Review Article

Fatty liver disease - non alcoholic to metabolic - A transition of concepts!!

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Abstract

Metabolic dysfunction associated fatty liver disease (MAFLD) was a concept suggested lately. Initially, the only criterion for the diagnosis of MAFLD was the absence of alcohol intake. With rising prevalence and studies assessing this condition, certain "positive criteria" were put forth. Experts from 22 countries proposed a simple yet comprehensive definition for the condition independent of other liver diseases. The presence of hepatic steatosis in addition to diabetes mellitus type 2, metabolic dysregulation, and obesity is generally observed. Criteria to define MAFLD-associated cirrhosis were also proposed. Reaching an agreement on MAFLD criteria will help define a protocol (for example: for International classification of Diseases (ICD) - coding), which will improve clinical care and advance the clinical and scientific field of liver research. As it is a condition that increases the risk of diabetes mellitus, chronic kidney disease (CKD), cirrhosis, hepatocellular carcinoma, and cardiac disorders it is important to recognize it at an early stage which makes it essential part of family medicine and primary care.

Keywords: Hepatic steatosis, MAFLD, metabolic dysregulation, obesity

Background

"MAFLD or metabolic dysfunction associated fatty liver disease" is a new term coined for nonalcoholic fatty liver disease (NAFLD). A total of 25% of the population suffers from it thereby making the disease an economic burden and major health problem.[1,2] A rise in the number of cases has been observed due to a sedentary lifestyle and unhealthy diet.[3] Given the prevalence and the lack of clear terminology to explain liver disease in a nonalcoholic population, an international panel of experts proposed coining this phenomenon as "MAFLD".[4] Initially, excluding excess alcohol intake and chronic liver disease was essential for the diagnosis of MAFLD. With a better understanding of the pathogenesis, the need for a set of criterion was put forth.

At present, the criterion for diagnosis of MAFLD is steatosis in more than 5% of hepatocytes in the absence of recent or ongoing alcohol consumption or other causes of liver disease.[5,6]

Biopsy, blood biomarkers/imaging in addition to one of the three criteria (overweight/obesity, diabetes mellitus type 2, and metabolic dysregulation) have been proposed for the diagnosis of MAFLD. Ultrasonography (USG) is used as first-line diagnostic modality but provided sub-optimal results in patients with a BMI of >40 kg/m^2. Vibration-controlled transient elastography or fibro scan can be used. The area under the curve of 0.87 is used for the diagnosis of steatosis with biopsy for a reference standard.[7] Magnetic resonance imaging (MRI) and computed tomography (CT) can be used for the diagnosis of moderate to severe steatosis. Magnetic resonance spectroscopy may be

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used for fat estimation in the liver but has limited availability. MRI-derived proton density fat fraction is more practical and is hence used in clinical trials.[8] No serum biomarker have been isolated as such but in given time with further studies, these may replace imaging modalities. In the current scenario, this is of utility for large epidemiological studies with markers like fatty liver index (FLI).[6] There are three criteria for defining MAFLD, obesity being one of them. Obesity can be classified as metabolically healthy obesity and metabolically unhealthy obesity[9] MHO and MAFLD have a significant risk of developing hepatic fibrosis.[10] About 70% of the patients with type 2 diabetes mellitus have MAFLD.[11,12] Patients with MAFLD who are persistently metabolically unhealthy but not obese are at a higher risk of cardiovascular disease and liver damage.[13] Progression from steatosis to bridging fibrosis occurs concurrently with transition through steatohepatitis.[14]

Pathogenesis

The presence of fibrosis, rather than any histological characteristic of Non-alcoholic steatohepatitis (NASH), is the most important predictor of poor outcome. Significant mortality does not occur with Early F1 fibrosis, but the incidence increases with increasing stages like bridging fibrosis (F3) and cirrhosis (F4).[15] The development of fibrosis is relatively slow in NAFLD than with NASH.[16] Age, increased basal metabolic index (BMI), and diabetes are all risk factors for progressive illness. Cardiovascular disease is the leading cause of death. A "multi-hit" model [Figure 1] integrating numerous interlocking processes, such as lipotoxicity, innate immune activation, and the micro-biome has supplanted the "two-hit" concept, which included genetic and environmental components[17]

