

## REVIEW ARTICLE

## Non-Alcoholic Fatty Liver Disease and other Non-Communicable Diseases: Time for an Integrated Approach

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### Abstract

Non-Alcoholic fatty liver disease (NAFLD) is a broad term covering a spectrum of conditions ranging from hepatic steatosis, steatohepatitis and cirrhosis. NAFLD is highly prevalent across all regions of the world with its global prevalence of 25.2%(95%CI:22.1-28.7). It is commonly referred as the 'hepatic manifestation' of metabolic syndrome (MetS). Moreover, it is strongly associated with the individual components as well as MetS as a whole. NAFLD has been independently associated with other non-communicable diseases (NCDs) like chronic kidney disease (CKD), Polycystic ovary Syndrome (PCOS), Stroke and Cancers. This strong association of NCDs with NAFLD not only affects the prevalence but also the progression and management of the disease. Thus, this review aims at highlighting the association of NAFLD with other NCDs. A literature search was undertaken in the MEDLINE database using the necessary MeSH terms. The review concludes NAFLD is a systemic disease, not just confined to liver-specific morbidity and mortality, but also associated with numerous extra-hepatic manifestations, such as metabolic syndrome, cardiovascular diseases, chronic renal diseases, and malignancy. With co-existence of NAFLD with various NCDs it is expected to become the most overwhelming liver disease in the world in coming years. Hence, to reduce medical and economic impact associated with these comorbidities, it is recommended that all countries should estimate and predict the burden on comorbidities associated with NAFLD and galvanize its health resources in providing integrated therapeutic approaches for management of NAFLD and related comorbidities at an early stage.

### Keywords

NAFLD; Non-Communicable Diseases; Diabetes Mellitus; Metabolic Syndrome; Obesity

### Introduction

Non-Alcoholic fatty liver disease (NAFLD) is a broad term covering a spectrum of conditions ranging from hepatic steatosis, steatohepatitis and cirrhosis, which is either identified by imaging or histological analysis(1). It majorly comprises of two pathologically distinct states - non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH). NAFL is a condition characterized by the presence of ≥5% hepatic steatosis in absence of any evidence of hepatocellular injury, whereas, NASH is characterized as inflammation with hepatocyte injury

with or without fibrosis in addition to ≥5.0% hepatic steatosis(1). NAFLD is highly prevalent in all the regions of the world. The estimated global prevalence from a recent meta-analysis is 25.2% (95%CI:22.1-28.7). There is a noticeable variation observed in the prevalence of NAFLD across different regions of the world. The global prevalence of NASH is estimated to be 1.5–6.5% in the general population(2). NAFLD is commonly referred as the 'hepatic manifestation' of metabolic syndrome (MetS) and is a key driver for components of the MetS. In addition, it is strongly associated with the individual components of metabolic syndrome (MetS), which

includes abdominal obesity, hyperglycemia, hypertension, high triglycerides and low HDL levels as well as MetS as a whole. Hence, the prevalence of NAFLD correlates with the prevalence of MetS because most of the metabolic covariates of NAFLD are highly prevalent in the population.

NAFLD has been independently associated with other non-communicable diseases (NCDs) like chronic kidney disease (CKD), Polycystic ovary Syndrome (PCOS), Stroke and Cancers. This strong association of NCDs with NAFLD not only affects the prevalence but also the progression and management of the disease. Several studies have reported the association of NAFLD and other non-communicable diseases; however, these studies need to be summarized to better delineate this association. Hence, this review aims at highlighting the association of NAFLD with other NCDs.

## Material & Methods

A literature search was performed in the MEDLINE database using the MeSH term: 'Non-alcoholic Fatty Liver Disease'. The search strategy was further narrowed by adding the MeSH term related to the non-communicable diseases – 'Diabetes Mellitus', 'Hypertension', 'Dyslipidemias', 'Obesity', 'Metabolic Syndrome', 'Renal Insufficiency, Chronic', 'Cardiovascular Diseases', 'Polycystic Ovary Syndrome' 'Stroke' and 'Neoplasms'. We limited our search to English studies and, when possible, we excluded case reports or case series. We accessed full text articles of the included studies.

