RESEARCH ARTICLE

Journal of Ecophysiology and Occupational Health, *Vol 24(2), DOI: 10.18311/jeoh/2024/36032, 123-130, June 2024*

ISSN (Online) : 0972-4397
ISSN (Online) : 0974-0805

Association of Non-Alcoholic Fatty Liver Disease (NAFLD) with Metabolic Syndrome in Adult Population: A Narrative Review

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Abstract

Non-Alcoholic Fatty Liver Disease (NAFLD) is swiftly evolving into a prevailing liver condition on a global scale and within the United States, it stands as the primary contributor to chronic liver disease. Previously viewed as a Western disorder, obesity and NAFLD are gaining increased recognition within the Asian community. Notably, NAFLD has been observed to have strong associations with Type 2 Diabetes Mellitus (T2DM), Chronic Vascular Disease (CVD), and Chronic Kidney Disease (CKD).

Keywords: Chronic Vascular Disease (CVD), NAFLD, Obesity

1. Introduction

The definition of NAFLD involves the presence of macrovascular steatosis in 5% or more hepatocytes, without any secondary cause such as alcohol or drug-related factors[1]. The spectrum of NAFLD spans from the less severe Non-Alcoholic Fatty Liver (NAFL) to the more critical end, characterised by Non-Alcoholic Steatohepatitis (NASH)[2]. In NAFLD, hepatic steatosis is observed without signs of inflammation. On the other hand, in NASH, hepatic steatosis is accompanied by lobular inflammation and apoptosis, which may progress to fibrosis and cirrhosis[2]. Some experts propose that Metabolic Associated Fatty Liver Disease (MAFLD) is an improved term than the abbreviation NAFLD because NAFLD is significantly connected with all components of metabolic syndrome[3].

Metabolic and cardiovascular complications, exemplified by conditions like obesity, insulin resistance, hypertension, dyslipidemia, and Type 2 Diabetes (T2D) are intertwined with hepatic issues, giving rise to the manifestation of NAFLD[4]. In the United States NAFLD has emerged as the predominant cause of chronic liver disease. This condition is closely linked to metabolic disorders, including T2DM, hypertension, dyslipidemia and obesity[5].

Obesity, accompanied by its related conditions such as T2D, ischemic heart disease, chronic renal disease and various cancers, stands as a leading cause of worldwide mortality. The incidence of NAFLD, affecting a quarter of the global population has notably increased in recent years. Notably, NAFLD has become the second most prevalent cause of liver transplantation and ranks as the

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Article Received on: 31.12.2023 Revised on: 12.02.2023 Accepted on: 26.02.2024

third significant factor contributing to Hepatocellular Carcinoma (HCC) in the United States[6].

Obesity is linked to a range of liver issues collectively referred to as NAFLD. This condition is characterised by an elevation in Intrahepatic Triglyceride (IHTG) content, commonly known as steatosis. It may manifest with or without inflammation and fibrosis, referred to as steatohepatitis. The prevalence of NAFLD has made it a significant public health concern. Its potential progression to severe liver disease coupled with its association with critical cardiometabolic abnormalities such as T2DM, metabolic syndrome, and Coronary Heart Disease (CHD) further underscores its importance[7]. Obesity has emerged as a pervasive global issue experiencing a substantial surge in recent decades. As a result, obesity and its related disorders now pose a significant and imminent threat to the present and future health of populations worldwide[8]. The present review offers a comprehensive survey of the literature delving into the metabolic syndrome associated with NAFLD and the robust connection between obesity and NAFLD. Additionally, a concise discussion of the risk factors for NAFLD is included.

2. Risk Factors for NAFLD

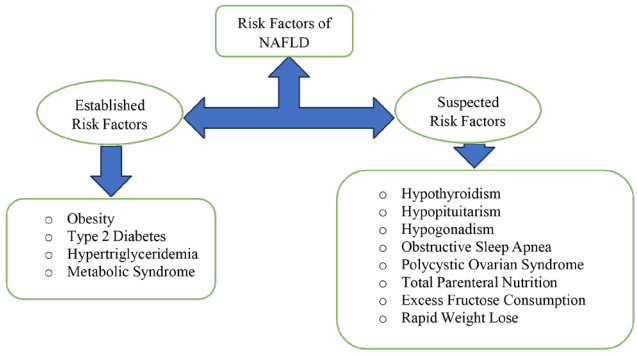

Figure 1. Main risk factors of NAFLD[9].

