Diabetes Updates

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Diabetes and MAFLD: Antidiabetic Medications and the Therapeutic Potential for Improving MAFLD

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Abstract

Non-alcoholic fatty liver disease (NAFLD) is the hepatic manifestation of the metabolic syndrome that affects more than half of people with type 2 diabetes mellitus (T2DM). At this time, there are no FDA- approval therapies for nonalcoholic steatohepatitis (NASH). According to worldwide standards, lifestyle modification is the cornerstone for treatment of NAFLD.

Until now, many anti-diabetics medicines have been examined in patients with NAFLD due to the shared epidemiological and pathophysiology aspects between both diseases. The rationale for such investigations, as well as their outcomes, are discussed in this review.

Introduction

NAFLD is the most common chronic liver disease that affects up to 25.2% of people globally with a greater prevalence among patients with T2DM (55.5%) [1]. NAFLD encompasses a wide range of conditions, from mild steatosis to nonalcoholic steatohepatitis (NASH) and cirrhosis [2].

Experts agreed that NAFLD does not accurately reflect current knowledge, and metabolic (dysfunction) associated fatty liver disease (MAFLD) was recommended as a more appropriate overarching term [3].

Although clinical trials end-points for NAFLD have changed over the years, liver biopsy is still remains the gold standard for diagnosing and assessing of NAFLD. However, due to the invasive nature of liver biopsy and patient apprehension. it is rarely used in clinical trials, posing a significant hurdle to treatment development in NAFLD As a result, several noninvasive serum biomarkers or imaging modalities have been developed for diagnosing or assessing response to treatment for NAFLD, and they are increasingly used benefitted to define endpoints in clinical trials [4].

Because NAFLD and T2DM share many epidemiological and pathophysiology aspects, several antidiabetic medications have been investigated in NAFLD patients throughout the years. The reasoning for these investigations, as well as their findings, are reviewed in this review.

Metformin

Metformin is an insulin sensitizer that has been exposed to improve insulin resistance (IR) and it is considered a first-line oral medicine for the treatment of T2DM, according to global recommendations [5].

Metformin has been noticed to improve the biochemical and histological aspects of NAFLD as mentioned previously [6]. Metformin has also been proven to influence the synthesis of tumor necrosis factor and interleukin-6, which helps to prevent fat accumulation in the liver by increasing β-oxidation of free fatty acids and reducing de novo lipogenesis [7].

For around a year, Bugianesi et al [8] investigated 110 non-diabetic nonalcoholic fatty liver disease patients who were administered either metformin or vitamin E or diet (a control group). This study indicated that ALT levels of patients who received metformin were considerably lower. Also, follow-up biopsies of 17 patients revealed improvements in steatosis, necroinflammation, fibrosis, and the NASH index.

The TONIC trial, a well-designed randomized controlled trial which enrolled 173 non-diabetic patients with biopsy-proven NAFLD and a sustained elevation in ALT levels detected that metformin administration didn't reduce ALT levels and has no effect on liver histology when compared to placebo [9].

It was distressing to learn that metformin medication was less successful in alleviating liver fibrosis in NAFLD patients in some research trials [10,11]. Despite its smaller effects on liver fibrosis, metformin effectively reduced the damage to hepatocytes and decreased the levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) which resulted in improvement in both necroinflammation and ballooning degeneration scores [12].

As a result, metformin has been generally recommended for the treatment of adult NAFLD patients with T2DM rather than those without T2DM in numerous guidelines.

Metformin medication has been linked to a reduction in the occurrence of HCC and liver-related mortality. According to a case–control study, cirrhotic individuals who used metformin had an 85 percent lower risk of developing HCC than those who took exogenous insulin or insulin secretagogues [13].

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Thiazolidinediones

Thiazolidinediones (TZDs) are agonists of the peroxisome proliferator-activated receptor (PPAR) that work as insulin sensitizers in adipose tissue, muscle, and the liver. TZDs improve insulin and glucose levels, alter adipose tissue distribution via reducing visceral fat and boosting subcutaneous fat leading to an enhancement in liver lipotoxicity.

A Randomized, placebo-controlled, double-blind clinical trial including 101 patients with NASH and either prediabetes or diabetic who randomly administrated either pioglitazone (45 mg/dL), or placebo for 18 months, followed by an 18-month open-label phase with pioglitazone treatment was established to determine pioglitazone's safety. Approximately, ≥ 2-Point reduction in NAFLD activity score (NAS) was noticed in 58% of pioglitazone-treated patients versus 17% in the placebo group indicating no non-significant improvement of fibrosis. Additionally, resolution of NASH occurred in 51% of pioglitazone-treated patients versus 19% in the placebo group. Weight gain of about 2.5 kg was unfortunately the main side effect detected after using this medicine for 3 years [14]. This is in line with PIVENs trial which also observed weight gain in patients who administrated 30 mg of pioglitazone versus both Vit E and placebo [15].

According to a meta-analysis that summarized the effect of the Pioglitazone treatment on NASH, it was concluded that usage of pioglitazone decreased fibrosis in individuals with NASH either diabetic or not [16].

