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New Anti Hyperglycemic Drugs on Metabolic Associated Fatty Liver Disease: A Mini Review

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Abstract

Non-alcoholic fatty liver disease is a chronic condition characterized by the accumulation of fat in the liver. Steatosis, defined by fat accumulation in more than 5% of hepatocytes, is an active status that can regress or progress to liver cirrhosis. Therefore, an early diagnosis and treatment are critical to prevent an irreversible condition. Metabolic-associated fatty liver disease has been proposed as a more appropriate term to describe the liver disease associated with metabolic dysfunction. There is a gap in pharmacotherapy for earlier stages of non-alcoholic fatty liver disease. These new diagnostic criteria will encourage the initiation of drugs that promote weight loss early to prevent irreversible damage. The European Association for the Study of the Liver have been proposed different models that combine clinical and biochemical parameters to improve both, the diagnosis and early approach. Weight loss is the more straightforward strategy to improve prognosis. It is necessary to achieve a 7%-10% weight loss to improve most of the histopathological features, including fibrosis. The new antihyperglycemic drugs glucagon-like peptide 1 receptor agonists and sodium-glucose cotransporter 2 inhibitors may improve liver histology and clinical outcomes, mainly through weight loss and improved insulin resistance.

Keywords: Fatty liver; Steatosis; Fatty liver index; Hepatic steatosis index

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Introduction

Non-Alcoholic Fatty Liver Disease (NAFLD) is a chronic condition characterized by the accumulation of fat in the liver without excessive alcohol consumption, steatogenic drugs, or monogenic hereditary disorders [1]. The worldwide estimated prevalence of NAFLD is above 25%, but in subjects with type 2 diabetes is around 60% [2]. Isolated steatosis, defined by fat accumulation in more than 5% of hepatocytes, is relatively benign. However, when steatosis coexists with inflammation and deposition of collagen fibers, the condition term is Non-Alcoholic Steatohepatitis (NASH) [1]. NASH is an active status that can regress to isolated steatosis or progress to liver cirrhosis. Therefore, an early diagnosis and treatment are critical to prevent an irreversible condition.

From NAFLD to MAFLD: The “Multiple Hit Model”

Which is the mechanism of the progression from steatosis to steatohepatitis? The "two-hit hypothesis" tries to explain the pathophysiology [3]. The “first hit” corresponding to steatosis is related to increased liver fat through hepatic triglycerides accumulation and insulin resistance. Liver fat occurs due to hyper caloric diets and sedentary lifestyles in genetically predisposed subjects. The "second hit" includes activating inflammatory cytokines, adipokines, mitochondrial dysfunction, and oxidative stress. So, the “multiple-hit model” theory, involving the interaction of genetic and environmental factors as well as changes in crosstalk between adipose tissue, pancreas, gut, or liver in a genetically predisposed patient, better encompasses the syndemic model [4]. However, obesity and insulin resistance still seems to represent the “first hit."

In this regard, Metabolic-Associated Fatty Liver Disease (MAFLD) has been proposed as a more appropriate term to describe the liver disease associated with metabolic dysfunction [5]. The diagnosis of MAFLD requires the presence of hepatic fat accumulation as demonstrated by histology, imaging, or serum biomarkers and one of the following three criteria, overweight/obesity, type 2 diabetes mellitus, or evidence of metabolic dysregulation. Metabolic dysregulation requires two of the following:

- Waist circumference ≥ 102/88 cm in Caucasian men and women or ≥ 90/80 cm in Asian men and women, respectively.

- Blood pressure ≥ 130/85 mmHg or specific drug treatment.
- Plasma Triglycerides ≥ 150 mg/dL (≥ 1.70 mmol/l) or specific drug treatment.
- Plasma HDL-cholesterol <40 mg/dL (<1.0 mmol/L) for men and <50 mg/dL (<1.3 mmol/L) for women or specific drug treatment.
- Prediabetes (i.e., fasting glucose levels 100 to 125 mg/dL (5.6 to 6.9 mmol/L), or 2-hour post-load glucose levels 140 to 199 mg/dL (7.8 to 11.0 mmol) or HbA1c 5.7% to 6.4% (39-47 mmol/mol).
- Homeostasis model assessment (HOMA-R) score ≥ 2.5.
- Plasma High-Sensitivity C-Reactive Protein (hsCRP) level >2 mg/L.

