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Can combination of SGLT2 inhibitors and DPP-4 inhibitors be combination of choice for T2DM associated MAFLD?

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1. Abstract

Globally, metabolic associated fatty liver disease (MAFLD) is the leading cause of liver disease and the most common cause for liver transplantation. Type 2 Diabetes mellitus (T2DM) is major risk factor for development of MAFLD with Indian prevalence of 56.5% T2DM patients suffering from MAFLD. MAFLD and T2DM are pathophysiological linked with IR, T2DM, and obesity significantly contributing to MAFLD. Treatment with anti-diabetic agents in T2DM patients at risk of MAFLD may reduce the risk of MAFLD progression. Sodium glucose cotransporter 2 (SGLT2) inhibitors are reported efficacious in early preliminary non-clinical and clinical studies. SGLT- 2 inhibitors contribute to MAFLD alleviation by reduction of hyperglycaemia, enhancement of systemic insulin resistance, increased caloric loss and body weight reduction substantially due to glycosuria. Gliptins or dipeptidyl peptidase 4 (DPP-4) inhibitors prevent inactivation of incretins, such as glucose-dependent insulinotropic polypeptide (GIP) and glucagon like peptide (GLP)-1 by DPP-4 enzyme. SGLT2 inhibitors (dapagliflozin) are also shown to lower the blood level of soluble dipeptidyl peptidase-4, which is strongly correlated with liver enzymes. Moreover, DPP-4 inhibitor lowers HbA1c without having any clinically meaningful impact on body weight. According to reports, sitagliptin lowers NASH scores and reduces hepatic steatosis. Thus, the combination of SGLT2 inhibitors and DPP-4 inhibitors can be a treatment of choice in MAFLD patients with T2DM. The current review discusses the role of SGLT2 inhibitors and DPP-4 inhibitors in combination in patients with T2DM associated MAFLD

2. Introduction

Recently metabolic associated fatty liver disease (MAFLD) is newly coined term for previously known non-alcoholic fatty liver disease (NAFLD). Globally, MAFLD is the leading cause of liver disease and is becoming the most common cause for liver transplantation. MAFLD is increasingly burdensome condition, both clinically and economically due to expanding epidemic of obesity worldwide [1].

MAFLD consists of all fatty liver disease states included in NAFLD. NAFLD represents a spectrum of liver disorders associated with insulin resistance. The progression of NAFLD is initiated with "benign" steatosis (NAFL), through to non-alcoholic steatohepatitis (NASH), which is the inflammatory state that can lead to advanced fibrosis or cirrhosis (Figure 1) [1].

3. Risk Factors for MAFLD

The association between MAFLD and metabolic syndrome (MetS) is very well understood and is one of the most discussed problems. Studies have demonstrated the strong association between MAFLD and obesity in patients with multiple cardiovascular risk factors. Other risk factors such as, type 2 diabetes mellitus (T2DM), obesity, dyslipidemia, and hypertension elevate the risk of disease progression and development of NASH and fibrosis in MAFLD patients (Figure 2) [2].

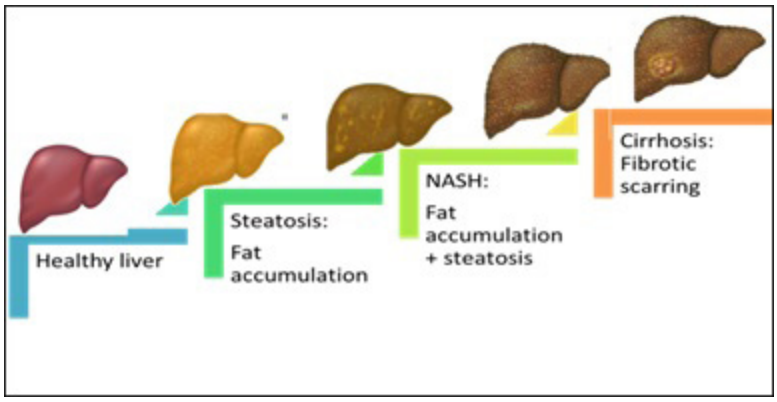

Figure 1: Advancement of MAFLD condition (MAFLD to Cirhossis) [1]
MAFLD: Metabolic associated fatty liver disease, MAFLD: non-alcoholic fatty liver disease

