

Research Progress on Non-Alcoholic Fatty Liver Disease

Lizhu Wu ¹, Ronglin Peng ¹, Jianwei Zhou ¹, Wei Chen ¹, Honglei Zhao ^{2, *}

¹ Shenzhen Nanshan Medical Group Headquarter, Shenzhen, Guangdong, China

² Fuwai Hospital Chinese Academy of Medical Sciences, Shenzhen, Guangdong, China

* Corresponding author: Honglei Zhao (Email: zhaohonglei@nsqyljtz.cn)

Abstract: Non-alcoholic fatty liver disease (NAFLD) is one of the leading causes of chronic liver disease worldwide. With the prevalence of overweight and obesity in the Chinese population, NAFLD is no longer a disease exclusive to Western developed countries, and has become one of the most common metabolic diseases in the world. The global prevalence of NAFLD is as high as 37.8%, and the prevalence of NAFLD in the Chinese population is 23.3%. In recent years, with the global epidemic of obesity and metabolic syndrome, the prevalence of NAFLD has gradually increased. The risk factors of NAFLD are closely related to obesity, diabetes, hypercholesterolemia, hypertriglyceridemia, hyperuricemia and other diseases. When NAFLD co-exists with these metabolic diseases, it often increases the risk of cirrhosis, liver cancer, and even death. At the same time, it can aggravate other chronic liver diseases, promote disease progression, and is closely related to the occurrence and development of atherosclerosis and type 2 diabetes. With the progression of NAFLD disease, the related clinical burden and economic burden of NAFLD and its impact on patients' quality of life are becoming more and more serious. Therefore, early identification, early diagnosis, early prevention, early treatment and standardized management of NAFLD are conducive to the control of the risk of cirrhosis, liver cancer and cardiovascular diseases. This article will review the epidemiology, hazards, and related risk factors of NAFLD.

Keywords: Nonalcoholic Fatty Liver; Metabolic Syndrome; Prevalence; Risk Factors; Summary.

1. Introduction

Non-alcoholic fatty liver disease (NAFLD) is the most prevalent liver disease worldwide and a major contributor to liver-related morbidity and mortality [1]. NAFLD is a metabolic stress-induced liver injury caused by significant fat accumulation in hepatocytes without a history of excessive alcohol consumption. Its development is closely associated with insulin resistance (IR) and genetic predisposition. The disease spectrum includes non-alcoholic fatty liver (NAFL), non-alcoholic steatohepatitis (NASH), and progression to liver cirrhosis and hepatocellular carcinoma (HCC) [2, 3].

2. Epidemiology of NAFLD

NAFLD has become a global public health concern. A 2022 study by Kiarash Riazzi et al. reported a global prevalence of NAFLD at 32.4%. This rate has increased significantly over time, rising from 25.5% before 2005 to 37.8% after 2016 [1]. In China, the prevalence of NAFLD has ranged between 13% and 43% in the general population over the past two decades, with an annual increase of approximately 4% [4]. Prevalence rates vary across different regions and populations, influenced by factors such as geography, occupation, age, gender, lifestyle, and dietary habits.

For instance, a study in Shenzhen reported a NAFLD prevalence of 27.41% among elderly residents, while a study of 71,462 employees in the Beijing Electric Power sector found a prevalence of 26%. In Ningbo, 26.91% of 11,826 individuals were diagnosed with NAFLD, while in Foshan, the prevalence among 21,797 individuals was 25.84%. Additionally, a 2014 study in Ningyang, Shandong, reported a prevalence of 34.3% among 6,849 participants [5-10].

3. Risks and Complications of NAFLD

Without timely intervention, NAFLD can progress from

simple steatosis, where fat accumulates in $\geq 5\%$ of hepatocytes, to necroinflammation and fibrosis, leading to non-alcoholic steatohepatitis (NASH). In some cases, this may further progress to cirrhosis and hepatocellular carcinoma [11]. Although the percentage of NAFLD patients who progress to NASH remains uncertain, it is estimated to exceed 10% [12]. Studies have shown that 29.9% of biopsy-confirmed NASH occurs within the NAFLD population [13].

Besides hepatic complications, NAFLD significantly increases the risk of atherosclerotic cardiovascular diseases and various malignancies [14]. For instance, between 2012 and 2017, global deaths from liver cirrhosis and hepatocellular carcinoma increased by 11.4% [14]. Although chronic viral hepatitis remains a leading cause of cirrhosis and liver cancer, the burden of NAFLD is growing at a faster pace [15]. In addition to its association with metabolic disorders like dyslipidemia, hypertension, type 2 diabetes, and hyperuricemia, NAFLD may also increase the risk of asymptomatic brain injury, cognitive impairment, dementia, and ischemic or hemorrhagic strokes.

NAFLD has also been linked to an increased risk of extrahepatic malignancies, such as colorectal cancer, gastric cancer, endometrial cancer, pancreatic malignancies, breast cancer, and lung adenocarcinoma. Furthermore, NAFLD is associated with higher incidences of gallstone disease, sarcopenia, osteoporosis, sleep apnea syndrome, and chronic kidney disease [14]. The rising prevalence of NAFLD and its complications is increasingly burdening healthcare systems, affecting patients' quality of life, and reducing life expectancy. Early diagnosis and intervention are therefore essential.

