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Fatty liver disease: An updated overview of risk factors

Abdullatif Suliman Alsayegh
KSA, National Guard Health Affairs

Mohammed Abdullah Alduaybi
KSA, National Guard Health Affairs

Hamoud Ghayyadh Alanizi
KSA, National Guard Health Affairs

Nada Abdulrahman Amer Alajmi
KSA, National Guard Health Affairs

Shahad Mohammed Bin Saeed
KSA, National Guard Health Affairs

Meshal Ibrahim Zaid Al Owias
KSA, National Guard Health Affairs

Adel Awad Al Rashedi
KSA, National Guard Health Affairs

Asma Saad Alqahtani
KSA, National Guard Health Affairs

Bader Sayah Alanezi
KSA, National Guard Health Affairs

***Abstract*---Background:** Nonalcoholic fatty liver disease (NAFLD) represents a growing global health concern, affecting approximately 25% of the population and serving as a precursor to severe liver conditions such as cirrhosis and hepatocellular carcinoma. The complexity of NAFLD is compounded by various risk factors, including obesity, diet, type 2 diabetes mellitus (T2DM), genetic predispositions, obstructive sleep apnea (OSA), and alterations in gut microbiota. **Aim:** This article aims to provide a comprehensive overview of the risk factors associated with the development and progression of NAFLD,

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***Corresponding email**: akk29337@gmail.com*
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emphasizing their interrelated roles. **Methods:** The literature was reviewed, focusing on epidemiological studies, cohort analyses, and meta-analyses that elucidate the connection between these risk factors and NAFLD. Key databases were searched for relevant publications, and data were synthesized to present a cohesive understanding of the current landscape of NAFLD research. **Results:** The findings underscore obesity and central obesity as significant contributors to NAFLD, with increased body mass index (BMI) and waist circumference directly correlating with the disease's prevalence. Dietary factors, particularly high fructose consumption, were linked to enhanced lipogenesis and mitochondrial dysfunction. Additionally, T2DM was identified as a substantial independent risk factor for hepatic fibrosis. Genetic variations, such as those in the PNPLA3 gene, further complicate the risk landscape. OSA and gut microbiome disturbances also play critical roles in NAFLD's pathogenesis. **Conclusion:** NAFLD is a multifactorial disease influenced by a spectrum of risk factors. Effective management strategies targeting obesity, diabetes, dietary habits, and genetic counseling are crucial for reducing the burden of NAFLD. Future research should focus on the interplay between these factors to develop targeted prevention and treatment approaches.

***Keywords*---**Nonalcoholic fatty liver disease, NAFLD, obesity, type 2 diabetes, genetics, obstructive sleep apnea, gut microbiome.

Introduction

Nonalcoholic fatty liver disease (NAFLD) is the most prevalent hepatic disorder, with an estimated global prevalence of around 25% [1,2]. NAFLD serves as an overarching term that encompasses a range of liver conditions, including simple steatosis (nonalcoholic fatty liver), steatohepatitis (nonalcoholic steatohepatitis, NASH), and cirrhosis [3]. Furthermore, NAFLD is recognized as the primary contributor to liver cirrhosis, hepatocellular carcinoma, and mortality [1]. Projections indicate that the incidence of NAFLD will continue to escalate between 2015 and 2030, leading to increased prevalence and mortality rates [4]. Specifically, the prevalence of NAFLD was approximately 25.8% across all age groups in 2015, with expectations of rising to 28.4% by 2030. Additionally, mortality rates among individuals with NAFLD are anticipated to rise by 23% by 2030, contributing to 13% of total deaths [5]. Patients diagnosed with NAFLD face an elevated risk of liver-related mortality; however, cardiovascular disease remains the predominant cause of death, presenting a 1.5-fold increased risk [6,7]. The likelihood of developing cardiovascular disease escalates with the severity of NAFLD (odds ratio [OR] 2.58) [8]. The incidence rate ratios for liver- and cardiovascular disease-related mortality within the NAFLD cohort are 0.77 and 4.79 per 1,000 person-years, respectively [9]. Another significant contributor to mortality in individuals with NAFLD is neoplasia [9-11]. The overall incidence of cancer in patients with NAFLD is 1.3 times greater than that in control subjects (hazard ratio: 1.32, $P<0.001$) [11]. Hepatocellular carcinoma, along with other gastrointestinal malignancies such as colorectal and stomach cancer, as well as