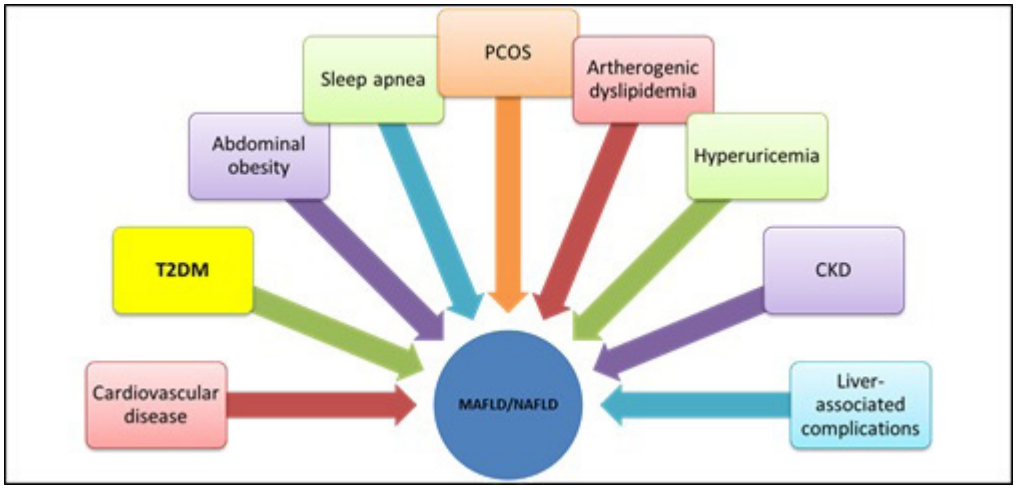

Figure 2: Risk factors for MAFLD [2]
MAFLD: Metabolic associated fatty liver disease, MAFLD: non-alcoholic fatty liver disease, T2DM: Type 2 diabetes mellitus, PCOS: Polycystic ovary syndrome, CKD: Chronic kidney disease

4. Prevalence of MAFLD in T2DM

Global pooled prevalence of MAFLD by imaging is reported to be 25.24% (95% confidence interval [CI]: 22.10–28.65%) among general population. The association between MAFLD and T2DM is well established. Compared to non-diabetics patients suffering from T2DM are at elevated risk of developing MAFLD and its progression to NASH or cirrhosis [3].

In a systemic review and meta-analysis conducted among 80 studies from 20 countries including 49,419 individuals with T2DM (mean age 58.5 years, mean body mass index 27.9 kg/m2, and males 52.9%) reported MAFLD global prevalence of 55% (95% CI 47.3-63.7) among T2DM patients. Highest prevalence of MAFLD was reported in studies from Europe (68.0% [62.1-73.0%]). The global prevalence of NASH and advanced fibrosis in T2DM patients was reported to be 37.3% and 17.0%, respectively [4].

The prevalence of MAFLD in general Indian population is 9-32% with higher incidence rate amongst obese and diabetic patients. A Clinical study conducted by Kalra S, et al. determined frequency and risk factors of MAFLD in non-alcoholic Indian type 2 diabetic (T2DM) patients (n = 954). Out of 924 patients (355 female/569 male) 522(56.5%) T2DM patients were identified as having MAFLD. Based on gender differences, the prevalence of MAFLD was higher in females (60%) than in males (54.3%) with T2DM. The prevalence varied from 44.1% in western India to 72.4% in northern states [5].

5. Diabetes and MAFLD: The pathophysiological Link

Patients with MAFLD are at increased risk of T2DM whereas, patients with T2DM may develop MAFLD [6,7]. Thus, the pathophysiological links suggesting a close association between MAFLD and T2DM are multiple, complex and only partially understood (Figure 3) [6]. Patients with MAFLD are at increased risk of T2DM whereas; patients with T2DM may develop MAFLD.

5.1. The multi-hit theory

The pathogenesis of MAFLD is not completely understood. The common proposed mechanism includes multi-hit theory. The first hit in liver steatosis is characterized by accumulation of fats in >5% of hepatocytes (hepatic cells). The accumulation of fats in liver is associated with imbalance between fatty acid storage and their digestion in liver. Triglycerides (TGs) produced from acyl-coenzyme A (derived from free fatty acids (FFAs)) are produced by liver. This production is based on acyl-CoA synthetase and L-glycerol 3-phosphate

formed from glycolysis [6]. In T2DM, the deposit of TGs in liver increases causing steatosis of liver. However, the exact pathophysiological mechanism is not fully elucidated. Insulin resistance may have a significant role in fat deposition in liver [6,7].