NAFLD the name

NAFLD was first classified as a diagnosis of exclusion, meaning it only arises when other disorders such as viral hepatitis B and C, autoimmune diseases, or alcohol use above a certain threshold are not present. However, as our understanding of the underlying pathological processes improves, it is obvious that it is a disease that should be defined by inclusion rather than exclusion. Fatty liver disease is very well-known, owing to its high incidence in most affluent nations, particularly those that consume a westernized diet. This new understanding must be reflected in the terminology for fatty liver disease and the diagnostic criteria.

Second, the safe limit of alcohol consumption is still a point of contention. Updating a NAFLD diagnosis to zero or near-zero alcohol intake, as some have urged, is clearly impossible as addressed lately. Furthermore, there are significant methodological challenges in questionnaires used to measure alcohol consumption, such as documenting prior and lifetime use, low amounts of intake, patient underreporting, and recall bias as well as the potential for coexistence with other conditions such as viral hepatitis, autoimmune diseases, and alcohol with synergistic effects on disease progression. Adaptive experiment, though this will introduce significant diversity in defining concepts like "social drinking" and "bingeing" in people with NAFLD. It's problematic to link metabolic fatty liver disease, which is a separate entity to alcohol in its name. Furthermore, incorporating the term "nonalcoholic" in the name is discouraging to abstinent patients and associates this entity with the stigma of alcoholism. Confusing terms in the names of these disorders should be replaced with sometimes redundant but more accurate and straightforward ones as has previously been done with primary biliary cirrhosis becoming primary biliary cholangitis. More critically, it is critical to recognize concurrent metabolic and alcohol liver disease so that proper treatment can be provided. Patients with pure or predominant alcoholic cirrhosis are not included in this group. Patients with NASH are currently excluded from all clinical trials.

Third, while we divide patients into those with NASH and those without in clinical practice, whether this is appropriate is a point of contention. As we all know, metabolic liver disease has a lot of plasticity over time, and there's a lot of evidence that fibrosis is a big factor in poor outcomes. As a result, the existing classification may be misleading, and metabolic dysfunction-associated fatty liver disease should be treated similarly to other chronic liver illnesses with some activity and fibrosis stage, rather than being classified as NASH or non-NASH. This will improve disease classification from a pathological standpoint, at least in the setting of liver biopsy.

Fourth, because fatty liver disorders are so diverse, they can't be considered or treated as a single problem with a "one-size-fits-all" treatment approach. Our capacity to clearly describe the natural history of fatty liver phenotypes, to adequately select for clinical trials that are weighted to demonstrate meaningful benefits, and to compare or pool outcomes from the trials is hampered by a lack of consideration of heterogeneity. For these reasons, establishing an updated and acceptable disease nomenclature is the first step toward the deconvolution of disease heterogeneity.

The majority of respondents in the first round of the survey suggested that the words "metabolism, fat, and liver" be included in some form in the name based on the above; the majority of respondents in the second round of the survey suggested that the words "metabolism, fat, and liver" be included in some form in the name based on the above. As a result, the panel recommends that the word "NAFLD" be dropped from the vocabulary and replaced with "metabolic associated fatty liver" (MAFLD). The name "MAFLD" refers to the overarching umbrella of the common disease we treat, and it will be divided into sub-phenotypes based on the disease's primary cause. Obviously, many, if not all, patients will have overlapping contributions from other, different liver illnesses ranging from alcoholism (in any quantity) to viral hepatitis. These people's natural histories are likely to be quite different from those who have a pure metabolic disorder.[18]

