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**GOSPODARKA I INNOWACJE**

LABORATORIUM WIEDZY Artur Borcuch

***Volume: 48 | 2024***

**Economy and Innovation**
**ISSN: 2545-0573**

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# ANTIDIABETIC DRUGS IN THE TREATMENT OF NON-ALCOHOLIC FATTY LIVER DISEASE: A LITERATURE REVIEW

**Jabbarova Nafisa Mamasolievna**
*Samarkand State Medical University, Uzbekistan*

**A R T I C L E I N F O.**

**Keywords:** hepatic steatosis, NAFLD, NASH, insulin resistance, antidiabetic drugs, SGLT2 inhibitor.

**Abstract**

Non-alcoholic fatty liver disease (NAFLD), as one of the factors of metabolic syndrome (MS), is currently the most common liver disease worldwide. Currently, no specific drug therapy for this condition has been developed; its treatment is based on the treatment of the main risk factors. The initial accumulation of triglycerides in the liver parenchyma, in the presence of inflammatory processes, mitochondrial dysfunction, lipotoxicity, glucose toxicity and oxidative stress, can develop into non-alcoholic steatohepatitis (NASH). The primary goal is to identify factors contributing to this evolution, as untreated NASH can progress from fibrosis to cirrhosis and ultimately be complicated by hepatocellular carcinoma (HCC). Several groups of drugs have undergone clinical trials for use as specific therapies for NAFLD; most of them are drugs used to treat type 2 diabetes mellitus (T2DM), which is one of the main risk factors for the development of NAFLD. Among the most studied of them are PPAR-γ agonists, the so-called thiazolidinediones (pioglitazone), glucagon-like peptide-1 receptor agonists (GLP-1R), and dipeptidyl peptidase-4 inhibitors (DPP-4). In fact, the most promising category is sodium-glucose cotransporter 2 inhibitors (SGCT2). We will consider the main pathogenetic mechanisms and modern methods of treating NAFLD, paying special attention to the use of SGLT2 inhibitors.



Non-alcoholic fatty liver disease (NAFLD) is currently the most common chronic liver disease worldwide. According to a recent systematic review and meta-analysis, the global prevalence of NAFLD increased from 25.3% in 1990–2006 to 38.0% in 2016–2019 [1]. In parallel, non-alcoholic steatohepatitis (NASH), a more active form of NAFLD characterized by hepatic steatosis, inflammation and swelling of hepatocytes, is emerging as a leading cause of cirrhosis, cirrhotic complications, hepatocellular carcinoma (HCC) and liver death[2]. NASH is also the fastest growing indication for liver transplantation in the United States and a rapidly growing indication elsewhere in the world[3,4,5].

The main risk factors for the development of the disease are associated with the state of insulin resistance and, consequently, with MS (visceral obesity, T2DM, dyslipidemia, arterial hypertension), which is its phenotypic expression. Not only are the conditions that characterize the metabolic syndrome highly prevalent in patients with NAFLD, but the presence of one or more of these conditions increases the risk of developing NAFLD itself [5,7].

This bidirectional relationship between NAFLD and components of the metabolic syndrome is so well established that NAFLD is considered the hepatic manifestation of the metabolic syndrome and usually coexists with T2DM, which is a risk factor for its progression to fibrosis, cirrhosis, and cancer [8,9].

Based on liver histology, approximately 37.3% of patients with T2DM develop NASH, and 17% develop progressive fibrosis. The development of non-alcoholic fatty liver disease, and hence insulin resistance, then type 2 diabetes mellitus in obese patients is of great importance in the choice of treatment tactics, duration and possible ambiguous outcomes in the progression of NAFLD. Weight loss is associated with significant improvements in steatosis, NASH, and fibrosis in individuals with NAFLD, and is also highly effective in preventing the onset of T2DM in individuals at high risk [6].

