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MAFLD-Epidemiology, Natural History, Outcomes and Prevention

Aimun Raees, Muhammad Kamran, and Wasim Jafri

ABSTRACT

Scientists have recently modified the term Non-Alcoholic Fatty Liver Disease (NAFLD) to Metabolic Dysfunction-Associated Fatty Liver Disease (MAFLD) in an attempt to improve the understanding and overall outcomes of the disease. The leaping prevalence and formidable mortality rate of fatty liver disease throughout the world is quite worrisome. Due to the lack of appropriate knowledge of the natural history of disease, suitable pharmacotherapy could never be devised. Thus, the management solely relies on patients' earnest co-operation with fierce lifestyle changes such as exercise, weight loss and dietary modifications. In this era, it is essential to come up with strategies to curtail the underlying risk factors in order to prevent the rapid progression of MAFLD. In this review, we will discuss the epidemiology of NAFLD and the newly found evidence on prevalence of MAFLD as well as the disease outcomes and preventive measures.

Keywords: Epidemiology, MAFLD, NAFLD, Natural history, Prevention.

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I. Introduction

A steady progress has been observed in the awareness of Non-Alcoholic Fatty Liver Disease (NAFLD) on account of its rising burden, yet no significant innovations could be achieved in the therapeutic field. A major part of this has always been attributed to the inadequacy of the term NAFLD, as it fails to narrate the associated metabolic factors of the disorder, rather shedding undue light on an unrelated etiology- Alcohol. To overcome the negative connotation linked to this title, various scientists collaborated to offer an upgrade in the nomenclature. Hence, the term Metabolic Dysfunction-Associated Fatty Liver Disease (MAFLD) was proposed, designed to represent the disease and underlying etiologies in a more approachable and positive way. The criteria brought forward to diagnose MAFLD includes evidence of hepatic steatosis on the basis of histopathology, imaging or biochemical markers in addition to obesity or type-2 Diabetes Mellitus (T2DM) or at least two metabolic abnormalities [1].

Fig. 1 shows the diagnostic criteria for MAFLD.

Since its introduction, MAFLD has been under substantial scrutiny, slowly making its way towards replacing the old term NAFLD. As this terminology is fairly new and most of the available data is on NAFLD, therefore both these terms may be used interchangeably in this article owing to the similarities of both medical conditions.

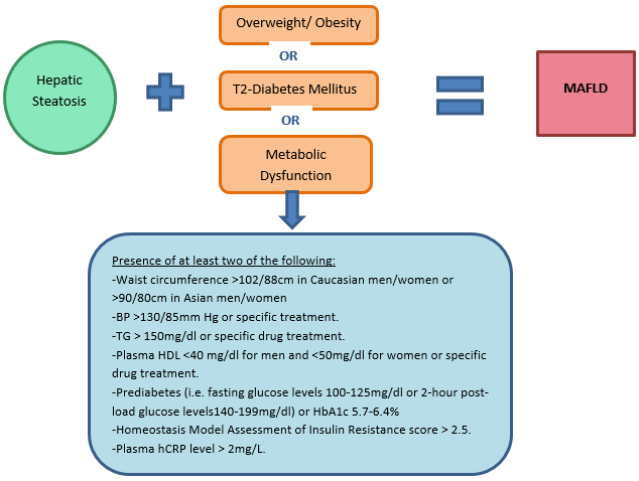

Fig. 1. Diagnostic criteria of MAFLD.

II. Epidemiology

MAFLD is a multi-system disease that stems from interaction between metabolic, environmental, and behavioral factors on the background of genetic predisposition. The data on MAFLD alone is scarce as its still under the process of being accepted as an updated term for NAFLD. Globally, owing to the soaring pandemic of obesity and type-2 Diabetes Mellitus (T2DM), MAFLD has swiftly become the leading cause of end stage liver disease in all age groups along with hepatocellular carcinoma (HCC) and an

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indication of liver transplant [2], [3]. As of now, approximately 25% of the world's population is estimated to have NAFLD but its prevalence greatly varies according to regional differences as well as exposure to risk factors. Overall, prevalence is noted to be highest in Middle East, while in Asia, NAFLD seems to be the most prevalent in China [4].

Table I shows region wise prevalence of NAFLD in descending order.