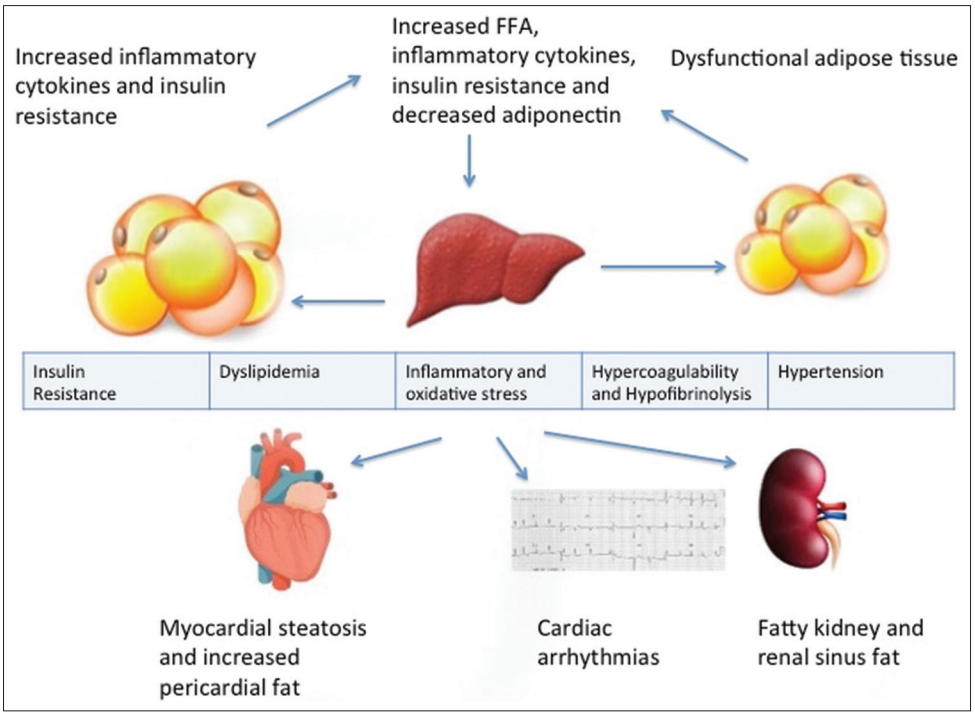

Figure 1: The hypothesized pathways behind NAFLD's contribution to an elevated risk of cardiovascular disease (CVD), chronic kidney disease (CKD), and various structural and arrhythmic cardiac consequences are depicted in this diagram. Because of the complex and intertwined interactions between NAFLD, abdominal obesity, and insulin resistance, determining the specific role of the liver and the underlying mechanisms responsible for the link between NAFLD and the risk of developing CVD, CKD, and other structural cardiac complications (e.g., aortic valve sclerosis, cardiac dysfunction/hypertrophy, CHF, and AF) is extremely difficult. Such issues may be linked to NAFLD as a result of common cardiometabolic risk factors and co-morbidities, or as a marker of ectopic fat deposition in other organs. For example, cardiac steatosis and increased pericardial fat volume, as well as fatty kidney and increased renal sinus fat volume, might have local deleterious effects on the myocardium and kidneys, resulting in structural and functional derangements. However, emerging data suggest that NAFLD is not only a simple marker of vascular/cardiac and renal damage, but also may have a role in the pathogenesis of CVD, CKD, and other cardiac problems in this risky and complex setting. Through the hepatic synthesis of lipids, atherogenic lipoproteins, induction of hepatic/peripheral insulin resistance, and dysglycemia, NAFLD may directly contribute to the development and progression of these vascular/cardiac problems and systemic release of inflammatory mediators