breast cancer in females, are the most frequently observed neoplasms associated with the NAFLD population [9,11,12]. This discussion aims to explore the risk factors linked to the development and progression of NAFLD.

Risk Factors:

Obesity And Central Obesity:

Obesity, characterized by an elevated body mass index (BMI), is closely linked to nonalcoholic fatty liver disease (NAFLD) in a dose-dependent relationship, with an approximate 20% increase in the likelihood of developing NAFLD for each unit increase in BMI [13]. Additionally, childhood obesity is correlated with fatty liver and heightened overall mortality [14]. Children diagnosed with NAFLD exhibit a 5.88-fold increased rate of all-cause mortality compared to the control group, with specific hazard ratios for various causes: cancer (hazard ratio 1.67 vs. 0.07 per 1,000 person-years), cardiometabolic disease (hazard ratio 1.12 vs. 0.14 per 1,000 person-years), and liver disease (hazard ratio 0.93 vs. 0.04 per 1,000 person-years) [14]. A retrospective cohort study has highlighted the relationship between central obesity and nonalcoholic steatohepatitis (NASH) as well as advanced fibrosis in lean patients with NAFLD [15]. Notably, both lean (odds ratio [OR] 5.8; P=0.004) and overweight or obese (OR 4.2; P=0.0001) individuals with NAFLD exhibiting central obesity (waist circumference >102 cm for men, >88 cm for women) are significantly associated with substantial hepatic fibrosis [15]. Meta regression analysis conducted on this cohort (n=11,400) indicated that waist circumference influences metabolic syndrome-related factors and fasting plasma glucose levels (slope: 1.55, P=0.14). While numerous studies emphasize the connection between general obesity and NAFLD risk as determined by BMI, increasing evidence points to the greater significance of central obesity—defined by waist circumference or waist-to-hip ratio—in the progression of NAFLD [16].

Diet:

Patients with NAFLD exhibit significantly higher total caloric intake; however, no substantial differences are observed in the consumption patterns of macronutrients (e.g., proteins, fats, and carbohydrates) or micronutrients (e.g., vitamins, iron, or zinc) when compared to control groups [17]. Nonetheless, certain dietary components, particularly saturated fats and fructose, have been closely associated with the development of NAFLD [18]. The consumption of fructose promotes lipogenesis while impairing mitochondrial fat oxidation, resulting in increased uric acid production and depletion of adenosine triphosphate (ATP) within the mitochondria. This process initiates a cascade of reactions that may induce oxidative stress [19,20]. Furthermore, fructose metabolism has the potential to alter intestinal permeability and contribute to dysbiosis, thereby playing a role in the pathogenesis of NAFLD [21]. Conversely, a study utilizing the Rotterdam cohort conducted by Alferink et al. [22] could not establish a definitive association between NAFLD and the consumption of monosaccharides and disaccharides.

Type 2 Diabetes Mellitus (T2dm):

The estimated global prevalence of NAFLD, NASH, and advanced hepatic fibrosis among individuals with T2DM stands at 55.48%, 37.33%, and 17.02%, respectively [23]. The presence of prediabetes or diabetes in patients with NAFLD correlates with an increased risk of severe hepatic steatosis (OR 2.00, P<0.005), significant lobular inflammation (OR 2.25, P<0.005), hepatic ballooning (OR 1.54, P=0.069), and notable fibrosis (OR 1.30, P=0.45) [24]. The incidence of confirmed NASH is significantly higher among patients with prediabetes/diabetes compared to those with normal glucose tolerance (48.4% vs. 29.9%; P<0.001) [24,25]. Among the T2DM group, 17.9% of patients exhibited both significant and advanced fibrosis, in contrast to 4.9% and 1.8% in the nondiabetic control group, respectively [26]. These findings strongly indicate that T2DM serves as an independent risk factor for hepatic fibrosis [15]. Moreover, the presence of T2DM is identified as the most significant predictive risk factor for hepatic fibrosis, even among lean patients with NAFLD [26].