## Results and Discussion

### 1.1. NAFLD and Components of Metabolic Syndrome

Clinical-epidemiology of NAFLD in patients with MetS documented a concomitant prevalence of NAFLD as 69%, with waist circumference being the most common risk factors associated with NAFLD followed by insulin resistance(3). Thus, evidences suggest NAFLD participants have greater possibility of presence of other components of MetS(4,5). Studies have documented that longer the duration various metabolic components, more is the risk of progression of NAFL to NASH-related cirrhosis and hepato-cellular carcinoma (HCC)(6).

Apart from cross-sectional association, a study recognised NAFLD as a risk factor for individual components of metabolic syndrome(4,7). Moreover, addition of NAFLD to Adult Treatment Panel III (ATP III) criteria significantly improved prediction of insulin resistance and diagnostic accuracy indicating pathophysiological role of accumulation of fat in development of insulin resistance(8). In addition to this, pooled incident estimates suggest a relative risk of 3.22 (95%CI:3.05-3.41) for MetS among ultrasound diagnosed NAFLD patients during a 5-year follow-up period(9). This body of evidence points towards a bidirectional association between the two metabolic conditions.

### 1.1.1. Insulin Resistance and Type II Diabetes Mellitus

T2DM appears to be closely tied to the risk of developing NAFLD and NASH. A recent meta-analysis with 49,419 T2DM patients (mean age 58.5 years) estimated the prevalence of NAFLD to be 55.5% (95%CI:47.3–63.7). To elaborate further, prevalence of NAFLD in diabetic patients was two-times higher when compared to general population(10). In addition to this, few studies have suggested the prevalence of NAFLD and NASH among T2DM patients as 50% and 56% respectively(11). Furthermore, presence of T2DM among NAFLD patients have adversely affected the long-term outcomes specifically HCC and liver-related mortality(12). A recent meta-analysis on incident data of ultrasound diagnosed NAFLD patients, determined the pooled relative risk of developing T2DM is 1.86 (95%CI:1.76–1.95) over a median period of 5 years(9). These evidences highlight the bidirectional relationship between NAFLD/NASH and T2DM via a common pathogenic mechanism(13).

The bi-directional interaction between NAFLD and T2DM is complex in nature and the precise mechanism is still being studied. There are numerous proposed mechanisms for their coexistence including direct hepatocyte lipotoxicity, hepatocellular oxidative stress due to increased oxidation of free fatty acids, release of inflammatory cytokines and peripheral adipocytes, impaired gut microbiota composition, mitochondrial dysfunction and hepatocellular regenerative response(14).

A group of scientists documented NAFLD initiates development of T2DM by elevating glucose production in the liver, which further impairs hepatic insulin resistance through activation of hepatic protein kinase and some liver-secreted proteins with diabetogenic properties. This leads to intra-hepatic fat accumulation which initiates liver inflammation. On the other hand, T2DM and systemic insulin resistance promotes production of free fatty acid flux from peripheral tissues to the liver. This leads to the development and progression of NAFLD. Furthermore, T2DM drives the progression of NAFLD from simple steatosis to cirrhosis(14).

### 1.1.2. Overweight and Obesity

Abdominal obesity has been reported that NAFLD is more strongly correlated with abdominal obesity than BMI(15). In addition, a higher fat mass, greater central obesity, and increased visceral fat are strongly associated with MetS (16).

While obesity is the most common risk factor for NAFLD, it is not sufficient in itself to explain the risk of NAFLD. The interaction of insulin resistance, dyslipidemia and prevalence of Visceral adipose tissue (VAT) forms the framework to explain adiposity and risk of NAFLD(17). Increased VAT, a surrogate for increased BMI, is detected in NAFLD patients irrespective of their fibrosis state. It is also independently associated with increased risks of NASH and NAFLD with significant fibrosis(18).

Moreover, according to a cohort study with 4.4 years of median follow-up time, increased VAT area was longitudinally associated with higher risk of NAFLD cases in a dose-dependent manner. The hazard ratio (HR) of NAFLD for 1-standard deviation (SD) increase in VAT was 1.36 (95%CI:1.16–1.59). In addition to this higher amount of subcutaneous adipose tissue area was associated with regression of fatty liver disease with HR per 1 SD increase being 1.36 (95%CI:1.08–1.72)(19).

