Review article

Non-Alcoholic Fatty Liver Disease and Type 2 Diabetes Mellitus: A Global Problem Including Bangladesh Perspective

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Abstract:

Nonalcoholic fatty liver disease (NAFLD) is commonly associated with type 2 diabetes mellitus (type 2 DM). The global prevalence of NAFLD is rising and 70% of these patients have type 2 DM, obesity and insulin resistance. NAFLD progresses from simple steatosis to non-alcoholic steatohepatitis (NASH), cirrhosis of the liver and hepatocellular carcinoma. In BANGLADESH, the prevalence is the same. NAFLD prevalence is higher in the urban population, because of their lifestyle, obesity and increasing incidence of type 2 DM. Assessment and staging of disease are based on clinical parameters such as age, sex, BMI, liver function test, lipid profile and imaging modalities. In response to these threats, clinical care pathways for NAFLD and guidelines for metabolic dysfunction associated with fatty liver disease have been improved in developed countries. But in Bangladesh, pathways for NAFLD are still not developed. Several anti-diabetic agents have been evaluated for their potential hepatic benefits with some hopeful results. However, despite the wealth of knowledge in NAFLD and type 2 DM, lack of awareness of the disease and its consequences remains a major challenge, especially for clinicians. Because they may not be in the field of hepatology and gastroenterology. We proposed the urgent necessity of NAFLD management and awareness of NAFLD.

Key words: Nonalcoholic fatty liver disease, type 2 diabetes mellitus, non-alcoholic steatohepatitis, cirrhosis of the liver, hepatocellular carcinoma.

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Introduction

Nonalcoholic fatty liver disease (NAFLD) is one of the leading causes of chronic liver disease in Bangladesh as well as other parts of the world. One-fourth of the world's population, impacting approximately 1 billion people is affected by this condition.[1] Non-alcoholic fatty liver disease (NAFLD) refers to the condition in which excessive amounts of fat accumulates in the liver in non-alcoholic persons which results in the development of chronic liver disease. It encompasses a number of conditions that includes progressive steatosis, non-alcoholic steatohepatitis, cirrhosis and hepatocellular carcinoma (HCC).[1,2] The pathogenesis and progression of NAFLD are complex involving multiple environmental and genetic factors.[1] Insulin resistance, found in patients with obesity, type 2 Diabetes Mellitus & metabolic syndrome is strongly associated with NAFLD.[3] Diagnosis of NAFLD is done usually in the absence of any secondary cause for steatosis by various invasive and noninvasive tests.[4] Compared with non-diabetic subjects, people with type 2 diabetes appear to have an increased risk of developing NAFLD and have a higher risk of developing fibrosis and cirrhosis.[4] According to the latest report from the International Diabetes Federation, 10.5% of the world's adult population have diabetes.[5] According to the National guideline of Bangladesh on diabetes mellitus 2023 edition-"13.1 million of the total population with a prevalence being 14.2% in the adult population". This incidence has increased from 15% in 2005 to 25% in 2010. So, the illness is expected to become the primary cause of liver failure shortly.[2] About

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70% of type 2 diabetic patients may have some form of NAFLD, but the exact prevalence is unknown.[4] A recent meta-analysis has found that patients with type 2 DM have two times more risk of NAFLD development than that of the general population. The incidence has already reached to nearly 60% and one third of them presented with NASH.[5] Since, the incidences of NAFLD & DM are rising and they are often co-existed, it is logical to think that it will continue to rise. Evidence from the past decade clearly indicates that NAFLD is responsible for the increased risk of hepatic events as well as that of other extra-hepatic systems (especially the cardiovascular system).[6] Moreover, the sedentary lifestyle, and the escalating prevalence of type 2 diabetes are projecting that, a notable increase in NASH-related hepatic phenomenon by 2030 will be more evident. These alarming incidences are calling for a comprehensive public health response to combat this global health crisis, among the clinicians especially hepatologists, primary care physicians, diabetes care providers, and endocrinologists.[5] Because there are very small number of studies related to NAFLD in diabetic patients more comprehensive and detailed studies are needed in this field to know about the prevalence and clinical spectrum of NAFLD in diabetic patients in Bangladesh with a view to preventing the social & economic burden in the long run.[4]

Therefore, the objective of this review is to investigate the recent prevalence of NAFLD associated with type-2 diabetes in the Bangladeshi population, to highlight the established management and to create awareness among our clinicians.

Epidemiology

Both NAFLD and Diabetes are interlinked non-communicable diseases that have been increasing in an alarming way and have become major threat globally as well as in Bangladesh.