The prevalence of nonalcoholic fatty liver disease (NAFLD) among individuals with type 2 diabetes mellitus (T2DM) has been highlighted in various studies. In a comprehensive analysis conducted by Younossi et al. [23] in 2019, which included 80 studies with a total of 49,419 patients, the prevalence rates for NAFLD, nonalcoholic steatohepatitis (NASH), and advanced fibrosis were reported at 55.48%, 37.33%, and 17.02%, respectively. Similarly, Le et al. [27] (2019) observed a prevalence of NAFLD at 72% in a cohort of 3,691 patients. The study also tracked the prevalence of NASH over two distinct time periods, noting rates of 2.82% from 2003 to 2006 and 5.20% from 2011 to 2014, with advanced fibrosis rates of 0.30% and 0.34%, respectively, during the same periods. Additionally, Kwok et al. [28] (2016) reported a prevalence of 72.8% for NAFLD among 1,799 patients assessed using controlled attenuation parameter (CAP) measurements, while advanced fibrosis was identified in 17.1% of the cohort assessed with liver stiffness measurements (LSM). Collectively, these studies underscore a significantly higher prevalence of NAFLD and its complications among patients with T2DM compared to control groups.

Genetic Polymorphism:

The pathogenesis of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) is intricate, influenced by a range of pathogenic factors, including adiposity, lipotoxicity, insulin resistance, and genetic variations, all interacting synergistically [29]. One critical aspect of genetic influence is the presence of single nucleotide polymorphisms (SNPs), which have significant implications for disease susceptibility. Ethnic diversity and genetic predisposition indicate that SNPs play a vital role in the pathogenesis of NAFLD [30]. Recent advancements in genome sequencing have facilitated the identification of specific genetic variations linked to the development of NAFLD. Notably, patatin-like phospholipase domain-containing 3 (PNPLA3) and transmembrane 6 superfamily member 2 are among the most prominent variants identified [30]. Additionally, newer variants such as 17-beta hydroxysteroid dehydrogenase 13, glucokinase regulator, and protein phosphatase 1 regulatory subunit 3B have been the focus of recent investigations [30,31]. The 17-beta hydroxysteroid dehydrogenase 13

variant is particularly interesting as its wild-type form is believed to offer a protective effect against liver inflammation [30].

The rs738409 C>G SNP, which encodes the I149M variant of PNPLA3, and the rs58542926 C>T SNP, which encodes the E167K variant of transmembrane 6 superfamily member 2, are among the most extensively studied genetic predispositions associated with NAFLD. Within the PNPLA3 variants, three genotypes are identified: CC, GC, and GG. The distribution of these genotypes varies significantly between individuals with and without NAFLD. The CC genotype, which is the wild-type, is more prevalent in those without NAFLD (30.8% vs. 60.2%), while the variant genotypes GC and GG are found more frequently among NAFLD patients (43.0% vs. 35.6% and 26.2% vs. 4.2%, respectively) [31]. Interestingly, SNPs are also linked to NAFLD pathogenesis in lean individuals. A recent study indicated that the non-CC allele of PNPLA3 is more frequently found in lean patients with NAFLD compared to those who are overweight or obese [32]. Furthermore, a larger proportion of lean patients exhibit variations in the transmembrane 6 superfamily member 2 gene SNP [15]. A critical finding is that the PNPLA3 I148M variant is associated with an increased risk of liver disease mortality [33].