The dietary interventions, physical activity, in addition to nutritional and psychologic counseling were found to be efficacious measures in the treatment of NAFLD associated with obesity in children and adolescents(20). In addition to this, the available evidence suggests that at least 5% weight loss can improve NAFLD whereas some impact on NASH and fibrosis can be seen with a weight loss of 7–10%. Evidences from observational studies and small randomized trials suggest restriction of carbohydrate and reduction in caloric intake through specific diets can promote weight reduction and eventually improving NAFLD and liver-related outcomes.(21) However, larger studies are required to demonstrate the standardization of diets is required and to compare the role of various forms of exercise in the progression or regression of NAFLD.

### 1.1.3. Hypertension

Though the studies assessing the association between NAFLD and Hypertension (HTN) are limited, there is no space of doubt that both the conditions are inter-related. A clinical study demonstrated higher prevalence of NAFLD among hypertensives. The authors also reported that the risk of NAFLD increased gradually across the blood pressure classes(22). Significantly higher prevalence has been reported among individuals having hypertension when compared to their counterparts (30.9% v 12.7%;  $p < 0.041$ )(23). Furthermore, the pooled prevalence of NAFLD in diabetic patients among hypertensives was 66.50% (95%CI:57.63–74.82%) as compared to non-hypertensives (55.78%,95%CI:49.06–62.39%)(24). Interestingly, a study demonstrated lean NAFLD was more strongly associated with the risk of HTN and other cardiometabolic diseases when compared with the obese NAFLD patients this could be attributable to different biochemical indexes when compared to obese group.(25) The evidences from large cohort studies demonstrated, HTN as an independent predictor for development of NAFLD diagnosed by ultrasound. However, these studies also documented the HTN was a weaker predictor than obesity and hyperlipidemia in development of NAFLD(26). A strong association between high FIB-4 risk score was found with HTN status of the individual. In addition to this, control of blood pressure among hypertensives decreases the odds of development of NAFLD and may offer protection against progression of liver fibrosis(27). These findings have been reemphasized by a longitudinal study with 6-year follow-up among biopsy diagnosed

NAFLD cases. The HTN had an independent role in worsening of fibrosis among NAFLD cases(28). The Framingham Heart Study participants documented increased odds of HTN among NAFLD cases with a high risk of fibrosis, based on NAFLD fibrosis score(29).

The Framingham Heart Study also highlighted that NAFLD was associated with an increased risk of developing HTN, indicating the reverse causality(29). Korean cohorts have suggested the changes in fatty liver status over a period of time could induce the risk of developing HTN(30). There is evidence that NAFLD is prospectively associated with incident HTN and degree of fibrosis can predict the risk of development of HTN(31). This evidence suggests a bi-directional association between HTN and NAFLD, which can be probably explained by Insulin resistance and activation of the renin-angiotensin-aldosterone system.

### 1.1.4. Dyslipidemia

Higher levels of total cholesterol (TC) and triglyceride (TG), low-density lipoprotein cholesterol (LDL-C) and lower high-density lipoprotein cholesterol (HDL-C) were reported in NAFLD patients as compared to control group. Moreover, ratio of TG to HDL-C was closely associated with NAFLD and a predictive factor for insulin resistance, T2DM, cardiovascular disease and hypertension(32). A recent cohort study stated, hypertriglyceridemia in 23% of NAFLD patients, low HDL-C in 10% suggesting evidence for higher prevalence of dyslipidaemia in patients with NAFLD (33). Unlike other components of MetS, lipid profile do not necessarily show any more abnormalities in advanced stages of NAFLD(34).

Studies suggest that in NAFLD patients, intrahepatic lipid accumulation results from abnormalities in lipid metabolism. These altered abnormalities in lipid metabolism are linked to an induction of inflammation and oxidative stress along with abnormal adipokine production that affect signalling pathways(35). Another emerging pathophysiological mechanism of NAFLD involves gut microbiota that can affect inflammatory, immune pathways as well as lipid metabolism, known as “gut-liver” axis(36).