Associated factors

1. NAFLD and Diabetes Mellitus Type 2 diabetic patients are at a threefold higher risk of developing a chronic liver disease which is mainly attributable to MAFLD.[19] Imbalance between energy utilization and energy intake causes adipose deposition in the body. When this occurs at sites not designed for the accumulation of fat, it is called ectopic fat deposition. The liver is one such site and this, in turn, causes inhibition of insulin signaling, increased gluconeogenesis, decreased glycogen synthesis, and secretion of hepatokines.[20] Insulin resistance, in turn, causes chronic inflammation, fibrosis, cirrhosis and may lead to hepatocellular carcinoma. Fibroblast growth factor, tumor necrosis factor (TNF)- a, C-reactive protein (CRP), fibroblast growth factor, interleukin (IL)-6, and retinol-binding protein-4 directly affect carbohydrate metabolism and insulin signaling.[21]
2. NAFLD, cardiac diseases, and CKD: Several studies have established an association between cardiovascular disease (CVD) and NAFLD as observed by F-fluorodeoxyglucose positron emission tomography.[22] Patients with NAFLD have epicardial fat deposition and impaired myocardial energy metabolism as measured by P-magnetic resonance spectroscopy. Early changes in myocardial substrate mechanism producecardiac structural and functional changes which may precipitate heart failure. Two cohort studies have shown raised liver enzymes in patients with heart failure.[23] Framingham Heart Study cohort showed mildly elevated liver enzymes in patients with atrial fibrillation[24] Several other studies have shown a direct association of NAFLD with AF.[25]

Multiple studies have associated CKD with NAFLD. USG and biopsy have been used to diagnose NAFLD. Patients with cirrhosis and end-stage renal disease were excluded from the study. An association was established between NAFLD and stages of CKD.[26] CKD, CVD, and NAFLD share common risk factors, therefore, making this a multisystem disease with multiple bidirectional and cause-effect relationship.

Discussion

NAFLD is generally a condition that has no specific presentation. Most of the symptoms are either incidental in nature or are associated with varied conditions. These conditions as described above are frequently associated with nonalcoholic fatty liver disease and are thus predominantly of importance when

suspecting this pathology. Diabetes is one of the most commonly associated comorbidity and is likely to present with increased frequency of micturition, increased thirst, hunger, tingling and numbness, nonhealing ulcer, and other complications if uncontrolled. Cardiovascular conditions may present with chest pain, breathlessness, palpitations, syncope, *paroxysmal nocturnal* dyspnea (PND), orthopnea, sweating, or dry cough. Decreased urine output, malaise, breathlessness, and edema may be the likely presenting features seen in patients with chronic kidney disease. Evaluation of NAFLD involves evaluating risk factors that may precipitate its development. History of conditions like myocardial infarction, angina, heart failure, stroke or other cardiovascular disease symptoms in the past. Family history of type 2 diabetes mellitus or early ischemic heart disease typically in an age group of 55 years in males and 65 years in females, especially first-degree relatives. Co-morbidities like diabetes mellitus type 2 (fasting glucose level of 7 mmol/L or HbA1c of 6.5 percent, 2 - h glucose level of 11.11 mmol/L during a 75 - g OGTT, or "random" glucose level of 11.11 mmol/L in the context of hyperglycemic symptoms), hyperlipidemia (mostly hypercholesterolemia or atherogenic dyslipidemia; exclude the existence of familial hypercholesterolemia if LDL cholesterol >4.9 mmol/L), obesity (defined for Europeans as a BMI of 30 kg/m^2 or a waist circumference of 102 cm in men and 88 cm in women), hypertension (i.e., blood pressure ≥140/90) and metabolic syndrome. Metabolic syndrome is a disorder in which the metabolism is disrupted (as described by the International Diabetes Federation and the American Heart Association/National Heart, Lung, and Blood Institute in 2009). Chronic kidney disease (eGFR 60 mL/min/1.73 m^2 and/or inappropriate albuminuria) is a condition in which the kidneys do not function properly. Smoking in itself can be considered as an independent risk factor in the development of nonalcoholic fatty liver disease. Examination of the patient is key in confirming any risk factor thought to have precipitated its development. Hence, height, weight, BMI, general examination findings, and systemic examination are important for the proper evaluation of the case. Laboratory investigations like complete blood count, liver and renal function tests, fasting lipid profile, urine routine and microscopy, electrocardiogram, ultrasound of the abdomen, carotid doppler in addition to other relevant parameters must be done to confirm the diagnosis and decide the appropriate modality of management.[25] Recognition of these factors and NAFLD is important in early diagnosis and management in primary care facilities as a result of the various effects that contribute to morbidity and mortality among patients.