3. Diagnosis

The presence of three elements is required for the diagnosis of NAFLD. The patient must not be an alcoholic, steatosis must be detected using imaging or histology and other liver diseases must be properly ruled out[10]. Recent discoveries from two studies employing Magnetic Resonance Spectroscopy (MRS) to gauge Intrahepatic Triglyceride (IHTG) content in a significant number of participants offer additional insights into defining a "normal" IHTG level[7]. The evaluation of steatosis through Magnetic Resonance Imaging (MRI) and Computed Tomography (CT) seems to exhibit greater accuracy and sensitivity. However, it is worth noting that MRI, despite its higher precision, remains less accessible and considerably more expensive than CT. For the diagnosis of steatosis by CT, the liver-to-spleen attenuation ratio is less than 0.9. CT also has drawbacks for diagnosing steatosis, such as inadequate sensitivity for detecting mild steatosis, patient exposure to X-rays and inaccessibility for those with hemosiderosis[11]. The recently introduced "LDE system" serves as an exemplification of a potential artificial descriptor for factors associated with the Liver (L), individual patient-specific Disease-causing elements (D) and the degree of Extrahepatic involvement (E), characteristic of systemic disorders such as NAFLD[11].

4. Prevalence

With rising Body Mass Index (BMI), NAFLD prevalence rates rise as well. Males were more susceptible than females to MAFLD, which is a fatty liver condition associated with metabolic dysfunction[12]. The recorded prevalence rates of NAFLD are as follows: Globally, 25.2%; Asia, 27.4%; the Middle East, 31.8%; North America, 24.1%; South America, 30.5%; Europe, 23.7% and Africa, 13.5% (Figure 2). Additionally, estimates for the prevalence of NAFLD around the world have climbed from 20.1% in 2000-2005 to 23.8% in 2006–2010 and 26.8% in 2011-2015[13,14]. Over time, there has been a notable rise in the prevalence of NAFLD in Asia. It increased from 25.3% in the period 1999-2005 to 28.5% in 2006-2011 and subsequently further elevated to 33.9% during the years 2012-2017[14,15].

According to a recent systematic analysis, Asia had a 29.6% overall prevalence of NAFLD, which has been steadily rising over time[15]. According to estimates, 7% to 20% of non-obese people in Asia with a BMI under 25kg/m^2 have NAFLD[16-18]. In South Korea, the total prevalence of NAFLD was 30.3%, with a minor rise from 29.0% to 31.0% over a roughly 10-year period[19]. As per a systematic review carried out in Japan, the general prevalence of NAFLD was reported at 25.5% displaying variations dependent on the residential location and demonstrating an upward trend over time. Projections suggest an anticipated prevalence of 39.3% in 2030 and 44.8% in 2040[20]. The prevalence of NAFLD is significantly lower (10%) in rural India which is known

for its traditional diets and lifestyles, but it is comparable (16%-32%) in urban areas in other Asian countries[21,22]. Reports suggest that the prevalence of adult NAFLD in India varies widely, ranging from 6.7% to 55.1%[23]. The prevalence of NAFLD wasdetermined to be 73.6 per cent in the 106 patients who were morbidly obese[24].

5. Metabolic Syndrome

The most critical concern is NAFLD impacting 25% of the global population and is correlatedwith other metabolic disorders such as obesity, hypertension, T2D, and CVD[4]. As outlined by the International Diabetes Federation (IDF), the diagnosis of the metabolic syndrome involves an increased waist circumference along with at least two of the following criteria: Diminished levels of HDL cholesterol, elevated triglycerides, high blood pressure or an elevated fasting serum glucose[25].