Obstructive Sleep Apnea (OSA)

Obesity is a significant contributor to the onset of obstructive sleep apnea (OSA) and nonalcoholic fatty liver disease (NAFLD). Moreover, OSA has the potential to independently influence both the initiation and advancement of NAFLD [34]. A meta-analysis encompassing 18 cross-sectional studies revealed a pooled odds ratio (OR) of OSA correlating with the occurrence of NAFLD, ranging from 2.01 to 2.99 [35]. The emergence of NAFLD among patients suffering from OSA is closely linked to chronic intermittent hypoxia. Cycles of hypoxia followed by reoxygenation can directly induce fatty liver through the action of hypoxia-inducing factor-1, while simultaneously fostering inflammatory responses in tissues via the accumulation of free radicals and activation of NF-kB [36]. Furthermore, OSA activates the sympathetic nervous system, leading to systemic inflammatory responses and dysfunction of vascular endothelium. This sympathetic activation enhances platelet activity and aggregation, which can culminate in insulin resistance, dyslipidemia, and the development of metabolic syndrome [36].

Microbiome

The gut-liver axis describes the reciprocal relationship between the gut microbiome and the liver, facilitated by dietary, genetic, and environmental signals [37]. Disruption of this liver-gut axis is implicated in the pathogenesis of NAFLD through mechanisms such as compromise of the gut barrier, bacterial translocation, and subsequent inflammatory responses in the liver [38]. Although the precise mechanisms or direct causative relationships linking NAFLD to alterations in the gut microbiome remain elusive, various hypotheses are currently under investigation. For instance, research by Martinez-Gurin et al. [39] demonstrated that NAFLD does not arise from decreased lipid metabolism and intestinal absorption in germ-free mice, even when subjected to a high-fat diet.

The resistance to NAFLD observed in these germ-free mice is attributed to the inhibition of lipid metabolism due to disrupted enteroendocrine signaling (e.g., cholecystokinin) and fatty acid transport mechanisms (e.g., Cd36 and Dgat1). It was further confirmed that when high-fat diets were introduced following the transition from germ-free conditions to general breeding environments, intestinal fat absorption increased. These findings highlight how fat absorption is influenced by the status of intestinal microflora.

Sarcopenia

Sarcopenia is characterized by a progressive decline in muscle mass and strength, occurring more frequently in individuals with chronic medical conditions such as chronic obstructive pulmonary disease, chronic kidney disease, or NAFLD, compared to healthy populations [40-43]. The relationship between sarcopenia and NAFLD is bidirectional [44], operating independently of insulin resistance (IR) or obesity [41], as both conditions share overlapping pathophysiological mechanisms [40]. Furthermore, sarcopenia is linked to poorer clinical outcomes overall [43,45]. Skeletal muscle plays a pivotal role in glucose metabolism, being one of the largest organs responsible for glucose utilization. The deterioration of muscle mass, due to factors such as aging [45], nutritional deficiencies, or sedentary lifestyles, results in reduced muscle strength and disrupted metabolic functions. Skeletal muscle is one of the principal sites for insulin stimulation in the body, which is often implicated as a major contributor to IR [46]. A detrimental cycle involving local myosteatosis and muscle IR significantly contributes to systemic inflammation and IR. This cycle, referred to as the "metabaging cycle," encompasses dysfunction in lipid metabolism, lipotoxicity, IR, local inflammation, and lipolysis. Proinflammatory mediators, including interleukin-6 and tumor necrosis factor-alpha, perpetuate this cycle by enhancing cytokine secretion, ultimately transforming localized inflammation into a systemic problem [47]. Both IR and chronic inflammatory states are prevalent comorbidities among NAFLD patients, along with disturbances in lipid metabolism [48,49]. Hong et al. [40] suggested a negative correlation between NAFLD and sarcopenia, as indicated by homeostasis model assessment of IR and high-sensitivity C-reactive protein levels. Additionally, Koo et al. [42] found that the incidence of sarcopenia in individuals with NAFLD was significantly greater than in a control group (17.9% vs. 8.7%, $P<0.001$). The likelihood of developing NASH and significant fibrosis in patients with sarcopenia is 2.30 and 2.05 times greater than in the control population, respectively. The prevalence of significant fibrosis (≥F2) is notably higher in those with sarcopenia compared to those without (OR 2.01, 45.7% vs. 24.7%; $P<0.001$) [42]. Furthermore, the occurrence of Child-Pugh class C cirrhosis is more pronounced in patients with sarcopenia than those classified as class B or A (46.7% vs. 37.9% vs. 23.3%, respectively; $P=0.007$) [50]. This condition is also associated with a heightened prevalence of cirrhosis-related complications (81.82% vs. 62.24%, $P<0.001$) [45]. Patients with cirrhosis and sarcopenia exhibit significantly lower overall survival rates (relative risk 2.64) compared to those without sarcopenia. This association extends to cirrhosis-related complications such as ascites (relative risk of 1.82), spontaneous bacterial peritonitis (relative risk of 3.33), hepatic encephalopathy (relative risk of 1.96), and upper gastrointestinal varices (relative risk of 2.13) [45]. The five-year

