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ANTI-DIABETIC EFFECT IN PATIENTS WITH HYPERTENSION AND LIVER DISEASE: AN INTEGRATED THERAPEUTIC PERSPECTIVE

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ABSTRACT

The comorbidity that is also known as the co-occurrence of chronic diseases is a subject that has become a dominant topic in the global population health discussion. Some of the most common and clinically significant comorbid conditions include diabetes mellitus (DM), hypertension, and liver disease, particularly, non-alcoholic fatty liver disease (NAFLD). These diseases usually have common etiological risk factors and are co-occurring, thus a large burden on health-care systems across the globe. The current prevalence of type 2 diabetes mellitus (T2DM) is more than 500 million worldwide. Insulin resistance is one of the distinguishing features of T2DM and this predisposes individuals to numerous complications. Hypertension is the most common comorbidity among patients with diabetes, which is present in about 50-80 percent of them. The presence of diabetes and hypertension exacerbates the risk of cardiovascular disease, cerebral events, kidney damage, and early death significantly, thus making the successful treatment of this two-fold pathology a top clinical goal. The liver disease, especially NAFLD, is very common in people who are diabetic. Epidemiological research estimates a figure of 70 3/4th percentage of T2DM patients to show hepatic steatosis. There is a spectrum of NAFLD, including the simple steatosis and non-alcoholic steatohepatitis (NASH), hepatic fibrosis, and cirrhosis, which can eventually lead to liver failure. Together, this triad significantly increases the morbidity, morbidity and the general burden on health-care resources. The use of early preventive measures, which involve lifestyle change, weight control, and combined therapeutic options, are invaluable in terms of risk reduction and the improvement of long-term outcomes.

KEYWORDS: Diabetes mellitus, Hypertension, liver disease, Anti-diabetic drugs, NAFLD, Pharmacotherapy, Cardiovascular risk, Hepatotoxicity.

1. INTRODUCTION

Combination of diabetes mellitus (DM), hypertension and hepatic disease is a significant health issue in the world. Recent epidemiological evidence shows that over 500 million people around the globe have DM, and hypertension is the most prevalent comorbidity in this group of people [1]. Non-alcoholic fatty liver disease (NAFLD) is also very common, with a prevalence of up to 70 percent in patients with type 2 diabetes mellitus (T2DM) and resulting in severe hepatic steatosis. Together, all three triad significantly increase the morbidity, mortality, and burden of the healthcare systems [2]. The conditions have complex and multifactorial interdependence. Insulin resistance is one of the major pathogenic processes that maintain hyperglycaemia, hypertension, and lipid buildup in the liver. [3]. There are also other factors that contribute to the disease progression acceleration such as sustained inflammation, oxidative stress, endothelial dysfunction, and dysregulated lipid metabolism. [4]. The contribution of these overlapping mechanisms to clinical outcomes is not only an increase to a vicious cycle of deranged metabolism but also a self-perpetuating cycle that is itself resistant to traditional interventions [5]. Therapeutic management of DM in the presence of concomitant hypertension and liver disease presents unique challenges [6]. Pharmacologic regimens should be carefully chosen to attenuate the possible drug-drug interactions, organ-specific toxicity, and altered pharmacokinetics that can be blamed to hepatic impairment [7]. Traditional drugs like metformin, sulfonylureas, and insulin still are the primary pillars of the treatment; nevertheless, their applicability can be limited to patients with severe liver impairment or to those with increased cardiovascular risk [8]. New pharmacotherapeutic agents such as glucagon-like peptide-1 (GLP-1) receptor agonists and sodium-glucose co-transporter-2 (SGLT-2) inhibitors have also shown promising effects on glycaemic control and also provide cardiovascular and hepatic advantages [9]. To sum up, developing a well-rounded perspective on the multifaceted interaction of DM, hypertension, and hepatic disease is a requirement to provide maximum benefit to patients [10]. Complicated and combined care plans are critical towards reducing the severity and improving clinical outcomes [11].

2. Pathophysiological Interplay Between Diabetes, Hypertension, and Liver Disease

2.1 Shared Risk Factors

2.1.1 Obesity and Insulin Resistance:

Central obesity is one of the major causes of insulin resistance, which serves as a common mechanistic interplay between diabetes mellitus (DM), hypertension, and non-alcoholic fatty liver disease (NAFLD) [12]. Increased accumulation of the visceral adipose tissue triggers the release of free fatty acids and pro-inflammatory cytokines that disrupt insulin signal pathways and facilitate the development of metabolic dysfunction on a systemic basis of type 2 diabetes, hypertension exacerbation, and the hepatic steatosis onset, The results of these changes are hyperglycaemia, increased blood pressure, and lipid deposition on the liver [13]. In the long-lasting perspective, the insulin resistance leads to the development which highlights the central role of obesity in the interrelated pathophysiology of these chronic diseases [14].