The global incidence of NAFLD has consistently increased from 15% in 2005 to 25% in 2010. Currently the incidence of NAFLD is 25%. The illness is expected to become the primary cause of liver failure in the near future.[2] Among children, NAFLD affects approximately 3% to 10%, increasing to 40% to 70% in obese children.[7] The prevalence of NAFLD is 75% and 90% in obese and morbidly obese patients respectively and present in a high proportion (ranging 50%-75%) of patients with Type 2 Diabetes Mellitus.[3]

Diabetes mellitus is observed in 18%-45% NAFLD patients.[8] NAFLD is the most common liver condition in Western countries, affecting over 30% of the general population.[9]

Non-alcoholic steatohepatitis has become the third most prevalent etiology underlying liver transplantation in the United States, following hepatitis C and alcoholic liver disease.[10] An ultrasonographic study of patients with T2DM showed a 69% prevalence of NAFLD in Europe(4). Increasing incidence of NAFLD is reported in Asian countries like Japan and China.[8] NAFLD in Asia pacific region differs from that of western countries. An estimated 7%-19% persons in these regions with BMI <25 have NAFLD. Between 2019 and 2030, NAFLD cases are expected to increase 6%-20% in Singapore and South Korea, Hong Kong, Taiwan.[11]

According to National guideline of Bangladesh published in 2023, "there are 13.1 million of patients suffering from Type 2 DM with a prevalence of 14.2% in the adult population. By 2045, it is projected to move to the 7th position affecting 22.3 million people."[12] The prevalence of NAFLD in rural adult population of Bangladesh is 33% and is associated with female gender, obesity and features of metabolic syndrome.[13]

Pathogenesis

Role of hormones, nutrients and intestinal dysbiosis

High-fatty foods and sugars cause activation of opioid and dopamine receptors in the nucleus accumbent, responsible for the development of cravings. That causes an imbalance between high energy intake and energy expenditure results in obesity which is the major risk factor for non-alcoholic fatty liver disease.[14,15] Additionally, the macronutrient fructose is hypothesized to increase cerebral blood flow to areas of the brain involved in motivation and reward.[16] The activation of reward centers causes systemic reduction in gut-derived hormones that promote feelings of satiety, e.g., Glucagon Like Peptide 1 (GLP-1), as well as an increase in gut-derived hormones that stimulate hunger (e.g., ghrelin).[16,17] Consequently, overeating and failure to obtain satiety cause obesity. Moreover, pre-clinical studies suggest that diets rich in sucrose and fructose provoke intestinal dysbiosis or disruption of lipid metabolic pathways and hormones. All these may contribute to NAFLD development.[18] Also, these gut-derived hormones were found to be linked to increased circulating triglyceride levels, which contribute to the development of NAFLD.[19]

The role of insulin resistance, lipotoxicity and hepatic inflammation in disease

In the context of NAFLD, both elevated insulin levels and impaired insulin sensitivity play a central role.[20] In NAFLD patients, the development of insulin resistance manifests through several mechanisms: 1) enhanced lipolysis leading to elevated circulating free fatty acids available for hepatic uptake, 2) diminished hepatic glycogen storage and 3) increased gluconeogenesis. This systemic insulin resistance may be accompanied by or preceded by, hyperinsulinemia which amplifies hepatic de novo lipogenesis pathways.[21] The cumulative effect is increased intrahepatic lipid accumulation and

elevated secretion of very-low-density lipoproteins. This heightens lipid burden then circulates to adipose tissue, further exacerbating the diminished capacity of adipocytes to store these lipids in lipid droplets. As a result, hepatocytes expose to lipotoxic lipids. This lipo-toxicity further disrupts insulin signaling, induces oxidative damage, and stimulates inflammation and fibrosis.[22] These consequences are believed to drive the progression from NAFLD to NASH, as well as the development of fibrosis and HCC in patients with NAFLD.

The Contribution of Genetic Elements

The findings of Makkonen et al. provide strong evidence that genetic factors contribute to non-alcoholic fatty liver disease.[23]

Diagnosis

Non-alcoholic fatty liver is typically diagnosed initially by ultrasound, quantified by controlled attenuation parameter in routine clinical practice and by magnetic resonance imaging in research studies. [24]

Biopsy

Liver biopsy continues to be the predominant clinical standard for diagnosis, despite its limitations pertaining to sampling inconsistency, invasive procedure, and high financial burden.[25] Currently, despite the invasive nature of the procedure, liver biopsy is widely regarded as the gold standard for diagnosing non-alcoholic steatohepatitis and non-alcoholic fatty liver with mild inflammation, and non-alcoholic steatohepatitis, and of definitively assessing the presence or absence of even low-grade liver fibrosis.[26]