And one of the main directions of treatment for NAFLD is lifestyle changes in the form of regular exercise and a low-calorie diet for weight loss [6].Among the diets, the most influential is the Mediterranean diet (MD), a diet low in saturated fat and animal protein, rich in antioxidants and fiber, and with an adequate ratio of omega-6 to omega-3. [10]. The Mediterranean diet is based on substances such as polyphenols, vitamins and other compounds that have anti-inflammatory and antioxidant effects. In particular, polyphenols have various hepatoprotective activities. They are divided into flavonoid and non-flavonoid polyphenols [10,11]. In addition to influencing the taste and color of certain foods (for example, fruits and vegetables), flavonoids have anti-inflammatory and antioxidant effects [11-12]. One of the nonflavonoids, resveratrol, performs a hepatoprotective function by interacting with vascular homeostasis, platelet function, and the blood coagulation system [13].

A study of 261 patients with biopsy-proven NASH (66% with prediabetes or type 2 diabetes and 100% with overweight or obesity) assessed the effect of weight loss through diet and exercise over 52 weeks on the histological features of NAFLD. By the end of the study, 30% of patients had lost >5% weight, of whom 25% achieved resolution of NASH, 47% had a decrease in NAFLD activity, and 19% experienced regression of liver fibrosis. The majority of patients who lost 5 to 6.9% of weight experienced a decrease in hepatic stetosis (65%). The majority of patients who lost 7 to 9.9% of weight experienced resolution of NASH (64%), and all patients who lost >10% of weight experienced resolution of NASH, 90% had resolution of NASH, and 45% had regression fibrosis. In the overall group, the highest rates of NASH reduction, NASH resolution, and fibrosis regression were observed in patients with weight loss >10% [14].

In two other studies, diet and exercise for 12 and 26 weeks, compared with exercise alone, resulted in significant weight loss and improvement in NAFLD and NASH on liver biopsy [15,16].

However, diet and exercise regimen as a method of weight loss have several disadvantages. Its implementation can be difficult due to labor intensity, lack of motivation, high costs and poor adherence to a hypocaloric diet. Therefore, research is currently underway aimed at developing drug treatments for NAFLD.

To date, there are no specific standards for drug treatment of NAFLD, sinceno pharmacological agents have been approved by regulatory authorities for the treatment of NAFLD/NASH. All these questions currently remain open and require further development.

Several studies have examined the potential of vitamin E for treating NAFLD. Vitamin E supplementation in nondiabetic patients has been recommended because it has been associated with improvement in NASH in some studies. However, there are some safety concerns regarding long-term use of vitamin E. Although reliable data are insufficient to provide a definitive answer, it has been suggested that vitamin E use increases the risk of stroke and all-cause mortality [eleven],and the prthiazolidinedione class drug pioglitazone can lead to weight gain, edema, osteoporosis and heart failure as side effects [12-13].

At the same time, new antidiabetic agents, mainly glucagon-like peptide-1 receptor agonist (GLP-1 Ra),

sodium-glucose cotransporter 2 inhibitors (SGLT2 inhibitors) and dipeptidyl peptidase 4 inhibitors (DPP-4 inhibitors), have recently been evaluated specifically for the treatment of NAFLD in diabetic and nondiabetic patients and yielded interesting and promising results. Most of them were assessed by non-invasive methods, and only a few were assessed by liver biopsy (table 1). We looked at some of these drugs.