## 1.2. NAFLD and Cardio-vascular disease (CVD)

### 1.2.1. Cardiac Arrhythmias

Recent clinical studies discovered NAFLD could signify a risk factor for various types of arrhythmias including atrial fibrillation, Recent clinical studies discovered NAFLD could signify a risk factor for various types of arrhythmias including atrial fibrillation, cardiac conduction defects and ventricular arrhythmias. Two large population-based cohort studies documented the association between atrial fibrillation and NAFLD-diagnosed by elevated liver enzymes (ALT and AST)(37,38). Reverse association is also true. An increased prevalence and incidence of atrial fibrillation was seen in ultrasound diagnosed-NAFLD in a hospital-based study(39). A prospective study confirmed the findings and documented NAFLD was independently associated with an increased risk of incident atrial

fibrillation over a mean follow-up of 16 years(40). A meta-analysis with five observational studies and 238,129 participants documented NAFLD assessed by ultrasonography was associated with a nearly two-fold increase in the prevalence and incidence of atrial fibrillation(41).

### 1.2.2. Atherosclerosis

Two major meta-analyses have been conducted to-date regarding the relationship between atherosclerosis and NAFLD. NAFLD has been identified as a risk factor for atherosclerosis(42). Another meta-analysis analysed more than 8000 patients with NAFLD found a significant link between the presence of NAFLD and increased carotid intima-media thickness(43).

The pathophysiological mechanisms underlying the possible independent association between NAFLD and cardio-metabolic disorders have not been fully elucidated yet. However, some evidence suggests insulin resistance and visceral obesity play the central role in causing low-grade inflammation(44).

### 1.3. Chronic Kidney Disease (CKD)

A cross-sectional study on 515 elderly patients with NAFLD stated a higher prevalence of CKD (54.8%) as compared to obesity (28.7%). This indicates, in addition to obesity and diabetes, NAFLD is also associated with decreased renal function(45). Meta-analysis documented increased prevalence (odds ratio [OR] 2.12, 95% CI:1.69-2.66) and incidence (HR:1.79, 95% CI:1.65-1.95) of CKD in NAFLD patients. Furthermore, this association becomes stronger as the fibrosis stage advances from simple steatosis to advance fibrosis(46).

A cohort study on 11,695 adults with 43.3 years as the mean age, stated the prevalence of CKD among NAFLD cohort as 11.31%. Moreover, moderate to advanced stages of CKD among NAFLD patients was associated with overall mortality indicating the importance of prognostic implication of identification of CKD among NAFLD patients(47). Another study assessing the association between NAFLD and CKD demonstrated the prevalence of NAFLD as 17.9% in CKD patients. The median duration of follow-up after scanning was 5.4 years, with a median estimated GFR of 33.5 mL/min/1.73 m<sup>2</sup> in this population. In contrast to this, significant role of NAFLD was seen in CKD progression. However, CKD patients having NAFLD were at increased risk of having cardiovascular disease. (HR 2.00; CI:1.10-3.66)(48). These studies indicate, CKD is common among patients of NAFLD, prevalence varying from 10% to 50%(46). Existing evidences suggest the presence of NAFLD accelerates the development and progression of CKD, regardless of other risk factors like HTN and T2DM.

### 1.4. Polycystic Ovary Syndrome (PCOS)

Epidemiological studies from the literature have shown that NAFLD and PCOS share a common set of risk factors and hence a potential link exist between the two endocrine conditions(49,50). The prevalence of NAFLD

within the PCOS population is now estimated to be anywhere between 15% and 55%, depending on the diagnostic index used for both NAFLD and PCOS(51). A cross-sectional study on 600 Caucasian women diagnosed with PCOS stated NAFLD was more prevalent in women with PCOS (50.6%) than in controls (34%)(52).

It is noticeable that the risk remains elevated even in non-obese and non-diabetics, suggesting the role of hyperandrogenism in the development of liver steatosis(53). A longitudinal study with a large primary care database, evaluated NAFLD rates among 63,120 women with PCOS and 121,064 age, BMI and location-matched controls. Women with PCOS had an increased rate of NAFLD with hazard ratio 2.23 (95%CI:1.86-2.66, p<0.001) than controls, even after adjusting for BMI or dysglycemia. Further, increased serum and decreased sex hormone-binding globulin was associated with increased NAFLD hazard ratio(54).