NAFLD - How to tackle

Planning a diet

Carbohydrates: Low carbohydrate diet is more effective for weight loss in comparison to high carbohydrate diet.[27] Restricting carbohydrate intake to less than 50 gm/day causes rapid weight loss due to ketosis, breakdown of glycogen, and fluid loss. A low carbohydrate diet has an early weight-independent effect on hepatic steatosis.[28] meals with a high glycemic index were found to be associated with high-grade liver steatosis, which was assessed by ultrasound in particularly insulin-resistant subjects.

Fructose: fructose alters the gut microbiome, increases gut permeability, causes hyperuricemia and endotoxemia. It is mainly derived from corn syrup and table sugar.[29]

Fat: polyunsaturated fatty acids (n-3 and n-6) are present in fish oil. N3 puff down-regulates Sterol-regulatory element binding protein-1C (SREBP-1c) and up-regulates peroxisome proliferator-activated receptors (PPAR)- alpha that favor fatty acid oxidation and decrease steatosis.

Protein: high protein diet stimulates thermogenesis and causes satiety thereby improving weight management. Processed red meat and total red meat are both positively associated with increased risk of coronary artery disease.[30]

A high fiber diet increases incretin secretion, increased satiety, decreases absorption of CHO and protein, increases fermentation products, and modulates gut microbiota.

Increased coffee consumption is assisted with increased risk of cirrhosis and progression of fibrosis but not statuses. Coffee consumption is associated with a low risk of metabolic syndrome.[31]

Intermittent fasting: time-restricted feeding (TRF) and alternate day fasting are used as approaches for weight loss.

Therefore, a calorie restriction of 500-1,000 kcal/day and a low carbohydrate, low fat, and high protein diet is recommended.

Physical activity

Daily exercise attenuates the diet-induced loss of muscle mass which in turn increases physical functioning and insulin sensitivity. Resistance exercises and aerobic exercises both are effective in decreasing liver fat. Resistance exercises help prevent reduction in muscle mass and bone mass. The American heart association of intense cardiorespiratory activity recommends at least 150 minu per week of physical exertion or at least 75 min is adapted by European Association for the Study of the Liver (EASL) for NASH.[32]

Conclusion

Morbidity and mortality are a result of the conditions associated with NAFLD. It has now been established as an independent risk factor for type 2 diabetes mellitus. It also contributes to the progress of CKD and cardiac diseases. The possibility of *hepatocellular carcinoma* (HCC) with NAFLD being the only risk factor requires further evaluation. Therefore, the main approach to control underlying risk factors hyperlipidemia, diabetes mellitus, obesity, and other co-morbidities. Weight loss and later weight maintenance are key to preventing long-term complications.

Emerging therapeutic measures: Mostly a lifestyle disorder very few modalities have been developed to adequately target this condition. Energy disposal, lipotoxic liver injury, energy intake, and various other mechanisms responsible for cirrhosis in such patients make targeted drug therapy difficult to implement without lifestyle modifications. At present, modalities like angiotensin receptor blockers, statins, pentoxifylline, n-3 PUFA (poly unsaturated fatty acids), and vitamin E have proved to be effective. Further studies are required in order to assess other therapeutic strategies that might be beneficial in this condition.[33]

Summary

1. Nonalcoholic fatty liver disease is now referred to as MAFLD.
2. A "multi – hit" model integrating numerous interlocking processes, such as lipotoxicity, innate immune activation, and the micro-biome are considered in its pathogenesis.
3. Associated factors are diabetes mellitus Type 2, cardiac diseases, and CKD.
4. A calorie restriction of 500-1000 kcal/day and a low carbohydrate, low fat, and high protein diet are recommended along with the physical activity.
5. HCC with NAFLD may occur in some cases and thus makes it important to assess among patients.

Take home message

MAFLD has an increasing prevalence in the general population. Its early recognition in association with other risk factors is essential for optimal management of the patient. With rising morbidity and mortality as a result of its complications, it is crucial to screen patients as early as possible making it an important part of Family medicine and primary care.

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Conflicts of interest

There are no conflicts of interest.

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