**Table No 1. Pharmacological effects of the most commonly used antidiabetic drugs in NAFLD**.

| Antidiabetic drugs | Molecular mechanism | Weight change | Effect on NAFLD |
|---|---|---|---|
| Thiazolidinediones | -Activation of PPAR-γ and PPAR-α-IR in reversal of adipose tissue, liver and skeletal muscle-Improved glucose and lipid metabolism-Decreased HbA1c-Increased plasma adiponectin levels | Weight gain 3–5% | Pioglitazone: -Resolution of NASH in 47% without T2DM and in 60% with T2DM-ALT and decreased AST - prevention of fibrosis progression. Rosiglitazone: -No effect on lipotoxicity - Decreased ALT and AST -No effects on liver histology |
| GLP-1 receptor agonists | -Glucose-dependent release of insulin from pancreatic islets - Decreased gastric emptying -Inhibition of postprandial glucagon release -Decreased food intake -Decreased HbA1c | Liraglutide: weight loss:~8% (3 mg/day) Semaglutide: weight loss:~14.9% (2.4 mg/d) | Liraglutide and semaglutide: the only GLP-1R agonists associated with histological efficacy - Resolution of NASH - Prevention of fibrosis progression - reduction of ALT and AST |
| DPP-4 inhibitor | -DPP-4 inhibition Increased effect of GLP-1 incretin and postprandial decrease in glucose levels - moderate decrease in HbA1c | Neutral | Sitagliptin: -The most proven DPP-4 inhibitor -Moderate reduction in hepatic lipids -Variable reduction in ALT -No clear effects on liver histology |
| SGLT2 inhibitors | -Decreased reabsorption of glucose in the renal tubules without stimulating insulin release -Decreased HbA1c | Weight loss~3–5% | Canagliflozin and Dapagliflozin - Reduce ALT and AST - Reduce VPTH using non-invasive procedures - Effect on liver histology Ipragliflozin: - Significant improvement in fibrosis and NASH on liver biopsy |

PPAR-γ - peroxisome proliferator-activated receptor gamma; VPTG - intrahepatic triglycerides.

GLP-1 is a hormone produced by intestinal L cells due to the presence of nutrients and has its main effect by stimulating the glucose-dependent release of insulin from the pancreatic islets[17], also slows down gastric emptying [18],inhibits the release of glucagon after meals and reduces food intake. GLP-1 and glucose-dependent insulin tropic polypeptide (GIP) (both incretins) are cleaved by the enzyme

DPP-4[19]. Therefore, DPP-4 inhibitors exert their effect through incretins. On the other hand, SGLT2 functions through a novel mechanism of reducing glucose reabsorption in the renal tubules, causing a decrease in blood glucose levels without stimulating insulin release[20]. These drugs provide effective glycemic control without the risk of hypoglycemia.

Not all of these new antidiabetic drugs have comparable improvements in liver histology in patients with NAFLD. In a recent retrospective study of 637 patients with NAFLD diabetes mellitus, 472 received DPP-4 inhibitors for 12 months, GLP-1 receptor agonists or NGKT-2 inhibitors for 12 months, and 165 patients received other active antidiabetic drugs as a control group. Serum BMI, HbA1c, and aminotransferase levels were significantly reduced in the GLP-1 receptor agonist and SGLT2 treatment groups compared with the DPP-4 control group. Liver fatty index and fibrosis index (FIB-4) were reduced only by GLP-1 receptor agonists and NGCT2 inhibitor. The shift in FIB-4 values toward decreased progressive fibrosis persisted after additional adjustment [21].

In this regard, we reviewed and analyzed in detail multiple studies that assessed the effectiveness of SGLT2 inhibitors in the treatment of NAFLD [22]. In 2018, a randomized controlled clinical trial (E-LIFT study) conducted in India involving 50 patients with T2DM and NAFLD found that adding 10 mg empagliflozin to standard T2DM therapy for 20 weeks resulted in a significant reduction (from 16.2 % by 11.3%) liver fat at the end of treatment, according to MRI, decreased density and improved serum ALT levels [23].

Another study by Kahl et al (2020). In patients with T2DM, 80% with NAFLD compared a daily dose of 25 mg empagliflozin with placebo demonstrated a significant reduction in hepatic SCLC content using magnetic resonance spectroscopy [24].CPUS - controlled ultrasound attenuation parameter, is a non-invasive method based on controlled vibration elastography technology built into the fiberscan.

In addition, Shimizu et al. (2019) conducted a 24-week, open-label, controlled clinical trial involving 57 patients with T2DM and NAFLD, randomized to dapagliflozin (5 mg/day) (n=33) and a control group without dapagliflozin (n=24). Hepatic steatosis and fibrosis were assessed using fibroelastography to measure BCFA and liver stiffness, respectively. This study demonstrated a significant reduction in SCLC in the dapagliflozin group, as well as a reduction in liver stiffness [25].