TABLE I: REGIONAL PREVALENCE OF NAFLD

S. No.	Region	Prevalence
1	Middle East	31.79% [3]
2	South America	30.45% [3]
3	China	36.83% [5]
4	Asia	27% [4]
5	North America	24.13% [3]
6	Europe	20-23.7% [3]
7	UK	20.7% [6]
8	Africa	13.48% [3]

Table II shows prevalence of NAFLD according to associated risk factors.

TABLE II: NAFLD PREVALENCE IN VARIOUS GROUPS AT RISK

S. No.	Population At Risk	Prevalence
1	Morbid Obsecity	95% [7]
2	Hyperlipidemia	90% [8]
3	T2DM	57.80% [9]
4	Children	3-10% [10]
5	Obese Children	40-70% [10]

According to a recent meta-analysis, the global prevalence of lean NAFLD is 9.7% [5]. Exact prevalence of Non-Alcoholic Steato-hepatitis (NASH) is unknown due to lack of histological data. However, estimated prevalence of NASH in overall population ranges from 1.5-6.45% [6]. Among morbidly obese patients going through bariatric surgery, NAFLD prevails in over 95% whereas 20-50% are found to have NASH and 10% have fibrosis [7]. As per the National Health and Nutrition Examination Survey (NHANES), the prevalence of MAFLD in the United States from 2011 to 2018 was 34.8% with a higher percentage in men compared to women (38.5% versus 31.1%). MAFLD was more prevalent in older age, increasing from 23.2% for age 18-39 years to 43.8% in individuals older than 60 years. Concomitant liver disease was found in 7.6% patients that included 0.5% chronic hepatitis-B, 1.6% chronic hepatitis-C and 5.5% alcoholic liver disease [8]. The prevalence of MAFLD in Chinese population was found to be 26.1% [9]. Overall, the prevalence of MAFLD is predicted to shoot up exponentially in the coming years due to the increase in metabolic disorders alongside sedentary lifestyle. A recent study that used Markov model has demonstrated that the incidence of decompensated cirrhosis is expected to rise 168% by 2030 while that of HCC will increase by 137% [10].

III. NATURAL HISTORY AND OUTCOMES OF MAFLD

The true course of fatty liver disease is obscure, due to paucity of evidence on histologically proven disease and high risk of selection bias encountered while performing analysis of patients with liver biopsies. Nevertheless, NAFLD is considered a slowly progressive disorder that may not always result in end-stage liver disease. It evolves from steatosis without hepatitis to non-alcoholic steatohepatitis (NASH) that may eventually turn in to advanced fibrosis with associated hepatic and extra hepatic complications.

Generally, the histologic progression from one stage of fibrosis to another takes about 14.4 years in NAFLD and approximately 7 years in NASH [11]. Studies have shown that about 10-30% of patients with NAFLD may progress to NASH and out of those, 10-15% may develop cirrhosis over a period of 10-20 years [12]. Silent cirrhosis is revealed in about 10% patients on histological analysis. In decompensated cirrhosis, the prognosis is indistinguishable from other causes of chronic liver disease [13]. Risk of developing HCC is not very high in patients with NAFLD, about 0.44/1000 person years whereas among individuals with NASH, the incidence of HCC jumps up to 10-fold, estimating 5.29/1000 person years [14], ranging from 2.4% over 7 years to 12.8% over 3 years [15].

Fig. 2. represents the natural history of the fatty liver disease.

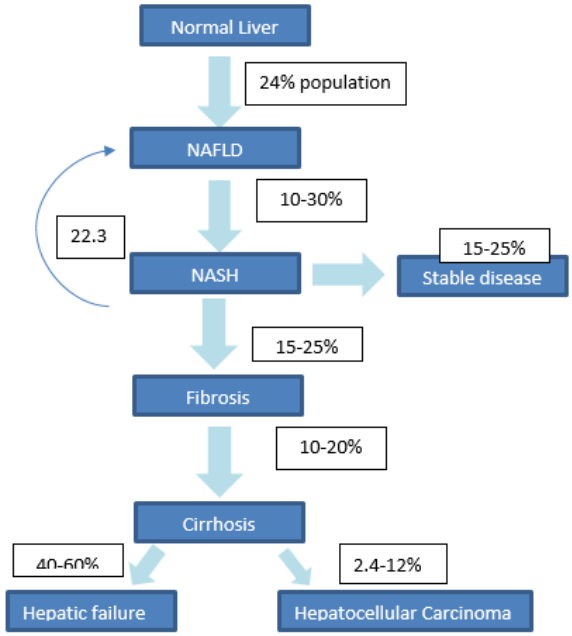

Fig. 2. Depiction of natural history of fatty liver disease.