2.1.2 Inflammation

Inflammation has been proved as playing a central role between diabetes, hypertension and hepatic pathology [15]. The continued low grade systemic inflammation triggers the changes in vascular homeostasis, leading to endothelial dysfunction and arterial stiffening, and ultimately promotes the onset of hypertension [16]. High levels of inflammatory biomarkers (primarily C -reactive protein and interleukin levels) are also involved in oxidative stress and weakening insulin signals, which increases insulin resistance [17]. The chronic stimuli of inflammatory process in the liver microenvironment has been linked to the onset of fibrogenesis, and thus, leading to the progression of non-alcoholic fatty liver disease (NAFLD), and in the worst case, cirrhosis [18]. Such state of chronic inflammation creates a self-perpetuating loop of metabolic derangements, vascular damage, and hepatic fibrosis, which further exacerbate each other in an overall increase in cardiometabolic disease burden [19].

2.1.3 Oxidative Stress

Oxidative stress is a life-threatening mechanistic pathway between diabetes mellitus, hypertension, and hepatic pathology. Prolonged hyperglycaemia facilitates the formation of surplus reactive oxygen species (ROS) by means of autoxidation by glucotoxicity and mitochondrial dysfunction.[20]. Likewise, hypertension causes oxidative stress by elevating the vascular shear forces, as well as activating the NADPH oxidase pathways [21]. The ensuing increase of reactive oxygen species triggers endothelial damage, reduces the bioavailability of nitric-oxide, and reduces vasodilatory ability, thus enhancing endothelial

malfunction and promoting vascular constriction.[3]. At the hepatic tissue, oxidative stress triggers lipid peroxidation, hepatocellular damage and hepatic stellate cell-activation, ultimately leading to fibrogenesis [22]. This chronic oxidative stress perpetrates a vicious cycle of metabolic imbalance, vascular damage and chronic liver disease [23].

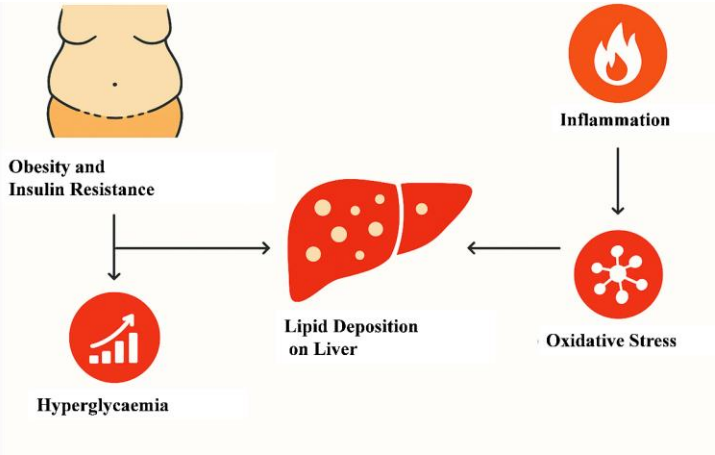

Fig.1 Pathophysiological interplay between diabetes, hypertension and liver disease.

2.2 Mechanistic Connections

2.2.1 Reninangiotensinaldosterone system (RAAS)

RAAS is a key factor in the nexus of diabetes mellitus, hypertension and hepatic disease. RAAS activity is upregulated in states with hyperinsulinemia and insulin resistance, thus increasing angiotensin 2 and aldosterone biosynthesis [24]. The Angiotensin II promotes vasoconstriction, sodium retention, and remodeling of the vascularity, which together lead to long-term hypertension. In addition, angiotensin II and aldosterone trigger oxidative stress and pro-inflammatory signalling cascades and accelerate endothelial dysfunction [25]. In hepatic tissue, RAAS stimulation enhances hepatic stellate cell activity and collagen deposition, and stimulates fibrogenesis in non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH). The ultimate result of dysregulation of the RAAS is, therefore, overlapping cardiovascular and hepatic sequelae [26].