Ito et al. (2017) compared ipragliflozin 50 mg with pioglitazone in addition to standard therapy using the primary outcome of change from baseline in liver-to-spleen ratio (L/S ratio) on CT scan at week 24. In this study, improvement in hepatic steatosis, assessed by L/S ratio, reduction in serum aminotransferase levels, and beneficial effects on glycemic parameters, was observed. Compared with pioglitazone, a significant reduction in body weight and visceral fat was observed [26].

A study by Ohki (2016) demonstrated the effectiveness of ipragliflozin in a group of patients not responding to incretin and DPP4 therapy in improving glycemic control, reducing body weight and reducing transaminase levels [27].

In 2020, researchers from Korea Han et al. conducted a study comparing the effects of 50 mg ipragliflozin in patients with T2DM NAFLD who were already receiving pioglitazone and metformin versus patients receiving pioglitazone and metformin alone. Outcomes were assessed by fatty liver index and NAFLD fatty liver score, with a significant reduction in patients treated with SGLT2, although this difference between the two groups was not demonstrated for CAP [28].

In a prospective study, nine patients with NAFLD complicated by T2DM were treated with canagliflozin 100 mg daily for 24 weeks and assessed for liver histology at baseline and 24 weeks after initiation of therapy. The primary endpoint was histological improvement, defined as a decrease in NAFLD activity score of one point or more without worsening fibrosis stage. All nine patients achieved histological improvement. Six patients showed improvement in insulin resistance, and another three patients showed partial improvement in insulin secretory function [29].

In T2DM patients with NAFLD, Inoue et al. in 2019, they assessed the effect of canagliflozin at a dose of 100 mg once a day for one year on serological markers and the general condition of the body. Body composition is measured using bioelectrical impedance analysis and liver fat is measured using MRI. Significant reductions in body weight and fat mass were shown at 6 and 12 months without a significant reduction in muscle mass. The liver fat fraction was reduced compared to baseline from 17.6% ± 7.5% to 12.0% ± 4.6% after 6 months and 12.1% ± 6.1% after 12 months, while while serum liver enzymes and type IV collagen concentrations improved. From a mean baseline HbA1c of 8.7%±1.4%, canagliflozin significantly reduced HbA1c at 6 and 12 months to 7.3%±0.6% and 7.7%±0.7%, respectively ($p<0$ .0005 and $p<0.01$) [30].

Further study by Nishimiya et al (2021). assessed the effectiveness of canagliflozin at a dose of 100 mg once daily in a group of 10 patients with T2DM and NAFLD in addition to ongoing therapy. The degree of steatosis was assessed using three different imaging modalities: MRI, computed tomography (CT), and fibroelastography. Biohumoral parameters of glycemic, lipid and liver function were assessed. A six-month study confirmed the effectiveness of canagliflozin in improving NASH, insulin resistance, fat tissue reduction and inflammation [31]. Also, Goutam et al. assessed the role of canagliflozin at a dose of 100 mg/day in reducing body weight, glycated hemoglobin and improving liver function parameters[32]. Sumida et al. (LEAD trial) and Shibuya et al. in their studies demonstrated that the use of luseogliflozin at a dose of 2.5 mg/day in patients with T2DM and NAFLD led to improvements in several parameters related to metabolism and liver function, as well as to reduce fat content [33,34].

In 2017, Seco et al. published a retrospective study to evaluate the effectiveness of SGLT2 in a group of patients with histologically proven NAFLD and T2DM treated for 24 weeks. A total of 24 patients received NGLT2 (canagliflozin 100 mg/day or ipragliflozin 50 mg/day). In this case, 21 patients were treated with DPP4-I (sitagliptin 100 mg/day). Additionally, in this retrospective study, the results encourage the use of SGLT2 inhibitors in patients with T2DM and NAFLD, demonstrating significant reductions in weight and glycated hemoglobin. Transaminase activity was equally reduced between the two groups[35].

## Conclusions

The natural history of NAFLD/NASH and the paucity, if not complete absence, of specific treatments for this condition require increased attention to the potential use of drugs intended to treat T2DM. Of particular interest in this regard are SGLT2 inhibitors, which have been shown to be effective in reducing liver fat, AST/ALT levels, and even liver stiffness in some studies, making this class of drugs one of the most promising future treatments for NAFLD.

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