Besides metabolic factors, aging, race, ethnicity, genetic and environmental risk factors have also been implicated in the disease process [16]. A synergistic effect between all of these mediates the overall progression of the disease. Knowledge and identification of these risk factors is important as it permits a personalized approach to advocate preventive strategies or pharmacotherapy as progression of MAFLD is subjected to alterations in these risk factors.

Studies have emphasized that visceral obesity, rather than BMI alone, is a more accurate predictor of severity of NAFLD. Dysfunctional and hypertrophied adipocytes activate macrophages and increase level of inflammatory cytokines such as interleukin-6 and Tissue necrosis factor-Alpha, directly affecting insulin resistance, which eventually leads to worsening of steatosis. The importance of visceral adipocyte accumulation can also be proved by the entity lean NAFLD, where patients with low BMI develop insulin resistance and liver damage due to high visceral adipose

tissue content and associated lipotoxicity and insulin resistance [17], [18]. According to a study, NAFLD was reported in 3-30% of non-Obese individuals, especially among Asian population [19]. The significance of obesity in the pathogenesis of disease progression also supports the diagnostic criteria for MAFLD. The estimated global burden of MAFLD among obese adults to reported to be as high as 51.3% in a recent meta-analysis [20].

Insulin resistance is directly proportional to the severity of histological lesions as well as fibrosis progression. It also serves as a potent link between T2DM and NAFLD. According to data, NAFLD is found in about 75% of diabetic patients while 25% of patients with NAFLD have T2DM [21]. The risk of hospitalization also escalates up to 3-5 folds in diabetic patients who have chronic liver disease secondary to NAFLD. The probability of HCC development is 2-4 times higher in patients with T2DM irrespective of other risk factors [22]. Consequently, screening of NAFLD in T2DM and vice versa was recommended [23]. As insulin resistance is one of the key driving factors for hepatic fat accumulation, therefore it has rightly been added as a major criterion for diagnosing MAFLD.

Emerging data has proved that environmental and genetic risk factors are as crucial as clinical factors in predicting fibrosis progression. According to the third NHANES study [24], Hispanics were found to have a significantly higher risk of NAFLD development while as per inter-ethnic studies, the risk was intermediate in Europeans and lower in Africans, independent of confounders [25]. Genetic polymorphism has also been highlighted as a determinant of susceptibility to MAFLD as well as steatosis severity. The most critical one is the palatin-like phospholipase domain-containing 3 (PNPLA3) gene, that accounts for a higher risk of disease in Hispanic population [26]. It has been described as an independent cause of hepatic steatosis irrespective of metabolic risk factors [27]. Early hepatic decompensation and development of HCC has also been linked to the homozygosity of this mutation [28], [29]. Other mutations responsible for regulating hepatic lipid content include Transmembrane 6 superfamily member-2 (TM6SF2) [30], Membrane bound O-Acyl Transferase 7 (MBOAT7) [31], Glucokinase regulator (GCKR) [32], LIPA gene [33], 17-beta hydroxysteroid dehydrogenase-13 (HSDL7B13) [34] and Protein phosphatase 1 regulatory subunit 3b (PPR1R3B) [35]. The last two serve as protective mutations while PNPLA3, TM6SF2 and MBOAT7 have a crucial part in amplifying the impact of MAFLD on hepatic outcomes [36]. Arterial hypertension, sarcopenia and environmental toxins exposure have also been related to worse disease outcomes.

Growing evidence suggests that NAFLD is a heritable disorder as the chances of progression seem to be greater in first degree relatives of NAFLD related chronic liver disease in comparison to general population, irrespective of risk factors [37]. The role of epigenetic changes is under experiment as few studies have displayed a positive correlation between disturbances in fetal and infancy and acquiring NAFLD in later life [38], [39]. Dysregulation of micro-RNA (mi-RNA) was shown to have an impact on both hepatic steatosis and fibrosis. [40]· Imbalance in gut microbiota may increase susceptibility to NALFD by enhancing free fatty acids absorption and increased bacterial permeability in small bowl, which in turn alters fat and glucose metabolism by generating inflammatory cytokines and activating Farnesoid X-receptors [41].

Fig. 3. depicts the associated risk factors and outcomes of MAFLD.

