PNPLA3* gene variants have been observed in the highest proportions among Hispanics and the lowest proportions among African Americans, likely explaining some of the ethnic variation [38]. Socioeconomic status and the strength of association of NAFLD lifestyle risk factors vary among ethnicities, painting a complex and yet-to-be-elucidated picture of drivers for disease pathogenesis [39].

Modifiable risk factors

Type 2 diabetes mellitus

Type 2 diabetes mellitus (T2DM) is among the most significant independent risk factors for NAFLD. The insulin insensitivity seen in T2DM causes a discrepancy between energy production and consumption, stimulating lipolysis in peripheral adipocytes and deposition of these excess triglycerides in the liver, resulting in steatosis. NAFLD is considered the hepatic component of "metabolic syndrome", and may in turn increase the risk of T2DM and cardiovascular metabolic complications [40].

55.5% of global T2DM patients have been diagnosed with NAFLD by MRS and 59.7% by ultrasound or aminotransferases. In the US, the rate of NAFLD among T2DM patients is estimated as 51.8% by MRS and 53.1% by other diagnostic methods, which is slightly lower, likely due to better disease management [41]. 37.3% of T2DM patients in the US progress to NASH when diagnosed by liver biopsy, with advanced fibrosis being observed in 17.0% of T2DM patients [41]. According to a recent estimate, 18.2 million people in the US have T2DM and NAFLD, with 6.4 million having NASH [42]. The global prevalence of T2DM rose from 4.7% in 1980 to 8.5% in 2014 [43], which may help explain the global rise in NAFLD over the same period.

T2DM increases the risk of unpreventable, significant disease burden from liver disease, and poorer long-term outcomes. T2DM predisposes to higher rates of fibrotic progression [44], cirrhosis [40], hepatocellular carcinoma [45], and mortality both due to liver-related and cardiovascular causes [46]. Over the next 20 years, NAFLD in T2DM is estimated to account for $55.8 billion in expenditures, 65,000 transplants, 1.37 million cardiovascular-related deaths, and 812,000 liver-related deaths [42].

Obesity and metabolic syndrome

Obesity is a related modifiable risk factor for NAFLD. Although obesity is highly associated with T2DM (both are components of the so-called "metabolic syndrome"), multivariate analysis has shown an independent association with NAFLD and NASH [47]. Obesity predisposes to insulin insensitivity, energy imbalance, and lipolysis, with a similarly suggested NAFLD pathogenesis as T2DM. NAFLD is also associated with hyperlipidemia (69% of NAFLD patients), hypertension (39%), and metabolic syndrome (42%), which is defined as all of the preceding conditions concurrently [15].

The global prevalence of NAFLD among the obese is estimated in the range 30-37% [15]. Meanwhile, among global NAFLD patients, 51% are reported to be obese [15]. Abdominal obesity in particular (so-called "an apple", as opposed to "pear", distribution) is most strongly associated with NAFLD [8], with increasing visceral adiposity increasing the risk of NAFLD in a dose-dependent manner [48]. Multiple studies have shown a correlation between weight gain and NAFLD incidence, with even a 2 kg gain within a normal BMI range resulting in a significantly increased risk of hepatic steatosis on ultrasound [49]. Obesity has also been shown to act as an additive risk factor for liver disease with alcohol consumption, increasing the risk of steatosis among drinkers by over 2-fold [2, 22].

Diet

While increased caloric intake is a risk factor for both obesity and T2DM, certain food groups may predispose to NAFLD in particular. Sucrose (sugar) is composed of both fructose and glucose. Unlike glucose and galactose, fructose has an unregulated entry from the gut lumen via the GLUT-5 channel and complete hepatic extraction, thus increasing the risk of "energy overload", diabetes, and NAFLD [50]. Consumption of beverages with sucrose or high-fructose corn syrup has increased five-fold in the US since 1950. One study found that drinking two such drinks daily for only six months induced features of NAFLD (markers of liver fat) and led to increased body weight and markers of cardiovascular disease [51]. In a separate study, NAFLD patients were also more likely to eat fast food often ($p = 0.049$) and not exercise regularly ($p = 0.02$) [20].

Sleep deprivation

Sleep deprivation and poor sleep quality are known to increase the risk of obesity by disrupting metabolic and hunger signaling, such as levels of glucocorticoids, leptin, peptide Y, and ghrelin. However, on top of the increased risk of obesity, population cohort studies suggest that sleep deprivation may be independently associ-

ated with NAFLD with an odds ratio of 1.28 in men and 1.71 in women. Poor sleep quality likewise increased the risk to a lesser degree [52]. Counterintuitively, a more recent study found that sleep duration of over 8 hours increased the risk of NAFLD development [53]. The relationship between sleep and NAFLD is complex and has been posited to be mediated by inflammatory cytokines such as interleukin 6 (IL-6) and tumor necrosis factor α (TNF-α) [54], leading to disturbances in the hypothalamic-pituitary-adrenal axis [55] as well as insulin/glucagon metabolic regulation [56].

Conclusions

NAFLD has become the most common chronic liver disease around the world and is only projected to grow in the coming decades alongside obesity and metabolic syndrome. NAFLD is projected to become the leading cause of liver transplant in the US by the year 2030. NAFLD refers to a family of progressive liver pathologies of unknown (non-alcoholic, infectious, or toxin-mediated) etiology, which can ultimately progress to cirrhosis and hepatocellular carcinoma, as well as increasing the risk of mortality from cardiovascular disease. The greatest risk factors for NAFLD include components of metabolic syndrome such as obesity and T2DM. The public health burden is compounded by the fact that these risk factors are particularly prevalent in underserved populations, decreasing the chance of early diagnosis, which could delay the progression of the disease. A stronger understanding of NAFLD pathogenesis and risk factors could inform public health measures and novel treatment approaches aimed towards curbing the growing disease burden from irreversible and fatal sequelae such as cirrhosis and hepatocellular carcinoma.

Disclosure

The authors declare no conflict of interest.

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