Besides weight gain which mentioned previously as the most prevalent negative effect of pioglitazone medication, women on thiazolidinediones may experience bone loss.

The detected weight gain may be due to enhanced adipose tissue insulin action and increased adipocyte TG production [17].

Pioglitazone is appropriate in biopsy-proven NASH either diabetic or not, but body weight (which we may address with lifestyle measures like exercise and diet), ALT, AST response, and DEXA scan must be monitored during the medication [18].

Sodium-Glucose Cotransporter 2 (SGLT2) Inhibitors

Sodium-glucose cotransporter-2 (SGLT-2) inhibitors are a new type of oral glucose-lowering medication that has been approved to treat T2DM. SGLT-2 inhibitors promote renal glycosuria and osmotic diuresis by diminishing renal ability to reabsorb filtered glucose, improving glucose control and exerting additional positive effects such as weight loss and blood pressure reduction [19].

SGLT2 inhibitors have been demonstrated to have various beneficial pleiotropic effects on patients' body weight and liver enzymes in addition to their hypoglycemic effects, which may help to slow or stop the progression of NAFLD [20].

A recent meta-analysis looked at the results of placebo-controlled or head-to-head RCTs that examined the efficacy and safety of several SGLT2 inhibitors for treating NAFLD in people with or without T2DM. There were no published RCTs with matched liver biopsy data available for the meta-analysis. Thus, changes in serum liver enzyme levels and liver fat content via imaging modalities were the primary outcome indicators. This meta-analysis included a total of twelve RCTs, with aggregate data on 850 middle-aged overweight or obese individuals with NAFLD (90 percent with T2DM), testing the efficacy of [dapagliflozin (n=six RCTs), empagliflozin (n=three RCTs), ipragliflozin (n=two RCTs), or canagliflozin (n=one RCT)] to specifically treat NAFLD for a median period of 24 weeks. Treatment with SGLT2 inhibitors reduced serum ALT [weighted mean differences (WMD): 10.0 IU/L, 95%CI 12.2 to 7.79 IU/L; I 2 = 10.5%) and gamma-glutamyltransferase (WMD: 14.49 IU/L, 95%CI 19.35 to 9.63 IU/L, I 2 = 38.7%), as well as the absolute percentage of liver fat content on magnetic resonance-based techniques (WMD: −2.05%, 95%CI −2.61 to −1.48%; I 2 = 0%)] [21].

Some of the potential mechanisms for SGLT2 inhibitors to help in NAFLD are to reduce inflammatory indicators and oxidative stress. Increased fatty acid oxidation rather than carbohydrate oxidation could help to reduce hepatic fat formation while also suppressing hepatic inflammation [22].

SGLT2 inhibitors have been demonstrated to reduce inflammatory markers, accelerate lipolysis, reduce glucose oxidation, reduce oxidative stress, and boost free fatty acid oxidation, all of which are significant in the treatment of NAFLD [23].

In individuals with T2DM and NAFLD, more study is needed to confirm the advantages and disadvantage of SGLT2 inhibitors, as well as to compare longer-term hepatic results with other anti-diabetic drugs in diabetic patients with NAFLD.

GLP-1 Receptor Agonists

Glucagon-like peptide 1 receptor agonists (GLP-1 RAs) are a type of medication that lowers blood sugar and can help you lose weight (on average 3–5 kg) and reduce your IR [24].

GLP-1 receptors have been found in both mice and human hepatocytes, and their activation may help to reduce hepatic steatosis via enhancing insulin signalling pathways, hepatocyte lipotoxicity, and mitochondrial function [25].

Interestingly, the liraglutide effect and action in diabetes program (LEAD) and LEAD-2 study evaluate the effect and action of liraglutide (a long-acting GLP-1RA) in patients with either biochemistry-based or imaging-defined NAFLD [26], while the LEAN trial evaluated the efficacy and action of liraglutide in patients with biopsy-proven NASH [27].

According to evidence from both of the previous trials, liraglutide reduced serum levels of liver enzyme and other metabolic end points (e.g., peripheral, hepatic, and adipose tissue IR), and it also promoted the improvement of hepatic steatosis and the resolution of hepatic inflammation and hepatocyte ballooning. Liraglutide, on the other hand, had no effect on liver fibrosis. The effects of liraglutide on the aforementioned histological liver outcomes could be related to weight loss and its direct hepatic action, implying a possible synergistic and multifactorial effect [28].

A recent meta-analysis that included a total of 935 obese or overweight middle-aged people with NAFLD or NASH treated with liraglutide or semaglutide for around 26 weeks was carried out to illustrate the efficacy and safety of GLP-1 RAs for treating NAFLD or NASH in persons with or without pre-existing T2DM. This meta-analysis indicated that GLP-1 RAs were linked to significant reductions in serum ALT and gamma glutamyl transferase (γ-GT) levels.