6. NAFLD and Type 2 Diabetes

T2DM is commonly acknowledged to coexist and interact with other conditions, amplifying the risk of adverse clinical consequences both within the liver and beyond. T2DM is also among the main contributors to NAFLD's accelerated transformation

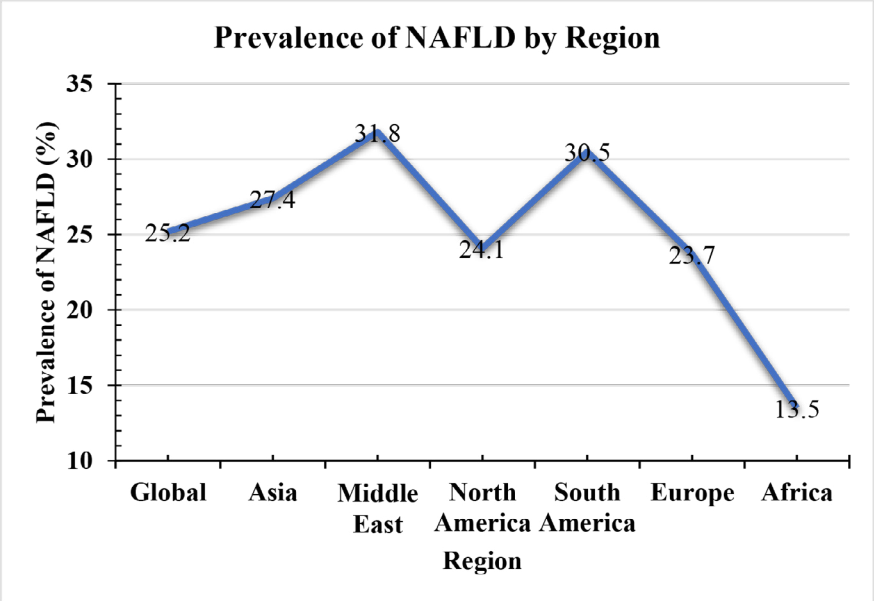

Figure 2. Prevalence of NAFLD by Region.

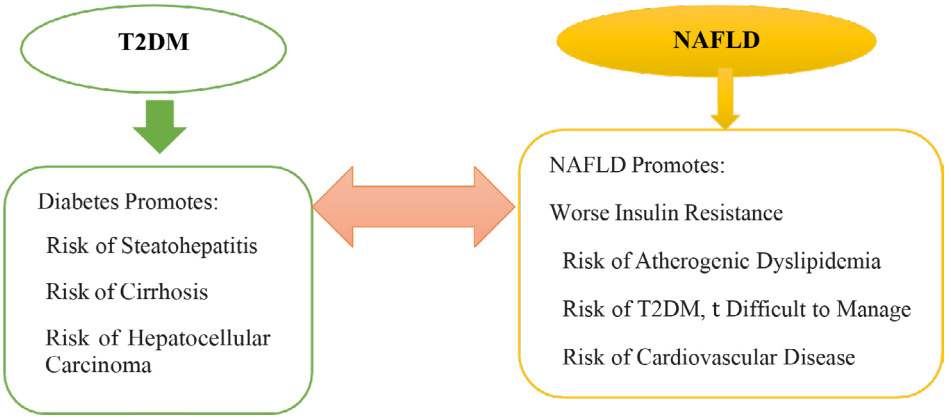

Figure 3. Relationship between T2DM and NAFLD. Both disorders have underlying pathophysiological pathways that worsen each other, increase comorbid conditions and make the original diseases worse[30].

into non-alcoholic steatohepatitis, advanced fibrosis, or cirrhosis[26]. It is widely known that the buildup of fat in the liver is connected to both hepatic insulin resistance and hepatic inflammation, both of which are important characteristics of NAFLD[27]. In a meta-analysis encompassing observational studies, it was found that the prevalence of NAFLD is significant among individuals with type 1 diabetes. The overall prevalence stands at 19.3%, while adults exhibit an even higher prevalence of 22%[28]. In their study, Kim *et al.*, identified a significant correlation between elevated liver fat and increased levels of serum IL-8 and NGF. Furthermore, they observed elevated Acute Insulin Response (AIR) and higher levels of insulin resistance as measured by Homeostasis Model Assessment (HOMA-IR) in individuals with elevated liver fat. These variables might have a big impact on the metabolic abnormalities that obese Hispanics experience in connection with elevated fat[29]. Relation between T2DM and NAFLD shown in Figure 3[30].