The increased fat deposition in liver increases its susceptibility to second hits caused by oxidative stress, endoplasmic reticulum stress, mitochondrial dysfunction, inflammatory cytokines, adipokines, gut microbiota, and glucocorticoids

FFAs reach liver and in hepatocytes they either undergo beta-oxidation in mitochondria, which brings either to ATP production, or to the synthesis of ketone bodies. In alternate option FFAs may be converted to TGs via esterification and stored as droplets into the hepatocytes or packaged in apolipoproteins and secreted as very low-density lipoproteins (VLDL) in the serum [6, 7]. Increased FFA in liver further contributes to lysosomal destabilization, activating inflammatory pathways such as the nuclear factor kappa B-dependent tumor necrosis factor-alpha pathway [7].

The third hit includes death of hepatocytes. The MAFLD progresses into NASH when mechanisms for inhibiting FFA-lipotoxicity exhausts and rate of hepatocyte apoptosis increases with reduced rate of hepatocyte regeneration [7]. This results in myofibroblasts activation which increases the production of liver progenitor cells, which further induces inflammatory immune response and differentiate to replace dead hepatocytes. This causes variable distortion of hepatic structure.

5.2. Role of insulin resistance

T2DM is characterized by hyperglycemia, IR, and insulin deficiency. The inability of pancreatic beta-cells to compensate IR through hyperinsulinemia plays a crucial role in T2DM pathogenesis. IR plays a key role in onset of MAFLD and lack of compensation of IR via beta-cells occurs in pathogenesis of T2DM. In such cases, to keep blood glucose levels normal, beta-cells secrete high amount of insulin (causing hyperinsulinemia); however, once beta-cell fails to produce enough insulin to compensate IR, it results in pathogenesis of T2DM due to increased blood glucose levels. Hyperinsulinemia results in hepatocellular ballooning and lobular inflammation [7]. Inflammatory pathways may further contribute to IR [7]. Available clinical evidence suggests that IR is the leading cause of T2DM when pancreatic beta-cells fail to produce enough insulin [6].

Although NAFLD and IR are interrelated, some genetic variants may also play a significant role in causing hepatic steatosis in cases where IR is absent.

The relationship between MAFLD and T2DM is not only epidemiological, but also pathophysiological. The understanding of these pathophysiologies will deepen the knowledge and may help to identify various pharmacological targets for management of MAFLD in patients with T2DM

6. Anti-Diabetic Treatments Used for Treatment MAFLD in T2DM

Patients with T2DM are at increased risk of MAFLD development and fibrotic progression. Anti-diabetic agents in such cases may help to reduce the risk of MAFLD development. Moreover, IR is a major cause of MAFLD development. Thus, anti-diabetic agents may be treatment of choice for management of MAFLD. Various anti-diabetic agents with different mechanisms of action are studied for its effects in patients with MAFLD. Commonly studied molecules includes metformin, thiazolidinediones (TZDs), glucagon-like peptide 1 receptor (GLP-1r) agonists, dipeptidyl peptidase 4 (DPP-4) inhibitors, and sodium/glucose cotransporter 2 (SGLT2) inhibitors [8].

7. Role of SGLT2 Inhibitors in MAFLD

SGLT2 inhibitors are reported efficacious in early preliminary non-clinical and clinical studies [9, 10, 11] and, based on their positive outcomes in cardiovascular [12] and renal conditions [13], they are used in management of T2DM [14]. Therefore, role of SGLT2 inhibitors in MAFLD have raised growing interest. SGLT2 inhibitors are reported as cardiovascular [15] and renal [16] protectants in T2DM patients with established CVD, whereas, current evidences suggests that, SGLT2 inhibitors may reduce liver fat content and may also possess liver-protective effects [17]. Worldwide commercially available SGLT2 inhibitors, such as canagliflozin, dapagliflozin, empagliflozin have demonstrated consistent positive results in patients with MAFLD [18].

7.1. Mechanistic role of SGLT2 inhibitors

SGLT- 2 inhibitors contribute to MAFLD alleviation by reduction of hyperglycaemia, enhancement of systemic insulin resistance, increased caloric loss and body weight reduction substantially due to glycosuria. Moreover, SGLT- 2 inhibitors play a hepatoprotective role via decrease of hepatic de novo lipogenesis, hepatic inflammation, apoptosis, ER- stress, oxidative stress, and increase of hepatic beta-oxidation. Reduced activation of hepatic satellite cells and p53/p21 pathways by SGLT- 2i leads to amelioration of hepatic fibrosis and HCC development (Figure 4) [19, 20].