survival probabilities for individuals with cirrhosis and sarcopenia are markedly lower than for those without (46.6% vs. 74.2%, P<0.001) [50].

Other Risk Factors:

Several additional risk factors contribute to the development of nonalcoholic fatty liver disease (NAFLD). Age is a significant factor, with the risk increasing notably in individuals over 50 years old. Additionally, sex plays a role, as males generally face a higher risk of developing NAFLD compared to females, although postmenopausal women also exhibit increased susceptibility. Another crucial factor is a sedentary lifestyle; physical inactivity can lead to weight gain and various metabolic disorders that predispose individuals to NAFLD. Dietary habits significantly influence the risk of NAFLD as well. A high-carbohydrate diet, particularly one rich in simple sugars, can lead to insulin resistance and fat accumulation in the liver. Similarly, a high-fat diet containing saturated and trans fats can promote the development of NAFLD, while a low fiber intake may negatively impact gut health and metabolism, further contributing to the condition. The presence of type 2 diabetes markedly increases the risk of NAFLD due to the associated insulin resistance and metabolic dysregulation. Furthermore, hypertension and dyslipidemia, characterized by abnormal lipid levels such as elevated triglycerides and low HDL cholesterol, are closely linked to NAFLD and often co-occur with metabolic syndrome. Genetic predisposition is another important risk factor. A family history of liver disease or conditions such as familial hypercholesterolemia can heighten an individual's likelihood of developing NAFLD. Additionally, certain medications, including corticosteroids and specific antiretroviral drugs, can contribute to fat accumulation in the liver, posing a risk to those undergoing treatment. Chronic kidney disease is also associated with NAFLD, as metabolic disturbances in these patients increase their susceptibility to liver complications. Moreover, sleep disorders, particularly obstructive sleep apnea, can exacerbate insulin resistance, making individuals more prone to developing NAFLD. Finally, endocrine disorders such as hypothyroidism and Cushing's syndrome can disrupt metabolism and further increase the risk of fatty liver disease. Understanding these diverse risk factors is essential for effective prevention and management strategies, highlighting the importance of lifestyle modifications, early detection, and appropriate medical interventions.

Conclusion

In summary, nonalcoholic fatty liver disease (NAFLD) is a complex hepatic disorder that presents significant public health challenges worldwide. The multifaceted nature of NAFLD is underscored by a variety of risk factors, each contributing uniquely to its pathogenesis and progression. Obesity, particularly central obesity, remains one of the most substantial risk factors, exhibiting a clear dose-response relationship with NAFLD development. This correlation emphasizes the importance of addressing obesity in NAFLD management strategies, particularly in pediatric populations, where rising obesity rates signal an impending increase in NAFLD cases. Dietary influences, especially the intake of saturated fats and fructose, have been shown to exacerbate the condition through mechanisms that promote lipogenesis and insulin resistance. The