7. NAFLD and Cardiovascular Disease

NAFLD stands out as the predominant liver ailment globally, while Cardiovascular Disease (CVD) remains a leading contributor to global morbidity and mortality. Zhou *et al.*'s meta- analysis unveiled a robust association between NAFLD and CVD, establishing a connection to subclinical atherosclerosis. The evaluation incorporated four surrogate markers: carotid artery intima-media thickness/plaques, arterial stiffness, coronary artery calcification, and endothelial dysfunction. In a meta-analysis conducted by Wu *et al.*, it was established that NAFLD did not demonstrate an association with overall mortality or Cardiovascular Disease (CVD) mortality. Nevertheless, the study unveiled a connection between NAFLD and an increased risk for specific cardiovascular conditions, comprising prevalent and incident Coronary Artery Disease (CAD), prevalent and incident hypertension, and prevalent atherosclerosis[31]. Most research indicates that there is no link between Non-Alcoholic Fatty Liver Disease (NAFLD) and Cardiovascular Disease (CVD), irrespective of established cardiovascular risk factors such as age, gender, body mass index, waist circumference, smoking habits, hypertension, or dyslipidemia[32-36]. A growing body of research indicates a connection between Non-Alcoholic Fatty Liver Disease

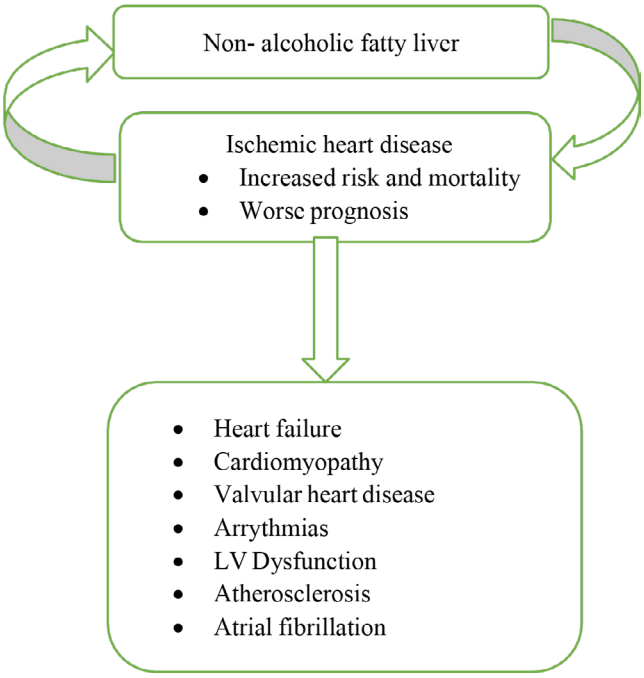

Figure 4. A description of the severity of hepatic and cardiac conditions that aggravate one another: Heart failure, cardiomyopathy, valvular heart disease arrhythmias and other cardiac disorders are all linked to NAFLD[37].

(NAFLD) and an elevated risk of Cardiovascular Disease (CVD) along with other cardiac complications, including left ventricular dysfunction, valvular heart calcification, and cardiac arrhythmias. These implications extend beyond direct liver-related issues, affecting the heart in various ways[36]. A descriptive of the severity of hepatic and cardiac condition shown below in Figure 4[37].

8. NAFLD and Chronic Kidney Disease (CKD)

Increasing evidence suggests a strong association between NAFLD and the prevalence and incidence of CKD, specifically identified by a glomerular filtration rate below 60mL/min/1.73 m^2, denoted as CKD stage 3. This stage of CKD is recognized as a significant risk factor for end-stage kidney disease, cardiovascular complications and premature mortality. Furthermore, there is an indication that NAFLD and CKD share common cardiometabolic risk factors and exhibit overlapping pro-inflammatory and pro-fibrotic molecular pathways. Notably, only two prior meta-analyses conducted in 2014 and 2018 have

delved into the relationship between NAFLD and the risk of incident CKD[38].

9. Obesity

Many research studies have utilised the BMI as a means to categorise individuals into overweight and obesity classifications. As per the World Health Organization (WHO), overweight and obesity are defined as abnormal or excessive buildup of fat that can potentially lead to health hazards. Although BMI is a practical measure in clinical and epidemiological contexts, it falls short as an accurate indicator of adiposity since it cannot distinguish between muscle and fat mass[39].