The mechanisms associated with improvement of MAFLD with SGLT2 inhibitors still remains unknown and at present, its effect is merely based on hypothesis. SGLT2 inhibitors significantly lower fasting and postprandial hyperglycaemia [12], and reduce body weight and fat mass [21]. MAFLD is known to be associated with increased hyperglycemia and adiposity. Yet, the part of better glucose control in managing MAFLD remains unclear. An open study conducted in Chinese patients with T2DM (not reported with MAFLD), the alleviation of hepatic dysfunction was evaluated by reductions in ALT and AST, which was partly mediated through hyperglycaemia control and possibly through improvement of insulin resistance independent of body weight changes [22]. In a study comparing emplagliflozin and other blood glucose reducing therapies reported a greater reduction

in liver fact content, as evaluated using Magnetic Resonance Imaging Proton Density Fat Fraction (MRI-PDFF) in patients receiving empagliflozin. Moreover, a significant decrease in serum liver enzymes was reported with SGLT2 inhibitor [23]. Compared to glimepiride, canagliflozin showed a slightly greater reduction in serum liver enzymes inspite of similar improvements in glucose control in both groups [24].

In patients with hepatic dysfunction, bariatric surgery is often performed to significantly reduce steatosis and serum liver enzymes [25]. The weight reduction after bariatric surgery is significant rather than modest weight reduction observed with SGLT2 inhibitors [26]. Another study reported significant improvements in HbA1c, body weight and fat mass, and insulin sensitivity [27]. A study comparing canagliflozin either with placebo or sitagliptin treatments demonstrated that canagliflozin led to improvements in liver function tests that were explained completely by its effects on of glycated haemoglobin (HbA1c) and body weight decrease with the SGLT2 inhibitor [29]. However, in the BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPAREG-OUTCOME), the ALT-lowering effect of empagliflozin vs. placebo considered independent of concomitant changes from baseline in HbA1c, and body weight averaged 76.0% after both 24 weeks and 164 weeks [29]. In a study, ipragliflozin resulted in marked improvement in liver dysfunction in patients with T2DM irrespective of body weight loss [11] whereas; another study reported that no significant correlations exist between liver fat reduction and improvement in HbA1c or body weight [30]. These reports indicate other subtle mechanisms may be responsible in improvement of MAFLD with SGLT2 inhibitors. A non-clinical, experimerntal study conducted in db/db mice showed that dapagliflozin not only controlled hyperglycaemia but also reduced the progression of diabetes-associated liver fibrosis (and glomerulosclerosis in kidneys) via reducing hyperglycaemia-induced tissue inflammation and oxidative stress [20]. In a clinical study conducted in humans, dapagliflozin, in addition to significant diminution of liver fat content, it also decreased all serum biomarkers of hepatocyte injury, indicating less cellular damage, better mitochondrial function, and decreased endoplasmic reticulum stress observed with MAFLD [31]. Therefore, based on above evidences, the potential benefits of SGLT2 inhibitors on inflammation and oxidative stress needs further investigations, as recently conferred [32].

When a post-hoc exploratory analysis of a head-to-head study showing greater improvement of serum liver enzymes with canagliflozin vs glimepiride [24] also investigated selected adipokines, inflammatory biomarkers and chemokines in both treatment groups [33], the results indicated that canagliflozin decreased median serum leptin by 25% and median serum interleukin (IL)-6 by 22%, while significantly increasing median serum adiponectin by 17% vs. glimepiride. With canagliflozin, decreases in serum leptin correlated with changes in body weight, whereas increases in adiponectin and decreases in IL-6 were independent of changes in HbA1c, weight or serum lipids [33]. Data on the association between MAFLD and circulating leptin and adiponectin levels are generally well established: leptin levels increase while adiponectin levels decrease, thereby increasing the severity of MAFLD [34].

Uric acid is associated with inflammatory biomarkers and induces inflammation by activating the nuclear factor (NF)-kB signalling pathway in HepG2 cells [35]. Increased serum uric acid levels are associated with CVD [36] and progression of CKD [37]. Interestingly, a relationship between high serum uric acid and risk of MAFLD has also been reported [38, 39]. Thus, as SGLT2 inhibitors consistently reduce serum uric acid levels [40], it may be speculated that this effect could be contributing not only to better cardiovascular [12] and renal [13] prognoses, but also to improvement of MAFLD.