Limited studies are available in the reverse direction but a cross-sectional study stated that prevalence of PCOS was more prevalent among women with NAFLD (43.7%) as compared to non-NAFLD controls (23.1%)(55).

Possible explanation for coexistence of PCOS and hepatic steatosis is associated with insulin resistance. Hyperinsulinemia, as a result of insulin resistance, leads to hepatic steatosis and blockage of oxidation of mitochondrial fatty acids, which contributes to the production of inflammation, necrosis and fibrosis that forces the progression of NAFLD(56).

### 1.5. Stroke

As study on association between ischaemic stroke and liver stiffness, stated proportion of significant fibrosis was higher in stroke group (9.2%) when compared to control group (1.8%). The adjusted OR for ischemic stroke was 1.27 (95%CI:1.18–1.36) per 1 kPa increase and 12.03 (95% CI 5.18–27.95) for significant fibrosis, compared with no fibrosis (p<0.05). The trends follow the same pattern even after adjusting for BMI, the degree of hepatic steatosis, and metabolic(57).

A study on ischaemic stroke patients stated that 41.5% had fatty liver and 9% had significant fibrosis. The study documented increased risk of all-cause and cardiovascular-related mortality with a HR of 8.14 (95%CI:3.03-21.90) for all-cause mortality and a HR of 4.29 (95%CI: 1.10-16.73) for cardiovascular mortality during the follow-up period of 2.7 years. However, hepatic steatosis was not an independent predictor of mortality(58). The study demonstrated that incidence of progression and stroke severity, were significantly higher in patients with NAFLD (2.24, 95%CI: 1.25–4.01, p<0.01) than in those without NAFLD(59).

### 1.6. Liver and Other Cancers

Hepato-cellular carcinoma (HCC) is the fifth most common cancer worldwide and in terms of cancer-related death, it secures the second position. A study demonstrated, NASH-related HCC increased 7.7-folds (from 2.1% to

16.2%;  $p < 0.001$ ) in 15 years(60). Mathematical modelling suggested that NAFLD-related HCC prevalence is estimated to increase, from 47% in Japan to 130% in the US; similarly, its incidence is also estimated to increase, from 44% in Japan to 122% in the US(61).

This hepatic manifestation is not restricted to liver rather, risk of cancer related to various systems can be affected. A Korean study on NAFLD patient defined based on the fatty liver index (FLI  $\geq 60$ ) revealed higher gastrointestinal cancers. Over a period of approximately seven years stated 0.4% ( $n=3792$ ) developed oesophageal, 6.11% ( $n=57,292$ ) had stomach and 7.34% ( $n=68,769$ ) had colorectal cancer(62).

Another study documented the prevalence of NAFLD in breast cancer patients as 15.8% which was significantly higher than in healthy controls (8.9%). However, no difference in overall survival was seen between the groups with and without NAFLD(63).

### 1.7. Obstructive Sleep Apnea (OSA)

A prospective study, conducted over a period of 6 months, including patients of NAFLD noted snoring in 76% and excessive daytime sleepiness in 34% cases. Moreover, Berlin questionnaire for OSA was positive for 65% of the NAFLD cases, stating a higher prevalence of OSA in NAFLD group(64).

A recent meta-analysis with 2272 participants from 9 studies, demonstrated that OSA may predispose NAFLD patients to development and progression of liver steatosis in terms of liver enzymes and histological alterations as OSA was significantly associated with ballooning and hepatic fibrosis when compared to controls(65). Similarly, in another meta-analysis, OSA increased risk of developing NAFLD in patients with OSA by two-folds(66).