2.2.2 Dyslipidaemia

Abnormal lipid metabolism exacerbates fatty liver progression and cardiovascular risk. Dyslipidaemia is a common metabolic imbalance in people with diabetes mellitus, hypertension and hepatic diseases, and therefore significantly contributes to the development of diseases [27]. Insulin resistance disrupts lipid homeostasis, which leads to hypertriglyceridemia, diminished high-density lipoprotein cholesterol, and the formation of small dense low-density lipoprotein subfractions. Such atherogenic lipoprotein assemblies

worsen endpoint dysfunction and hasten the atherogenic process, thus increasing cardiovascular morbidity and mortality [28]. In the liver tissue, excess free fatty acids are esterified and stored as triglycerides, which stimulates the progression of hepatic steatosis. The following progressive lipid deposition leads to lip toxicity, oxidative stress, and inflammatory cascades and promotes the progression of simple steatosis to non-alcoholic steatohepatitis and eventual fibrosis. Subsequently, a state of dyslipidaemia not only worsens the hepatic damage, but also cardiovascular sequels, creating a dual-organ pathology [29].

2.2.3 Endothelial Dysfunction

The presence of diabetes mellitus and hypertension has a particular element in common that leads to the impaired hepatic perfusion. Endothelial dysfunction plays a central mechanistic pivotal point in the interrelation between diabetes mellitus, hypertension, and hepatic pathology. Prolonged hyperglycemia and insulin resistance that is found in diabetes mellitus reduces the nitric-oxide bioavailability and reduces vasodilatory function. [30]. In the hypertensive milieu, sustained vascular shear's stress and activation of the renin-angiotensin-aldosterone system cause endothelial injury and occurrence of vascular remodeling. Suboptimal vascular function results in increased vascular stiffness, inflammation and a pro-thrombotic environment, which promotes cardiovascular risk [31]. In relation to hepatic implications, microcirculatory integrity and perfusion in the liver is impaired by endothelial dysfunction, worsening hypoxia and promoting fibrogenesis. All these changes together create a vicious cycle of vascular and metabolic damage, thus, connecting systemic vascular disease to the development of non-alcoholic fatty liver disease (NAFLD) [32].

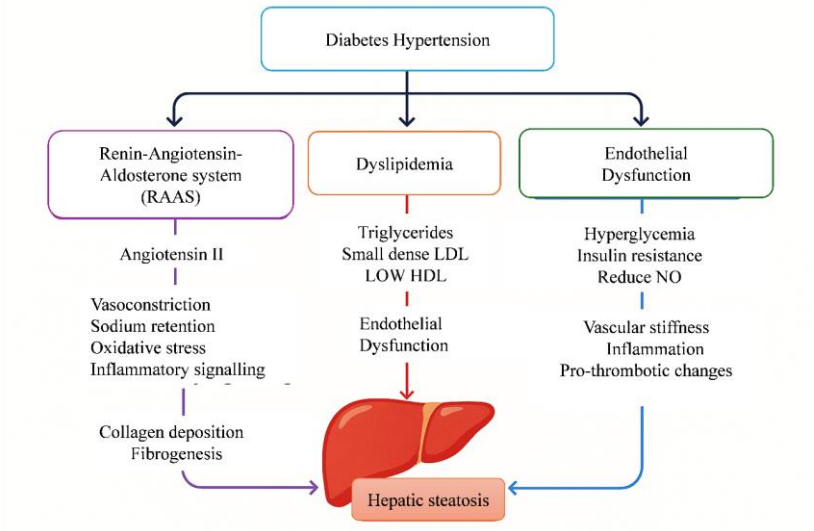

Fig.2 Mechanistic Connections with Renin angiotensin aldosterone system, Dyslipidaemia, Endothelial Dysfunction.

3. Anti-Diabetic Therapies in Patients with Hypertension

3.1 Metformin

Metformin improves insulin sensitivity and is associated with modest blood pressure reduction due to its vascular and metabolic benefits. It remains the first-line therapy in T2DM, though caution is required in advanced liver dysfunction due to lactic acidosis risk [33]. Metformin is the first drug treatment option in the management of type 2 diabetes mellitus (T2DM) due to the ability to increase insulin sensitivity and reduce hepatic gluconeogenesis. Along with the glycaemic control, metformin presents cardiovascular and metabolic benefits with small changes in blood pressure in the arteries and positive lipid profile changes [34]. It enhances the work of endothelial cells and reduces systemic inflammation and oxidative stress, which adds to a decreased cardiovascular risk profile. In hepatic pathology patients, the use of metformin can delay the onset of non-alcoholic fatty liver disease (NAFLD); however, its use requires caution in severe hepatic dysfunction where the clearance rate decreases, increasing the risk of occurrence of lactic acidosis, a severe side effect, which is uncommon but fatal [35].