7.2. SGLT2 inhibitors vs. Other anti-diabetics

Although the glucose management is similar, SGLT2 inhibitors significantly decrease blood levels of liver enzymes when compared to a number of other oral glucose-lowering medications, such as metformin and glimepiride [20]. Findings from non-clinical models are less persuasive when it comes to the first-line anti-diabetic medication metformin [20]. Other glucose-lowering medications, such thiazolidinediones (TZDs) and GLP-1 receptor agonists, have shown to be able to lower levels of liver fat and biological MAFLD indicators [20].

The effects of an SGLT2 inhibitor and a TZD in individuals with T2DM and MAFLD have only been compared in one study. Ipragliflozin had similar positive effects on MAFLD markers and glycemic control as pioglitazone. When compared to pioglitazone, ipragliflozin significantly reduced body weight (P 0.0001), visceral fat area (P = 0.0013), and subcutaneous fat area (P 0.0001), but the rise in serum adiponectin levels was greater (P = 0.0009) with the TZD than with the SGLT2 inhibitor [41].

In T2DM patients with MAFLD, GLP-1 receptor agonists have also demonstrated effectiveness in lowering liver fat burden. Despite the diversity of this pharmacological family, studies show that the effects of GLP-1 receptor agonists on MAFLD indicators are very consistent, indicating a class impact. This begs the issue of how the effects on fatty liver of SGLT2 inhibitors and GLP-1 receptor agonists differ. Furthermore, compared to commonly used incretins, an SGLT2 inhibitor has not yet been the subject of any significant clinical studies [20].

In a large observational study using the database of a Canadian diabetes registry, 3667 T2DM patients who had been prescribed canagliflozin, dapagliflozin, liraglutide, or sitagliptin had changes in their serum levels of ALT, the most specific liver enzyme for MAFLD, measured after a mean follow-up of 4.8 months [42]. Although all exhibited lower levels than in the controls (P 0.01 vs. no additional therapy), ALT levels were lower following treatment with SGLT2 inhibitors canagliflozin (4.3 U/L) and dapagliflozin (3.5 U/L) compared with incretins liraglutide (2.1 U/L) and sitagliptin (-1.8 U/L). Notably, after multivariable correction and propensity score weighting, only the SGLT2 inhibitor treatment groups retained substantial

ALT decreases compared to controls. In contrast to incretins, SGLT2 inhibitors (canagliflozin and dapagliflozin) lowered ALT levels independent of weight or HbA1c, and a dose-response relationship was seen with greater baseline ALT levels [42].

This encouraging result implies that patients with MAFLD and T2DM may have considerable advantages from the use of SGLT2i, either alone or in combination.

7.3. Dapagliflozin in MAFLD

A few randomized controlled trials (RCTs) assessing the use of dapagliflozin for the treatment of non-alcoholic fatty liver disease (MAFLD) were evaluated in A systematic review and meta-analysis. This meta-analysis included 11 studies involving 839 patients. Compared with the control conditions, dapagliflozin led to a greater decrease in alanine transaminase, aspartate transaminase, gamma-glutamyl transferase, triglyceride, body weight, body mass index, HbA1c, and fasting plasma glucose. No difference was found between the dapagliflozin and control groups in terms of total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, fibrosis 4 index, type IV collagen 7S, homeostatic model assessment of insulin resistance, or adverse events. The systematic review and meta-analysis concluded that dapagliflozin can markedly reduce hepatic enzymes and metabolic indicators and improve body composition, indicating its potential therapeutic efficacy [43].

Another randomized, active-controlled, open-label trial including 57 patients with type 2 diabetes and MAFLD investigated the effects of dapagliflozin on liver steatosis and fibrosis evaluated in patients with T2DM and MAFLD. Included patients were randomized to a dapagliflozin group (5 mg/d; n = 33) or a control group (n = 24) for 24 weeks. Transient elastography to measure controlled attenuation parameter (CAP) and liver stiffness was used to assess hepatic steatosis and fibrosis, respectively. At 24 weeks, a significant decrease in CAP from baseline was reported in the dapagliflozin group (314 ± 61 to 290 ± 73 dB/m ($p = 0.0424$)), whereas no significant change in the control group was noted. Liver stiffness measurement (LSM) reduced from baseline value of 9.49 ± 6.05 to 8.01 ± 5.78 kPa in the dapagliflozin group. In 14 patients from dapagliflozin group had LSM values ≥8.0 kPa which indicated significant liver fibrosis; however, LSM decreased significantly in this patients from 14.7 ± 5.7 to 11.0 ± 7.3 kPa ($P = 0.0158$) with dapagliflozin treatment for 24 weeks. The study concluded that dapagliflozin improves liver steatosis in patients with T2DM and MAFLD, and attenuates liver fibrosis only in patients with significant liver fibrosis. This reduction in reduction MAFLD state may be associated with decrease in body weight or visceral adipose tissue by dapagliflozin [30].