4. Risk Factors for NAFLD

4.1. Age and Gender

NAFLD is closely related to aging, with increasing age being one of the strongest epidemiological risk factors for

NAFLD, NASH, and liver fibrosis [16]. Aging limits physical activity, which, coupled with the metabolic syndrome, leads to worsening abdominal obesity, hyperglycemia, dyslipidemia, and hypertension [17]. Studies show that NAFLD prevalence increases with age, from 2.6% in children to 17.3% in adolescents, and up to 34% in adults [18-20]. Aging also increases the risk of mortality and disease progression to liver fibrosis and hepatocellular carcinoma. However, some studies indicate that the prevalence of NAFLD decreases in individuals over 60 years old, possibly due to a weakening association with metabolic diseases [21, 22].

The influence of gender on NAFLD remains unclear. Some studies report a higher prevalence in women, while others suggest men are more commonly affected. For example, a 2011 study found NAFLD prevalence significantly higher in women, while another research indicated the opposite trend [23-25].

4.2. Lifestyle Factors

Numerous studies suggest that dietary habits play a crucial role in NAFLD development [16]. Over recent decades, rapid economic growth and lifestyle changes, including shifts in dietary patterns and reduced physical activity, have led to an energy imbalance, contributing to obesity [26]. Globalization has also altered dietary habits, increasing the intake of carbohydrates, animal protein, refined sugars, and food additives, all of which play critical roles in NAFLD onset and progression [27, 28]. This imbalance in energy intake and expenditure has led to higher rates of obesity and insulin resistance, both of which are significant risk factors for NAFLD.

Furthermore, smoking has been associated with the progression of fibrosis in chronic liver diseases, including NAFLD. Research shows that smoking exacerbates NAFLD by accelerating hepatic fat accumulation and promoting inflammation. Smoking cessation should therefore be strongly encouraged among NAFLD patients [29-33].

4.3. Metabolic Syndrome

Metabolic syndrome (MetS), characterized by obesity, dyslipidemia, type 2 diabetes, and hypertension, is closely linked to NAFLD development [34]. The relationship between NAFLD and MetS is bidirectional, especially concerning diabetes and hypertension. MetS increases the risk of NAFLD, while treating NAFLD or NASH can improve certain aspects of MetS. This is significant, as MetS is also a major contributor to cardiovascular adverse events and mortality in NAFLD patients [35, 36].

In patients with MetS, excess hepatic fat accumulation and insulin resistance are commonly observed [37]. Normally, insulin suppresses very low-density lipoprotein (VLDL) production in the liver and reduces lipolysis in adipose tissue [38]. However, in NAFLD and MetS patients, insulin fails to inhibit VLDL production and lipolysis, leading to elevated serum triglycerides, which contribute to NAFLD progression and NASH development [39, 40].

4.4. Obesity

Obesity is a major risk factor for NAFLD, significantly increasing the likelihood of developing the disease [41]. Excessive energy intake in obese individuals promotes hepatic lipid accumulation and insulin resistance, resulting in elevated circulating free fatty acids, which are delivered to the

liver. This increases fat synthesis, overwhelming the liver's oxidative capacity and causing oxidative stress, mitochondrial dysfunction, and subsequent hepatocyte apoptosis or necrosis, leading to NASH and fibrosis [42, 43].

Studies have shown that NAFLD risk is 3.5 times higher in obese individuals than in those with a normal body mass index (BMI) [44]. The prevalence of NAFLD in obese populations ranges from 57.5% to 74% [45]. Thus, weight management through lifestyle interventions is essential for preventing NAFLD.

4.5. Dyslipidemia

Dyslipidemia is an independent risk factor for NAFLD [46]. NAFLD patients often exhibit elevated low-density lipoprotein (LDL) and triglycerides or reduced high-density lipoprotein (HDL) [47]. Between 20% and 90% of hyperlipidemia patients present with fatty liver, due to an imbalance in triglyceride synthesis and VLDL secretion, which contributes to hepatic fat accumulation [48, 49].

4.6. Type 2 Diabetes (T2DM)

The rising global prevalence of type 2 diabetes parallels the increase in obesity, and both are significant risk factors for NAFLD. Over 70% of individuals with T2DM also have NAFLD [50]. A meta-analysis reported that NAFLD prevalence among T2DM patients is more than double that of the general population, with nearly 60% of T2DM patients having NAFLD and one-third presenting with NASH [51]. T2DM accelerates NAFLD progression to cirrhosis and significantly increases liver-related and all-cause mortality.

A study involving 713 biopsy-confirmed NAFLD patients found that for every 1% increase in HbA1c levels, the likelihood of severe fibrosis increased by 15%, highlighting the importance of glycemic control in managing fibrosis progression in NAFLD patients [52, 53].

4.7. Hypertension

Hypertension is a critical component of metabolic syndrome and a significant risk factor for NAFLD development and progression [55]. Epidemiological studies have shown that approximately 50% of hypertensive patients have NAFLD, and the risk of developing hypertension is higher in individuals with a history of NAFLD [56]. Studies suggest that pre-hypertension is independently associated with an increased risk of NAFLD, with pre-hypertensive individuals having a 1.3-fold higher risk of developing NAFLD compared to those with normal blood pressure [57-60]. Furthermore, the severity of NAFLD is closely linked to hypertension, NASH, liver fibrosis, and hepatocellular carcinoma [61].

5. Conclusion

With the progress of NAFLD, the clinical burden and economic burden of NAFLD and its impact on the quality of life of patients are becoming more and more serious. Therefore, early identification, early diagnosis, early prevention, early treatment and standardized management of NAFLD are conducive to the control of liver cirrhosis, liver cancer and cardiovascular disease risk.

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