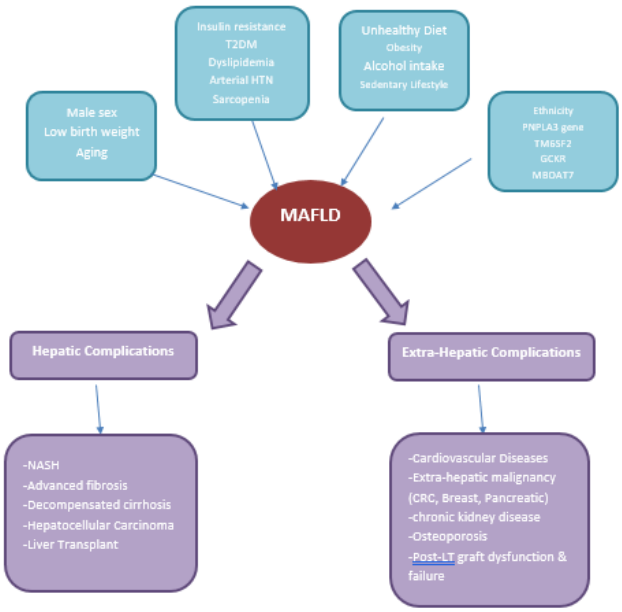

Fig. 3. Representation of risk factors and outcomes of MAFLD.

IV. Mortality

The rate and cause of mortality is greatly variable according to the stage of fibrosis. NAFLD alone may not have a great impact on mortality rate, but the prognosis differs as it transitions into subsequent stages. Regardless, patients with fibrosis always have a poor survival than patients without fibrosis [42]. According to a recent meta-analysis, the estimated all-cause mortality rate ratio for stage-I fibrosis was 1.58, worsening in accordance to fibrosis stages 2, 3, 4 to 2.25, 3.48 and 6.40, respectively [43]. Due to the identical predisposing factors, a strong correlation is found between fatty liver disease and cardiovascular disorders. The cumulative incidence of all-cause mortality was higher in MAFLD-group (26.2%) than in NAFLD-only group (10.6%) [44]. Among patients with NAFLD without or early NASH, cardiovascular events are seen to be the most frequent cause of death followed by extra-hepatic cancers and then liver related events [45]. Previously, a meta-analysis by Targher *et al* [46] had reported an odds ratio of 1.31 for fatal cardiovascular diseases in patients with NAFLD. Recently, in the largest nationwide cohort study done in Korea, Lee et al evaluated the incidence of cardiovascular adverse effects by using definitions of both NAFLD and MAFLD. Besides finding a higher prevalence of MAFLD, it was also noted that the hazard ratio for cardiovascular events escalated stepwise from 1.09 in the NAFLD group to 1.43 in the MAFLD group [47]. Another extra-hepatic outcome of MAFLD is the growing numbers of chronic kidney disease (CKD) among this group, that poses a negative effect on the overall prognosis of a patient [48]. NHANES 2017-2018 highlighted that the chances of developing CKD in MAFLD patients were much higher although there was no independent association

between the two. A recent cross-sectional study done on the data from NHANES-III revealed a considerably greater prevalence of CKD in individuals with MAFLD when compared to NAFLD group (29.60% versus 26.56%) [49].

Patients who have developed fibrosis, liver-related mortality is more predominant with an estimated rate of 11.77/1000 person years [50], [51]. Besides mortality, NAFLD-related cirrhosis and HCC have also become one of the most leading causes of liver transplantation in the West. Over the past decade, the need of liver transplant due to NAFLD has risen by 170% [52], [53]. According to a recent cohort study, the incidence of diabetic patients requiring liver transplant for decompensated cirrhosis due to NAFLD was 305/100,000 person years [54]. Contrary to the common belief that HCC is not very common in fatty liver disease, recent data reported a surge in the burden of HCC secondary to MAFLD [55]. HCC essentially contributes to death as demonstrated by a substantial rise in HCC-related mortality rate for NAFLD (19.1%) [56].

V. Prevention

Histological staging and fibrosis are the determinants of prognosis, in association with the metabolic factors. Management of the disease is thus aimed at slowing the progression of disease by altering the modifiable risk factors.