A prospective, single-center, open-label, uncontrolled, interventional, multidisciplinary cohort study conducted by Das C, et al. (2021) included Indian patients (n = 100) with T2DM and MAFLD to evaluate the effects of dapagliflozin, a sodium-glucose cotransporter-2 inhibitor used in these types of cases. Included patients were treated with dapagliflozin at 10 mg daily for six months. All patients were evaluated for anthropometric, biochemical, abdominal ultrasonography, and transient elastography at baseline and after therapy for a comparative analysis. After treatment with dapagliflozin the mean body mass index significantly decreased from baseline (27.31± 1.87 kg/m2 to 26.21 ± 1.51 kg/m2). The patients' transaminitis, dyslipidemia, and glycemic status significantly improved over the course of the therapy. Significant improvement in hepatic steatosis was reported by the end of the therapy. Transient elastography by FibroScan-measured hepatic fibrosis score (Echosens, Paris, France) significantly decreased from 6.95 ± 1.42 to 6 ± 1.44 kPa, hepatic fibrosis did not improve significantly ($p \geq 0.05$) following therapy. The study concluded dapagliflozin improved body mass index, transaminitis, dyslipidemia, glycemic status, and hepatic steatosis; however its effects on hepatic fibrosis were minimal [44].

In conclusion, based on available data dapagliflozin may have a strong potential to reverse MAFLD-associated changes in type 2 diabetic patients; however, more clinical studies demonstrating the effects of dapagliflozin for its expanded role in MAFLD needs to be elucidated.

8. Role of DPP-4 inhibitors in MAFLD

Gliptins or DPP-4 inhibitors prevent inactivation of incretins, such as glucose-dependent insulinotropic polypeptide (GIP) and glucagon like peptide (GLP)-1 by DPP-4 enzyme. DPP-4 inhibitors can increase insulin secretion, reduce hepatic glucose output, and limit glucagon release by extending the incretin effect [45].

8.1. Mechanistic role of DPP-4

Dipeptidyl peptidase-4 (DPP4) is a widely distributed cell surface peptidase whose action may be modulated to control a variety of systemic processes, including glucose metabolism. DPP4 is expressed and secreted by the liver, and the amount of hepatic DPP4 expression is correlated with the degree of hepatic steatosis in NASH patients. The expression of DPP4 in the hepatocytes was increased, which enhanced MAFLD formation [46].

Hepatic DPP-4 expression and serum DPP-4 activity are associated to the severity of MAFLD. Patients with MAFLD had considerably greater hepatic expression of DPP-4 than healthy individuals [47]. In order to address MAFLD, DPP-4 inhibitors have been researched as an unique therapy approach.

8.2. Sitagliptin: A widely studied DPP-4 inhibitor in MAFLD

Due to its extensive usage and the fact that it was the first DPP-4 inhibitor on the market, sitagliptin has been used in the majority of research examining DPP-4 inhibitors in MAFLD. DPP-4 inhibitors' impact on liver enzymes in patients with T2DM and MAFLD was examined in earlier trials. In the beginning, Iwasaki et al. discovered that sitagliptin 50 mg/day therapy for 4 months in 30 MAFLD patients was connected to substantial reductions in AST, ALT, and gamma-GTP levels, as well as improvements in the parameters of diabetes [48]. In a single-arm, open-label observational pilot research by Yilmaz et al. including 15 patients, sitagliptin medication for a year

was linked to a substantial decline in NASH scores and a tendency toward better hepatic steatosis. Body mass index, AST, and ALT values both significantly decreased [49]. Additionally, it was demonstrated in two retrospective assessments of individuals with T2DM and liver dysfunction that DPP-4 inhibitor therapy was linked to improvements in liver enzymes.

Although diverse kinds of chronic liver damage were present in both investigations, the majority of these individuals had MAFLD [50].