Table 1. International classification in adult underweight, overweight and obesity to body mass index

Classification	International	Asian
Underweight	< 18.5	< 18.5
Normal	18.5 – 24.9	18.5 – 22.9
Overweight	25.0 – 29.9	23.0 – 24.9
Obese Class I	30.0 – 34.9	25.0 – 29.9
Obese Class II	35.0 – 39.9	≥ 30
Obese Class III	≥ 40	

10. NAFLD and Obesity are Strongly Correlated

In developed Western nations, NAFLD is now present in 30% of the population, emerging as the most widespread liver condition globally. Hepatic steatosis, a characteristic feature of NAFLD, manifests without a background of excessive alcohol consumption or any other identified liver disorders. The Dionysos study, conducted in the general population revealed that fatty liver, as detected through ultrasonography, was observed in 10-15 % of non-obese individuals and surged to as high as 76% among obese participants who did not engage in hazardous alcohol consumption[40].

Primary and secondary NAFLD are two distinct forms of NAFLD that can be separated based on etiologic variables. Due to the metabolic syndrome, primary NAFLD develops. Infections, pharmaceutical use, parenteral nutrition and rare metabolic and congenital disorders all contribute to secondary NAFLD[40]. Numerous investigations have revealed that the onset of NAFLD is predominantly influenced by dysfunctions in adipose tissue. These dysfunctions include an elevated flow of Free Fatty Acids (FFAs) to the liver, de novo hepatic lipogenesis, and the generation of pro-inflammatory cytokines by macrophages in White Adipose Tissue (WAT)[41].

10.1 Physical Activity

Accordingly randomised clinical trials demonstrate vigorous and moderate exercise was closely associated with reducing intra-hepatic fat content in NAFLD and metabolic syndrome[42]. People who follow regular physical activity for 6 months improved aerobic capacity in the case of NAFLD and metabolic syndromes. For NAFLD patients, intense exercise may also help them lose weight, burn body fat, and lower their blood pressure[43].

10.2 Dietary Factor

The progression of NAFLD is markedly affected by dietary composition[44]. The Mediterranean diet, abundant in monounsaturated fatty acids, polyunsaturated fatty acids and polyphenols has demonstrated efficacy in enhancing insulin sensitivity and reducing hepatic steatosis. For individuals with obesity, high-protein diets have emerged as a viable option for weight loss and maintenance. Notably, a significant reduction in liver fat and an indicative decrease in liver fibrosis have been observed with a diet characterised by high protein, low-calorie intake, and high fibre content[4].

Opting for a Mediterranean Diet (MED) or a Low-Carbohydrate (LC) diet is more effective in decreasing Hepatic Fat Content (HFC) compared to a low-fat diet. Additionally, these dietary approaches offer greater benefits in reducing visceral fat[45]. The significance of reducing HFC is underscored by observed improvements in GGT, ALT, chemerin, and HbA1c. These improvements remained noteworthy even after adjusting total weight loss or changes in Visceral Adipose Tissue (VAT). Moreover, the MED/LC diet not only supported a reduction in cardiometabolic risk but did so independently of its impact on weight or VAT[45]. In a randomized clinical trial conducted by Chen J, it was discovered that both a low- carbohydrate diet and a high-fibre diet proved to be more effective in reducing body weight and fat among individuals with NAFLD. Additionally, these dietary interventions led to positive changes in various metabolic

indicators, including liver enzymes, blood glucose, blood lipid levels and uric acid. Interestingly, the study noted that female patients exhibited significantly better improvements in these indicators compared to their male counterparts[46].

11. Conclusion

The most widespread liver disease in the world continues to be NAFLD. The operational definition of NAFLD revolves around the presence of Fatty Liver (FL), characterized by an accumulation of lipids within hepatocytes exceeding 5% of the liver's weight. This definition explicitly excludes liver infections such as hepatitis B and hepatitis C viruses as well as instances of excessive ethanol intake. Currently, the most prevalent type of chronic liver disease in the US is NAFLD. Metabolic disorders, including T2D, hypertension, dyslipidemia, and obesity, are closely associated with NAFLD. T2DM significantly contributes to the accelerated progression of non-alcoholic steatohepatitis, advanced fibrosis or cirrhosis arising from NAFLD. NAFLD, representing a spectrum of hepatic conditions is intricately linked with metabolic and cardiovascular disorders, including obesity, Insulin Resistance (IR), hypertension, dyslipidemia and T2D.

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