There is Metabolically Healthy Obesity (MHO) and Metabolically Unhealthy Obesity (MUHO). Individuals with MHO are not protected from the development of cardiometabolic complications and remain at high risk for the development of hepatic fibrosis [6]. As MAFLD is commonly associated with overweight/obesity, this criterion would help us identify most patients with steatosis/steatohepatitis in routine care. The American Association for the Study of Liver Diseases (AASLD) guidance suggests that drugs should be limited to patients with NASH and fibrosis [7]. Consequently, there is a gap in pharmacotherapy for earlier stages of NAFLD. The new diagnostic criteria defining MAFLD will encourage the initiation of drugs that promote weight loss early to prevent irreversible damage.

Diagnostic Tools

Image tools

Liver biopsy-based assessments remain imprecise and are not without cost or risk to diagnose and monitor steatosis/fibrosis. Additionally, its scoring is associated with a significant inter and intra-observer variability.

Liver imaging is one of the most often used tools to diagnose moderate and severe steatosis/fibrosis. Ultrasound has the drawback of a limited sensitivity since it does not reliably detect steatosis when it is <20%. In addition, ultrasound is sub-optimal in subjects with a body mass index (BMI)>40 kg/m2. Elastography (FibroScan®) is an alternate image system with better ability than ultrasound to detect liver steatosis or fibrosis. It also needs a special transductor to screen very obese subjects. However, elastography has a reported area under the receiver characteristic curve of 0.70 for steatosis, using liver biopsy as the reference standard. Magnetic resonance quantifies hepatic steatosis by measuring the Proton Density Fat Fraction (PDFF), the fraction of MRI-visible protons bound to fat divided by all protons in the liver (bound to fat and water). Although MRI-PDFF is a highly accurate, reliable, and diagnostic tool for quantifying hepatic steatosis in NAFLD, its use in patients with more advanced liver disease is limited by the severity of fibrosis present. Since fibrosis has no molecular signature that current imaging techniques can detect, MRI-PDFF is weaker at fibrosis stage 4 [1].

Laboratory tests

Laboratory tests to diagnose the presence of steatosis/steatohepatitis and fibrosis include peripheral blood cell counts, and measurements of albumin, Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), Gammaglutamyl Transpeptidase (GGT), Alkaline Phosphatase (ALP), fasting glucose, fasting insulin, total cholesterol and triglyceride levels, glycosylated hemoglobin A1c (HbA1c), Free Fatty Acid (FFA), and ferritin among others. Type VI collagen 7S domain and hyaluronic acid correlated well with the degree of liver fibrosis among patients with NAFLD compared with several clinical variables [1].

Elevated hsCRP is predictive of T2DM and Cardiovascular Disease (CVD) and is a risk factor for steatosis. hsCRP can discriminate between steatosis and severe NASH and is associated with underlying fibrosis. ALT and hsCRP may reflect different aspects of the pathogenic process, and their mutual reduction may represent separate treatment effects [8].

Clinical and biochemical markers for the diagnosis of steatosis

The European Association for the Study of the Liver, the European Association for the Study of Diabetes, and the European Association for the Study of Obesity advocate using serum biomarkers for first-line risk stratification of steatosis [1]. Therefore, they proposed different models that combine clinical and biochemical parameters. Fatty Liver Index (FLI) and Hepatic Steatosis Index (HSI) are easy and accurate algorithms to predict the presence of steatosis. An FLI value <30 or >60 rules out/in steatosis with high sensitivity and specificity [9]. Similarly, an HSI value <30 rules out steatosis, and a value >36 is indicative of steatosis [10].

Interventions leading to decrease adiposity and weight reduce FLI and HSI values in longitudinal studies [11].