### 1.8. Osteoporosis

Low bone mineral density was seen at lumbar spine and femur neck in women with NAFLD as compared to controls(67). A study on Korean men revealed a significant negative relation between Femoral Neck Bone Mineral Density and NAFLD ( $\beta = -0.013$ ,  $p = 0.029$ ) whereas a positive correlation was seen between lumbar spine Bone Mineral Density and NAFLD in postmenopausal women ( $\beta = 0.022$ ,  $p = 0.005$ )(68) Evidences suggest, the prevalence of osteoporotic fractures are significantly higher in men with NAFLD (3.6 %) when compared with controls (1.7%). The existence of NAFLD was associated with increased odds of osteoporotic fracture (OR:2.53; 95%CI:1.26-5.07) in men after controlling for potential confounders. However, no significant association in prevalence of fractures and NAFLD was seen in women (3.4 vs. 2.6%)(69).

A systematic review from five studies with 1276 osteoporosis patients suggested 50% had NAFLD. Though significant association was seen between NAFLD and osteoporosis but the meta-analysis showed no significant difference in Bone Mineral Density between NAFLD patients and controls(70).

### 1.9. Psoriasis

The prevalence and severity of hepatic disease (55.8%) is higher among patients with psoriasis. A cross-sectional study on 439 patients suggested onset of psoriasis under the age of 40 years was independently associated with greater odds of NAFLD when compared to late onset (after 40 years)(71). Another study reported the higher prevalence of NAFLD in patients with psoriasis (44%) than in controls (26%). Evidence indicates that psoriasis is a significant independent predictor of advanced liver fibrosis. A systematic review on existing literature on 267,761 participants distributed over six studies suggested psoriatic patients exhibit increased risk of NAFLD as compared to their counterparts (OR:2.15;95%CI:1.57-2.94)(72). Both these conditions share multiple inflammatory and cytokine-mediated mechanisms and have genetic, clinical and pathophysiological features common with each other. Indeed, these suggest, the existence of multi-factorial mechanisms to explain their association.

### 1.10. Hypothyroidism

The alterations in the levels of thyroid hormones are mostly involved in various metabolic processes such as regulation of energy expenditure, body fat distribution, lipid utilization, and glucose homeostasis and have the potential factors to contribute to the development of NAFLD(73).

A retrospective cohort and a case-control study reported the relative risk of developing NAFLD in subclinical hypothyroidism patients is 1.27 (95%CI:1.09--1.47) and OR as 3.41 (95% CI:1.16-9.98)(74). A recent meta-analysis with a total of 12 cross-sectional studies revealed that hypothyroidism was associated with an increased risk of NAFLD with OR 1.42 (95%CI:1.15-1.77). However, meta-analysis of data from the three longitudinal studies documented subclinical hypothyroidism was not independently associated with risk of incident of NAFLD diagnosed by ultrasound over a median of 5 years with HR 1.29 (95%CI:0.89-1.86)(75).

## Conclusion

NAFLD is expected to become the most overwhelming liver disease in the world in coming years due to its prevalence and sequelae. Moreover, recent evidence indicates that NAFLD is a systemic disease, not just confined to liver- specific morbidity and mortality, but also associated with numerous extra-hepatic manifestations, such as metabolic syndrome, cardiovascular diseases, chronic renal diseases, and malignancy. In addition to these, NAFLD shares pathological association with Obstructive Sleep apnea, hypothyroidism, osteoporosis, PCOS, urolithiasis, and periodontitis. Hence, to reduce medical and economic impact associated with these comorbidities, knowledge about these associations need urgent attention. Thus, all countries can estimate and predict the burden on comorbidities associated with

NAFLD and galvanize its health resources in extensive multidisciplinary screening and should make use of integrated therapeutic approaches for management of NAFLD and related comorbidities at an early stage.

### Recommendation

Since NAFLD is strongly associated with the individual components of metabolic syndrome and other non-communicable diseases like chronic kidney disease, Polycystic ovary Syndrome, Stroke and Cancers, integrated therapeutic approaches for management of NAFLD and related comorbidities at an early stage would be beneficial in reducing the economic and medical burden

### Limitation of the study

The studies published in English language in Medline and through google search were included in this review. Studies published in other databases and in other languages have not been considered for the review.

### Relevance of the study

The study highlights the importance of utilizing integrated approaches for management of NAFLD and related comorbidities at an early stage.

### Authors Contribution

All authors conceptualized the ideas and designed the technical details, and performed the literature search for the existing review. AAR took the lead in writing the manuscript and AR and MP supervised the manuscript and contributed to the final version of manuscript.

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