All the scientific societies have concurred that weight loss is the most effective step in modifying disease process. Therefore, the recommended first line measure against fatty liver disease is physical activity along with consumption of a healthy diet [57]. Long term follow-up studies have demonstrated a positive effect of weight loss on both histological activity and fibrosis scores [58]. A dose-dependent response is observed between the amount of weight loss and change in histological stage. A 5% weight loss has been linked [59] with steatosis improvement while 10% reduction in weight leads to fibrosis regression [60]. In another prospective study, reduction in BMI and waist circumference were identified as independent factors for fibrosis regression and stable liver disease activity, noted in 25% and 48% of patients, respectively [61]. Bariartic surgery aids in accelerated weight loss and has been put forward as a suitable therapeutic modality, due to its favorable effect on liver histology. However, some studies also showed worsening of fibrosis [62]. The data available is not enough to draw conclusions and randomized control trials are needed to validate the true outcomes of bariatric surgeries. Endoscopic placement of intra-gastric balloons (IGB) is another less-invasive intervention that assists in weight reduction. Lately, a meta-analysis done on the patients with MAFLD undergoing IGB placement demonstrated significant improvement in the metabolic parameters of the disease. It is imperative to note that the merits of weight loss have been observed in both obese and lean patients [63].

The quality of diet plays a pivotal role in the development of MAFLD. Consumption of diet rich in saturated fats and fructose and poor in polyunsaturated fatty acids, fiber and antioxidants have deleterious effects on health. High glycemic index foods cause prolonged hyperglycemia and increase circulating insulin levels thus enhancing lipogenesis and hepatic fat accumulation [64]. Fiber deficiency in diet may alter gut microbiota eventually adding to hepatic fat burden [65]. Therefore, a high fiber diet, with low fat and carbohydrate content is recommended. To achieve that, Mediterranean diet has been proposed as a healthy eating choice. Increased consumption of vegetables, fruits, nuts, whole-grains, legumes and fish and low intake of red meat and alcohol are the characteristics of Mediterranean diet. A randomized study indicated that liver fat was relatively reduced by 40% in patients who consumed Mediterranean diet [66].

Physical activity itself, irrespective of weight loss, has illustrated beneficial effects on hepatic steatosis [67]. Exercise increases hepatic clearance of insulin and reduced its secretion from pancreatic cells and also activates AMPK5 (5'-Adenosine Monophosphate-activated Protein Kinase). Aerobic exercise is especially linked with diminished visceral obesity thus improving histological endpoints in MAFLD [68]. No predefined criteria exist regarding duration or intensity of workout required to produce favorable outcomes, but vigorous exercise alone was able to induce a notable reduction in NASH [69]. Combination of diet restriction and exercise has a more remarkable outcome than either of these alone.

Achieving these intense lifestyle modifications is quite hard and sustaining-even harder, hence a compulsion to devise pharmacotherapy arises for at least the progressive form of disease. Several drugs based on the commonly associated metabolic factors have been thoroughly investigated, from lipid lowering agents to hypoglycemic drugs, ursodeoxycholic acid and probiotics but none of these have had a remarkable effect in altering the course of disease. Vitamin-E based on its antioxidant properties succeeded in reducing hepatic steatosis but failed to have an impact on fibrosis. Nevertheless, it has been recommended for an off-label use, in patients with NASH without T2DM [70], [71]. Recently, a Farnesoid-X receptor agonist, Obeticholic acid, has demonstrated promising results in the improvement of both hepatic steatosis and fibrosis, confirmed via histological analysis [72]. FDA approval of this drug is eagerly awaited.

VI. Conclusion

In essence, the burden of NAFLD is overwhelming. The prevalence of the disease may increase even further once the diagnostic criteria of MAFLD will be put into use fur future studies. As per a recent study, MAFLD was able to capture more patients accurately in comparison to NAFLD, having a direct impact on the overall prevalence of the disease [73]. It is unfortunate that the disease that was once considered to be benign is currently on a trajectory to be the most leading etiology of decompensated cirrhosis, hepatocellular carcinoma, and liver transplant worldwide. The morbidity and mortality associated with extra-hepatic components such as cardiovascular events and extra-hepatic malignancies is also alarming. The heterogeneity observed in the course of the disease makes it even more challenging and incommodious. Therefore, as long as target pharmacotherapy is not available, vigilant screening and early preventive measures are required to curb the disease before it blooms. Awareness regarding the nature of disease and counseling sessions to emphasize on the vigorous life-style modifications

are mandatory. Further research is crucial to improve the understanding of the disease in order to provide better therapeutic strategies.

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