Non-invasive test for the diagnosis of steatohepatitis/fibrosis

There is a need to develop and test non-invasive biomarkers for the detection of liver fibrosis. In clinical practice, the NAFLD Fibrosis Score (NFS) [12] and the Fibrosis-4 index (FIB-4) scoring systems [13] run well to exclude advanced fibrosis. Thresholds for high and low NFS were >0.676 and ≤ -1.455, and for high and low FIB-4 were >2.67 and ≤ 1.30, respectively. The Enhanced Liver Fibrosis (ELF) test is another non-invasive biomarker test that highly correlates with aminotransferase levels and reveals a significantly high association with inflammation. The ELF test evaluates the impact of treatment directed at the underlying causes. Finally, the Hepamet Fibrosis Scoring System (HFS), another non-invasive test, discriminates between patients with and without advanced fibrosis with an AUROC of 0.85 shows the scores more useful in clinical practice to diagnose steatosis/steatohepatitis/fibrosis (Table 1) [14].

Table 1: EScores more useful in clinical practice to diagnose steatosis/steatohepatitis/fibrosis.

Score	Parameters and biomarkers	Cutt-off values	Sensibility (S)	Specificity (E)	
Fatty Liver Index (FLI)	BMI, WC, Tg, GGT	<30 rules out >60 rules in	87%	86%	Steatosis
Hepatic Steatosis Index (HSI)	ALT, AST, BMI, Sex (female), T2DM	<30 rules out	93%	92%	Steatosis
Steatotest	α2-macroglobulin, apolipoprotein A1, haptoglobin , GGT, Total Bilirrubin, Tg	<0.3 rules out >0.7 rules in	85%	80%	Steatosis
NAFLD Fibrosis Score (NFS)	Age, BMI, Hyperglycemia, Platelets count, Albumin, Tg	<-1.455 rules out >0.675 rules in	88-93%	82-90%	Steatohepatitis/ Fibrosis
Fibrosis-4 calculator (FIB-4)	Age, alt, AST, Platelets count	<1.30 rules out >2.67 rules in	97%	81%	Steatohepatitis/ Fibrosis
Hepamet Fibrosis Scoring System (HFS)	Age, Sex (Female), Albumin, T2DM, HOMA, Platele countts	<0.12 rules out >0.47 rules in	74%	97.20%	Steatohepatitis/Severe Fibrosis

Abbreviations: ALT: Alanine Transaminase; AST: Aspartate Transaminase; BMI: Body Mass Index; GGT: Gamma-Glutamyltransferase; HOMA: Homeostasis Model Assessment; T2DM: Type 2 Diabetes Mellitus; Tg: Triglycerides; WC: Waist Circumference.

The future

The advances in novel serum markers, including cytokeratin 18 fragments (CK18-F) and insulin-like growth factor-1 (IGF-1), have shown desirable performance in routine screening for NAFLD [15]. Nevertheless, a recent study shows that the well-validated biomarker panels for diagnosing different stages of NAFLD, such as simple steatosis, steatohepatitis, and advanced fibrosis, may underperform in patients with type 2 diabetes. The study suggests that patients with type 2 diabetes will require tailored specific prediction models of fibrosis. However, it may be late to take action in reversing the fibrosis stage. Therefore, it is crucial to detect steatosis and steatohepatitis to prescribe an effective treatment before developing fibrosis.

Treatment: What is the Best Moment to Start it?

The American Association for the Study of Liver Diseases (AASLD) guidance suggests that drugs should be limited to patients with NASH and fibrosis [7], leaving a gap in pharmacotherapy for an earlier stage of NAFLD. However, there are several factors easily detected at the office to prompt the diagnosis of MAFLD. The presence of type 2 diabetes and obesity, the rise in Gammaglutamyltrasferase, and the increase in the concentration of triglycerides suggest the presence of MAFLD. Weight loss is the more straightforward strategy to improve MAFLD prognosis. It is necessary to achieve a 7%-10% weight loss to improve most of the histopathological features of MAFLD, including fibrosis. The new antihyperglycemic drugs glucagon-like peptide 1 receptor agonists (GLP1RA) and sodium-glucose cotransporter 2 inhibitors (SGLT2i) may improve liver histology and clinical outcomes in NAFLD/MAFLD, mainly through weight loss and improved insulin resistance.