Also, a significant improvement in the absolute percentage of liver fat content, and a significantly greater histologic resolution of NASH with no worsening of liver fibrosis was detected with administration of liraglutide or semaglutide once-daily. In contrast, there were no significant differences in the percentage of patients who had an

improvement in liver fibrosis stage without worsening of NASH in both GLP-1-RA and placebo groups [28].

Another recent meta-analysis looked at the evidence for the effectiveness of GLP-1-RA in the treatment of NAFLD in T2DM patients [29]. Following therapy with a GLP-1-RA, they discovered significant changes in hepatic fat content, liver biochemistry, body composition, glucose parameters, lipid parameters, insulin sensitivity, and inflammatory markers. In comparison to metformin and insulin-based treatments, GLP-1-RA dramatically reduced hepatic fat content. Agonists for GLP-1-RA improved fibrosis markers as well, but the difference was not statistically significant [29].

DDP-4 inhibitors

Dipeptidyl peptidase 4 (DPP4) is a serine exopeptidase that removes N-terminal dipeptides from oligopeptides to inactivate them [30]. Because DPP4 is a hepatokine, it has been found to be high in chronic liver illnesses such as hepatitis C, hepatitis B, NAFLD, and HCC [31].

Serum DPP4 levels are higher in NASH patients and are related to the severity of the disease histopathologically. DPP4 levels are also linked to fibrosis of the liver and apoptosis of hepatocytes [32].

After a year of treatment, a small RCT in China found no difference between sitagliptin 50 to 100 mg and both diet and exercise on the liver function tests (AST and ALT), despite sitagliptin treatment being linked with a higher reduction in HbA1c ($P<0.01$) [33].

Larger studies on biopsy-confirmed NASH patients found that the same dose of sitagliptine (100 mg) given for a year improved NAS by alleviating steatosis and ballooning, regardless of diabetic state [34] and another 24-week administration trial found no superiority in reducing liver fat infiltration in prediabetic patients with NAFLD or those with DM and NAFLD compared to placebo [35].

Additionally, Vildagliptin (50 mg twice daily) for 12 weeks improved liver enzymes and steatosis grading, as measured by ultrasonography, in an RCT done in Pakistan [36].

Also in human clinical studies, twelve months of Alogliptin treatment (25 mg/day) in NAFLD patients with T2DM resulted in a reduction in NAFLD progression [37] as well as after 24 weeks of treatment with Saxagliptin, liver enzymes and hepatic steatosis were improved in 95 individuals with NAFLD and T2DM [38].

Omarigliptin (OMG), a potent selective DPP4 inhibitor with a half-life that allows weekly dosing, was recently investigated in NAFLD patients [39]. OMG significantly reduced levels of ALT, AST, γ-GT, homeostatic model assessment of insulin resistance (HOMA-IR), and high-sensitivity C-reactive protein (hsCRP), while it shows no effect in both HbA1c and BMI.

Moreover in the NASH patient, OMG improved liver function significantly, and levels of the hepatic fibrosis marker (FIB-4) dropped in tandem with HOMA-IR and hsCRP. On diagnostic ultrasonography, there appeared to be slight but noticeable improvements in intrahepatic fat deposition and fibrosis [39].

Sulfonylurea

These compounds increase insulin production by blocking potassium channels in Langerhans beta cells. Insulin production triggered by Sulfonylurea is unaffected by blood glucose levels [40]. The influence of this class of medications on NAFLD has been examined infrequently.

Goh GBB et al. (2014) looked at possible links between drug classes as risk factors and progressive fibrosis in diabetic patients with NAFLD, using data from 459 patients with biopsy-proven NAFLD. The bulk of the patients were obese, with 56.4 percent having hypertension and 47.9% having diabetes. In 132 cases, advanced fibrosis was found (28.8%). Insulin use and sulfonylurea use were linked to progressive fibrosis [41].

The report that anti-diabetic drugs impact the risk of HCC is consistent with the previous findings. Insulin and sulfonylurea use were linked to a 161% and a 62% increased risk of HCC, respectively, while metformin use was linked to a 50% reduction in HCC incidence [42].

Insulin

Retrospective investigations on the effect of insulin on the evolution of NAFLD in diabetic patients have appeared conflicting results. Insulin therapy was linked to advanced liver fibrosis in one study [41] and to improvements in liver fibrosis in another study [43]. In addition, insulin therapy has been linked to HCC in the past [44].

Insulin and sulfonylurea were both found to be risk factors for advanced hepatic fibrosis, suggesting that rising insulin levels in the blood may play a role in fibrosis development. During active fibrogenesis, the expression of insulin and Insulin-Like Growth Factor (IGF-1) receptors on collagen-producing Hepatic Stellate Cells (HSC) increases [45]. Insulin and IGF-1 also promote HSC proliferation in a dose-dependent manner. Insulin signalling via Phosphatidyl Inositol 3 Kinase (PI3K) and extracellular signal related kinase (ERK) also boosts collagen gene expression. Similarly, glucose and insulin increase the expression of connective tissue growth factor [CTGF], a protein that promotes the formation of connective tissue.

Conflicts of interest

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