Contrarily, a research by Fukuhara and colleagues in 44 patients with biopsy-proven MAFLD who were followed for 12 months found that, despite a decline in HbA1C levels, liver transaminases did not alter substantially following therapy with sitagliptin [51]. In a case-control research done by Arase and colleagues, no significant changes in liver enzymes were seen with sitagliptin medication throughout 48 weeks of follow-up. [52]

The impact of sitagliptin on NASH histologic and non-histologic markers was assessed in two recent randomized, double-blinded, placebo-controlled trials. 50 MAFLD patients with pre-diabetes or early-stage diabetes were involved in Cui and colleagues' study. They were randomized to receive sitagliptin 100 mg/day vs a placebo and were monitored for 24 weeks. According to MRI-based biomarkers of proton density-fat fraction (MRI-PDFF) in different liver regions, there was no statistically significant difference between the two groups in liver fat reduction (mean difference between the two groups: 1.3%; $p = 0.4$). When compared to baseline, there were no differences in the two groups' end-of-treatment MRI-PDFF results for sitagliptin (18.1% to 16.9%; $p = 0.27$); placebo (16.6% to 14.0%; $p = 0.07$). Other biomarkers, including ALT, AST, low-density lipoprotein, insulin resistance as assessed by the homeostasis model, and liver stiffness determined from MRE, did not differ significantly across groups [53].

Joy et al. conducted a clinical study in which sitagliptin 100 mg/day ($n = 6$) or placebo ($n = 6$) was administered to 12 individuals with biopsy-confirmed NASH. The participants were monitored for 24 weeks. There was no difference between the groups at the conclusion of the study in reduction of liver fibrosis score, as determined by a liver biopsy. Additionally, there was no difference between the two groups in the secondary histologic outcomes of NAS or the specific NAS symptoms (steatosis, lobular inflammation, and hepatocyte ballooning). However, sitagliptin administration was linked to reduced triglyceride and adiponectin levels, as well as an improvement in HbA1C. Other biomarkers or liver enzymes did not alter much either [54].

8.3. Other DPP-4 inhibitors in MAFLD

Alogliptin and vildagliptin, two DPP-4 inhibitor drugs, have also been investigated for their clinical effectiveness. Alogliptin treatment was observed to decrease the progression of MAFLD in a 12-month non-randomized, multicenter, single-arm trial of MAFLD patients with T2DM [55]. Additionally, Macauley et al. showed that vildagliptin usage had a substantial reduction of 27% in liver triglyceride levels as well as an improvement in ALT levels in a 6-month randomized controlled study in diabetic individuals with good glycemic control [55].

9. Combined effect of SGLT2i and DPP-4i in MAFLD

As T2DM and MAFLD are linked, it is important to evaluate effect of therapies on liver fat and other metabolic factors in addition to glycaemic management [56].

American Diabetes Association (ADA) recommendations encourage individuals with significantly increased glycated hemoglobin (HbA1c) values (1.5%–2% over goal) to seek first combination medication. As second-line treatments for T2D control, sodium-glucose cotransporter-2 (SGLT2) inhibitors and dipeptidyl peptidase-4 (DPP-4) inhibitors are suggested. [2] In addition, the ADA advises SGLT2 inhibitors for individuals with heart failure, renal disease, or established atherosclerotic cardiovascular disease, regardless of HbA1c levels [56].

In individuals with T2D, SGLT2 inhibitors lower fasting plasma glucose (FPG), HbA1c, systolic blood pressure (SBP), and body weight. Increased insulin resistance is associated with ectopic fat deposition, which includes liver fat. Losing weight causes the amount of fat in the liver to decrease. Therefore, in T2D patients, reducing hepatic fat content in addition to weight loss may help prevent the progression of liver disease [57].

Hepatocytes release soluble DPP-4 (sDPP-4), which causes inflammation in adipose tissue and insulin resistance. According to reports, SGLT2I (dapagliflozin) lowers blood levels of sDPP-4, which are positively connected with higher levels of HOMA-IR, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamyl transferase (GGT), and alanine aminotransferase (ALT). The change in blood sDPP-4 was favorably linked with changes in liver enzymes after dapagliflozin therapy, but not with changes in VAT volume or HbA1c [58].

Using a DPP-4 inhibitor lowers HbA1c levels without changing body weight. When compared to sulphonylureas, both medications have a minimal risk of resulting in hypoglycemia [56, 57].

In light of this, two clinical investigations evaluated the effectiveness of the combination of SGLT2i and DPP4i in individuals with elevated liver fat content and T2DM. The effects of dapagliflozin (10 mg) plus saxagliptin (5 mg) plus metformin (1500 mg as background therapy) versus glimepiride (1-6 mg) plus metformin (1500 mg as background therapy) on liver fat (proton density fat fraction) and visceral and subcutaneous adipose tissue volumes were compared in a 52-week multicenter, randomized, double-blind, parallel-group trial. Magnetic resonance imaging was performed on 59 patients; liver fat and adipose tissue volumes were analysed for 59 and 57 patients, respectively.