Glucagon-like peptide 1 receptor agonists (GLP-1RA)

In a recent randomized, placebo-controlled trial, liraglutide administered once daily reduced the progression of liver fibrosis. The patients on liraglutide showed a mean ± SD reduction of 5.5 ± 4.9% of body weight [16]. Liraglutide showed potential efficacy in improving liver histology and metabolic syndrome associated with NAFLD in patients with or without type 2 diabetes [17]. Compared with sitagliptin, pioglitazone or placebo liraglutide caused a more comprehensive weight loss. Exenatide also proved helpful in producing significant weight loss from baseline in patients with NAFLD and type 2 diabetes [18]. Dulaglutide administered once weekly showed improvement in liver enzymes consistent with a reduction in liver fat compared with placebo in a posthoc analysis of the AWARD program [19]. Semaglutide, another weekly administered GLP1-RA, reduced AST and hsCRP as markers of NAFLD in patients with obesity and, or, type 2 diabetes [20]. In a phase 2 trial involving patients with NASH, semaglutide once a week resulted in a significantly higher percentage of patients with NASH resolution than placebo, without a significant between-group difference in the rate of patients with an improvement in fibrosis stage [21]. In a phase 2b study, Cotadutide, a dual GLP-1 and glucagon receptor agonist, was used in subjects with overweight/obesity and type 2 diabetes showing improvements in lipid profile, AST and ALT levels, propeptide of type III collagen level, FIB-4 and NSH scores [22].

Sodium-glucose cotransporter 2 inhibitors (SGLT2i)

Data on the effect of SGLT2i on human liver fat content are scarce. Dapagliflozin, empagliflozin, and canagliflozin demonstrated improvements in hepatic steatosis and attenuation of liver fibrosis after twenty-four weeks of treatment [23-25]. In clinical trials in human subjects, ipragliflozin reduced liver fat at 12 weeks in patients with T2DM and NAFLD, as estimated by FLI scores [26].

GLP1RA plus SGLT2i in combination

Regarding GLP1RA and SGLT2i used in combination, a post-hoc analysis of the Duration 8 trial suggests that the combination could effectively reduce liver steatosis and potentially improve NASH and fibrosis in patients with type-2 diabetes [27]. In our recent report, these combination treatments improve serum enzyme levels and liver steatosis scores. The most significant reduction in liver biomarkers occurred in subjects with weight loss between 5-10% or higher. Moreover, more significant changes were achieved when both drugs were added to the previous treatment schedule than when both drugs were started simultaneously [11].

GLP1RA plus iSGLT2 for MAFLD: Beyond Glycemic Control NAFLD is a Metabolic Liver Disease (MAFLD) Closely Related to Type 2

NAFLD is a Metabolic-Associated Fatty Liver Disease (MAFLD) closely related to type-2 diabetes and obesity. The common substrate underlying is a state of chronic low-grade inflammation. The use of GLP1RA and SGLT2i reduces the values of inflammatory parameters like hsCRP, proinflammatory cytokines like Interleukin-6 or TNF-alfa; in addition, there is a decrease in reactive oxygen species and inhibition of AMPc activation [28]. The improvement correlates with reductions in body weight, waist circumference (the “first two-hit"), and inflammatory parameters.

Results and Discussion

Based on the literature, GLP1RA and SGLT2i demonstrated efficacy in treating steatosis/steatohepatitis without fibrosis. When treating patients with MAFLD, it is essential to understand the risk factors and the continuum disease. In addition to type-2 diabetes and obesity, metabolic dysregulation is the continuum key player. Our efforts should go to the prevention of the progression to advanced NASH. Few therapies are available, and as such, there is a substantial unmet clinical need. The beneficial effect of GLP1RA or SGLT2i on liver steatosis goes beyond glucose control, and it is driven predominantly by weight loss. The efficacy of GLP1RA and SGLT2i combination significantly reduce biomarkers such as hepatic amino transaminases, triglycerides, high-sensitivity C-reactive protein, or intra-abdominal fat. For many patients, early detection and intervention are essential to improving outcomes in MAFLD and could allow us to select the most efficient treatment options.

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All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published

Author’s Contributions

All authors contributed to the study conception and design. The first draft of the manuscript was written by Carretero Gómez J and Ena J and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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