Non-Invasive Imaging

Ultrasound-based transient hepatic elastography has demonstrated superior interobserver consistency, minimal sampling error, hence it has emerged as the first clinically feasible bedside approach for reliably assessing liver fibrosis. In patients with suspected liver fibrosis the test should be conducted immediately following abdominal ultrasound and routine laboratory testing.[27]

MRI-derived proton density fat fraction measurements help to detect hepatic fat content without the need for supplementary spectroscopy equipment.[28]

Biomarkers

Contemporary biomarkers for fibrosis such as FibroTest®, ELFTM, or Pro-C3 tests, as well as the identification of inflammation (such as circulating keratin 18 fragments etc.) help differentiate between patients with non-alcoholic steatohepatitis and advanced liver fibrosis, fibrosis progression over time and offer long-term prognosis.[29]

A recently reported noninvasive lipidomic serum test that uses two panels of triglycerides that accurately distinguish between NAFLD and NAFL, as well as between NASH and NAFL.[30] In situations where imaging techniques are not accessible or practical, serum biomarkers and assessment scores can serve as alternative methods for diagnosing steatosis, which is marked by a 2 to 4 fold increase in transaminases level.[24] Up to 78% of patients may have normal transaminases with AST/ALT ratio being typically less than 1. However, these levels can increase as the underlying fibrosis progresses.[25] Additionally, alkaline phosphatase and GGT concentrations may be heightened, yet the serum bilirubin level, prothrombin time, and serum albumin level are typical, except in the case of cirrhosis.[31]

Management

As we are concerned about both NAFLD and its association with TYPE 2 DM and their progression to life-threatening complications, in this review treatment options are mentioned based on limited available data on the management of NAFLD.

The management includes treatment of liver disease along with the associated metabolic comorbidities such as obesity, diabetes mellitus and hyperlipidemia and monitoring the disease progression. The mainstay of NAFLD treatment includes Lifestyle modification importantly, dietary restriction with increased physical activity and drug therapy.[6]

As patients with NAFLD without steatohepatitis or any fibrosis have excellent prognosis from a liver standpoint, pharmacological treatments aimed primarily at improving liver disease should generally be limited to those with biopsy-proven NASH and fibrosis.[27]

Non-Pharmacological Management

Alcohol abstinence

Since the effects of light and moderate alcohol consumption on disease progression are not clear, it is better to abstain from alcohol intake. [27]

Dietary modifications and exercise

To improve steatosis, one must lose at least 3% to 5% of his body weight. But losing greater than 7% to 10% of the body weight offers more improvement in histopathological features of steatohepatitis including fibrosis.

Weight reduction can be greatly achieved by a hypocaloric (daily reduction by 500-1000 kcal) and low-fat diet along with moderate-intensity aerobic

exercise. In different studies, this combination (diet and exercise) has shown effective results in reduction of weight, transaminase activities, hepatic steatosis & NAFLD activity score in obese patients with T2DM and NASH.[27,32] So, clinicians should emphasize on patient education about intensive lifestyle intervention along with pharmacological therapy.

Pharmacological

Pharmacological management is usually reserved for the patients who fail to obtain sufficient and sustained weight loss after lifestyle modifications.

PPAR Agonists

Peroxisome proliferator-activated receptors (PPARs) are ligand-dependent nuclear receptor proteins that play major roles in lipid and glucose metabolism. All three PPAR isoforms – PPARα, PPARβ/δ, and PPARγ – are implicated in the pathogenesis of NASH and hepatic fibrosis.[33]

Type	Tissue distribution	Effects	Synthetic agonists
PPARα	Liver, Muscle, Heart, Kidney	Fatty acid oxidation, Anti-inflammatory	Gemfibrozil, Fenofibrate, Clofibrate
PPARβ/δ	Ubiquitous, Muscle, Gastrointestinal tract, Adipose tissue, Macrophage, Heart	Glucose homeostasis, Insulin sensitivity	GW501516, GW0742
PPARγ	Adipose tissue, Liver, Kidney, Intestine	Adipogenesis, Insulin sensitization, Glucose homeostasis, Fatty acid oxidation	Thiazolidinediones

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Dual and pan-PPAR agonists

PPARα/γ and their agonists

PPARα/γ agonists are called glitazars. In NAFLD, Saroglitazar was found to be more effective than pioglitazone and fenofibrate for histological NASH regression in a mice model.[34]

PPARα/δ and their agonists: Elafibranor did not significantly resolve NASH in its phase III trial.[4]

pan-PPAR agonists:

Among several investigational pan-PPAR, Bezafibrate showed improvement in NAFLD and diabetes in mice models.[33]

Thyroid Hormone Receptor-B Agonists

US FDA approved Resmetirom, on March 14, 2024, for treating adult patients with NASH and hepatic fibrosis along with diet and exercise. (US FDA)

Incretin - Based Therapy

DPP-4 Inhibitors

DPP4 inhibitors were resulted in improved glycemic control with improving transaminase activities in a study of patients with ultrasonographic steatosis. It has shown effective reduction in hepatic triglyceride as measured by MRS in a study.[4]

GLP-1 Agonists

Glucagon-like peptide1 (GLP1) analogs can result in improved hepatic events significantly by weight loss. As NAFLD involves hepatic de novo lipogenesis, GLP-1 agonists directly inhibit lipogenesis in hepatocytes as a result, there is notable improvement noticed in insulin action in hepatocytes and adipose tissue.[4]

Treatment with liraglutide has shown a promising outcome in LEAN study in 2016. Tirzepatide, a dual agonist of GLP-1 and glucose-dependent insulinotropic polypeptide, remarkably improved transaminase activities, NASH marker and fibrosis marker in type 2 diabetes patients.[33]

A pilot study on short-acting GLP-1Ra exenatide produced a positive effect on liver histopathology.[6] Exenatide also resulted in an increased insulin sensitization in differentiated hepatocytes in patients with NASH.[4]

Sodium–Glucose Cotransporter 2 Inhibitors ("Glifozins")

Sodium-glucose cotransporter 2 inhibitor (SGLT2i) has already achieved extensive recommendation for use in type 2 diabetes patients because it has significant cardiac and renal benefit simultaneously. A meta-analysis came to a conclusion that SGLT2i significantly improved ALT levels and MRI proton density fat fraction. It is suggested that gliflozins may be useful in managing diabetes with fatty liver.[33]

Insulin Sensitizers

Metformin is not recommended for treating the patients with NASH.[27]

Farnesoid X Receptor (Fxr) Agonist

Recently Obeticholic acid has been reported to foster NASH remission in a phase II trial.[6]

Vitamin E

According to the PIVENS trial, Vitamin E acts as an antioxidant and it has improved hepatic enzymes, steatosis, inflammation and ballooning (except fibrosis) and NASH resolution has been prompted in 42% of patients.[4]

Lipid-Lowering Agents

Several studies reported an improvement in transaminase activities, fatty liver assessed by ultrasound and hepatic steatosis with statin treatment in patients with NAFLD or NASH. But the effects on necroinflammation were varied and fibrosis did not improve. Moreover, treatment with simvastatin did not affect transaminase activities or hepatic histology.[32]

Orlistat

In studies, Orlistat has been found to cause weight reduction, improved in transaminase activities, hepatic steatosis and fibrosis.[32]

Bariatric Surgery

Patients who are diagnosed with non-cirrhotic NASH and remain unresponsive to lifestyle intervention and other pharmacotherapy are the candidate for bariatric surgery.

Liver Transplantation

The only suggested treatment option for NASH-related end-stage liver disease (ESLD) and non-resectable HCC is liver transplant. It is astonishingly growing as an indication for NAFLD treatment.[35]

Monitoring

Every patient should be assessed at regular intervals to ensure that they have been able to achieve an optimum therapeutic response and to monitor disease progression, especially hepatic fibrosis.

Clinical and Laboratory[36]

- Patient should be monitored at least for every 6 months for the following -
    - Measurements of body weight, body mass index, waist circumference to see targeted weight loss.
    - Serum liver tests (transaminases, γ-glutamyl transpeptidase and alkaline phosphatase)
    - Serum metabolic tests (glucose, triglycerides, total and high-density lipoprotein cholesterol, insulin)

Monitor for fibrosis[37]

It is recommended to monitor these patients via noninvasive imaging (abdominal ultrasonography, VCTE) every 3 years.

Conclusion

The increasing prevalence of NAFLD makes it a big public health problem. NAFLD is usually associated with Type 2 DM and vice versa. NAFLD takes years to progress from steatosis to advanced liver disorders such as cirrhosis and hepatocellular carcinoma. It is gold standard practice to tailor a treatment plan to optimize the metabolic control to maintain and improve the liver phenotype. In Bangladesh, the prevalence of T2DM among the adult population is about 14% and among them majority have NAFLD. So, diabetic care providers should focus more on NAFLD and promoting the implementation of clinical care pathways through policymakers and stakeholders in the government and healthcare institutions. The underlying causes of NAFLD and its progression in T2DM should be evaluated and the result of newer antidiabetic and identification of additional targets require future research.

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