At week 52, dapagliflozin with saxagliptin plus metformin significantly reduced liver fat by >30% from baseline ($P = 0.007$) and adipose tissue volumes by >10% (P 0.01) compared to glimepiride

plus metformin. Over the course of 52 weeks, dapagliflozin with saxagliptin plus metformin reduced body weight and blood alanine and aspartate aminotransferase levels in the full-study group. According to the study's findings, dapagliflozin with saxagliptin significantly reduced liver fat and adipose tissue volume compared to glimepiride and decreased blood levels of liver enzymes, indicating a favorable metabolic profile in type 2 diabetics using metformin treatment [57].

To report the findings of a 104-week extension to a 52-week study in which participants with T2DM receiving background metformin responded better to dapagliflozin plus saxagliptin (DAPA+SAXA) than to glimepiride (GLIM) in terms of glycaemic control, liver fat, and metabolic variables, a global, multicentre, parallel group, active-controlled, double-blind study was conducted. The patients (n = 382) kept receiving once-daily DAPA+SAXA (10/5 mg) or GLIM (1-6 mg) with placebo. Reaching therapeutic glycaemic response, achieving HbA1c 53 mmol/mol (7%), changes in adipose tissue and liver fat on magnetic resonance imaging, and changes in adipose tissue and liver fat were the primary outcomes reported. DAPA+SAXA+MET required less treatment intensification throughout the course of the 156-week period than GLIM+MET (55.6%; hazard ratio 0.52; 95% confidence interval [CI] 0.39-0.68; P 0.001). At week 156, therapeutic glycaemic response was attained by 21.4% of DAPA+SAXA+MET individuals versus 11.7% of GLIM+MET participants (HbA1c 53 mmol/mol; odds ratio 2.1, 95% CI 1.23-3.42; P = 0.006). When compared to GLIM+MET at week 122, DAPA+SAXA+MET caused higher adjusted mean reductions from baseline in liver fat, visceral and subcutaneous adipose tissue volumes (least-squares mean difference from GLIM+MET 4.89%, 0.41 L and 0.44 L, respectively; nominal P values 0.008) [58].

In conclusion, based on the above studies, the combination of SGLT2i and DPP-4i may not only be effective in reducing HBA1C but also prevent progression of fatty liver along with significant weight loss. The combination may be effective and alternative therapeutic option for decreasing progression of MAFLD in patients with T2DM. However, further studies are warranted to confirm these effects.

10. Conclusion

Pathophysiologically, MAFLD and T2DM are related because MAFLD raises the risk of diabetes and diabetes raises the risk of MAFLD. Metabolic syndrome and obesity are linked to MAFLD and diabetes. Anti-diabetic drugs may be the preferred course of treatment for diabetic people to lower their risk of MAFLD. Recently created SGLT2 inhibitors and DPP4 inhibitors have demonstrated notable efficacy in decreasing hepatic steatosis and liver fat. Weight loss brought on by SGLT2i is accompanied by a decrease in subcutaneous, visceral, and total body fat volumes as well as total body fat mass. In individuals with T2DM and MAFLD, SGLT2 inhibitors (Dapagliflozin) are also shown to lower the blood level of soluble dipeptidyl peptidase-4, which is strongly correlated with liver enzymes. Regardless of the stage of T2DM, DPP-4 inhibitor lowers HbA1c without having any clinically meaningful impact on body weight. DPP4 is expressed and secreted by the liver, and the amount of hepatic DPP4 expression is correlated with the degree of hepatic steatosis in NASH patients. Increased hepatic DPP4 expression aided in the development of MAFLD. Hepatic DPP-4 expression and serum DPP-4 activity are associated to the severity of MAFLD. Patients with MAFLD had considerably greater hepatic expression of DPP-4 when compared to healthy individuals. For the treatment of MAFLD, DPP-4 inhibitors have been researched as a potential therapeutic approach. Additionally, sitagliptin is the most researched DPP4 inhibitors molecule for the therapy of MAFLD among other gliptins in diabetic patients. According to reports, sitagliptin lowers NASH scores and reduces hepatic steatosis.

In conclusion, based on above data, in T2DM patients with MAFLD, the combination of SGLT2 inhibitors and DPP4 inhibitors may significantly contribute to additive effects in lowering hepatic steatosis and enhancing liver function.

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