relationship between type 2 diabetes mellitus (T2DM) and NAFLD further complicates the clinical picture, as T2DM patients exhibit significantly higher rates of NAFLD and associated hepatic complications. The identification of genetic polymorphisms, such as those in the PNPLA3 gene, enhances our understanding of individual susceptibility to NAFLD, paving the way for personalized medicine approaches. Additionally, conditions like obstructive sleep apnea (OSA) and disturbances in gut microbiota introduce further layers of complexity, linking metabolic dysfunction with hepatic disease. The interplay between these factors highlights the necessity for an integrated approach to prevention and treatment, considering lifestyle modifications, dietary interventions, and potential pharmacological therapies. Overall, the increasing prevalence of NAFLD necessitates heightened awareness and proactive measures from healthcare providers and policymakers alike. Continued research into the mechanisms underlying NAFLD and its risk factors is critical for developing effective public health strategies aimed at reducing the burden of this disease and its associated complications. Addressing these factors holistically can lead to improved outcomes and a decrease in the rising trend of liver-related morbidity and mortality.

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مرض الكبد الدهني: نظرة شاملة محدثة حول عوامل الخطر.

الملخص:

الخلفية :يمثل مرض الكبد الدهني غير الكحولي (NAFLD) مشكلة صحية عالمية متزايدة، حيث يؤثر على حوالي 25% من السكان ويعد مقدمة لحالات كبدية خطيرة مثل تليف الكبد وسرطان الخلايا الكبدية. تعقيد NAFLD يتفاقم بسبب عوامل خطر متعددة، بما في ذلك السمنة، النظام الغذائي، داء السكري من النوع الثاني(T2DM) ، الاستعدادات الوراثية، انقطاع النفس النومي الانسدادي(OSA) ، والتغيرات في ميكروبيوم الأمعاء.

الهدف :يهدف هذا المقال إلى تقديم نظرة شاملة حول عوامل الخطر المرتبطة بتطور وتقدمNAFLD ، مع التأكيد على أدوارها المتداخلة.

الطرق :تم مراجعة الأدبيات، مع التركيز على الدراسات الوبائية، وتحليلات المجموعات، والتحليلات التلوية التي توضح العلاقة بين هذه العوامل و .NAFLDتم البحث في قواعد البيانات الرئيسية عن المنشورات ذات الصلة، وتم تجميع البيانات لتقديم فهم متماسك للواقع الحالي لأبحاث NAFLD.

النتائج :تؤكد النتائج أن السمنة والسمنة المركزية تعد من المساهمين الرئيسيين فيNAFLD ، حيث يرتبط مؤشر كتلة الجسم (BMI) ومحيط الخصر بشكل مباشر بانتشار المرض. تم ربط عوامل النظام الغذائي، وخاصة استهلاك الفركتوز المرتفع، بزيادة تكوين الدهون وخلل في الميتوكوندريا. بالإضافة إلى ذلك، تم تحديد T2DM كعامل خطر مستقل كبير لتليف الكبد. كما أن التغيرات الجينية، مثل تلك الموجودة في جين PNPLA3، تعقد من مشهد الخطر. تلعب OSA والاضطرابات في ميكروبيوم الأمعاء أيضًا أدوارًا حاسمة في مسببات.NAFLD

الخاتمة :يُعتبر NAFLD مرضًا متعدد العوامل يتأثر بمجموعة من عوامل الخطر. إن استراتيجيات الإدارة الفعالة التي تستهدف السمنة والسكري والعادات الغذائية والإرشاد الجيني ضرورية لتقليل عبء .NAFLD ينبغي أن تركز الأبحاث المستقبلية على التفاعل بين هذه العوامل لتطوير أساليب وقائية وعلاجية مستهدفة.

الكلمات المفتاحية :مرض الكبد الدهني غير الكحولي، NAFLD، السمنة، داء السكري من النوع الثاني، الوراثة، انقطاع النفس النومي الانسدادي، ميكروبيوم الأمعاء.