3.2 SGLT2 Inhibitors

SGLT2 inhibitors (e.g., empagliflozin, dapagliflozin) reduce hyperglycemia by promoting glucosuria. They also lower blood pressure via osmotic diuresis and natriuresis. Clinical trials demonstrate cardiovascular and renal benefits, making them attractive in hypertensive diabetics [36]. SodiumgetElementById cotransporter-2 (SGLT2) inhibitors, including empagliflozin and dapagliflozin, are a group of antidiabetic medications used orally, which reduces plasma glucose levels by blocking SGLT2 in the proximal convoluted tubules of the kidney, thus prompting glucosuria. The resulting glucosuria stimulates additional osmotic diuresis and natriuresis which in turn lead to a slight decrease in the blood pressure of the bodies and body weight decrease [37]. Besides the glycaemic effects, extensive randomized controlled trials have shown that SGLT2 inhibition has significant cardiovascular and renal outcomes, reflected in fewer hospitalizations with heart-failure and slower progression of chronic kidney disease [38]. Subsequently, SGLT2 inhibitors are especially beneficial to hypertensive, diabetic patients. However, their utilization can increase the risk of genital mycotic infections, atrophy of the volume, and as a rare but potentially dangerous event, diabetic ketoacidosis, which requires a care-taker to carefully monitor the condition [39].

3.3 GLP-1 Receptor Agonists

GLP-1 agonists improve glycaemic control and induce weight loss. Evidence suggests modest blood pressure reductions, mediated by improved endothelial function and

natriuresis.GLP-1 receptor agonists are a group of antidiabetic agents that resemble the activity of endogenous glucagon-like peptide-1, and they augment insulin secretions and inhibit glucagon releases in a glucose-dependent fashion [40]. These agents enhance glycaemic control and, in addition, cause considerable weight loss, mostly by suppressing the appetite and slowing gastric emptying. The clinical evidence suggests that GLP-1 receptor agonists are involved in the contribution of a small blood pressure reduction [41]. The mechanism is believed to constitute an enhanced endothelial activity, increased vasodilation, and slight natriuresis. Moreover, they have cardiovascular protective effects, and thus they are very useful in overweight, hypertensive, or high-risk cardiovascular patients with type 2 diabetes [42].

3.4 DPP-4 Inhibitors

These agents exert neutral effects on blood pressure but are valuable for glycaemic control in patient's intolerant to other drugs. Their cardiovascular safety profile supports their use in hypertensive diabetics [43]. Dipeptidyl peptidase-4 (DPP-4) inhibitors are oral antidiabetic agents, which stimulate insulin secretion by preserving the activity of glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), while inhibiting the release of glucagon in a glucagon-dependent manner [44]. The agents are usually weight-neutral and have low chances of causing hypoglycaemia making them suitable in a wide range of patients. DPP-4 inhibitor has a neutral effect on blood pressure; however, it is still useful in achieving glycaemic control, especially in patients who cannot be put under other antidiabetic agents. Their developed cardiovascular safety profile also supports their use in hypertensive diabetic patients particularly when weight loss or blood pressure is not a treatment priority [45].

3.5 Insulin

Exogenous insulin remains a cornerstone in uncontrolled diabetes but may exacerbate weight gain and fluid retention, potentially worsening hypertension. Exogenous insulin therapy has remained an essential part of the therapeutic arsenal in the provision of treatment to patients with uncontrolled diabetes mellitus, especially when oral hypoglycaemic agents or new injectable preparations are unable to achieve preset goals of glycaemic control [46]. Exogenous insulin reduces the occurrence of microvascular sequelae by significantly reducing hyperglycaemia, as well as promoting overall metabolic control. However, its treatment is often combatant with a gain in body mass, which can be explained by increased adipogenesis and reduced glycosuria and, as a result, reinforced adiposity and insulin resistance [47]. In addition, the insulin therapy could cause natriuretic retardation and

interstitial fluid sequestration, triggering or accelerating systemic hypertension. These pharmacodynamic effects require close attention to arterial pressure, dietary and physical activity interventions and in some cases, the antihypertensive agents should be co-administered in the patient receiving insulin therapy [48].

Table 1. Anti-Diabetic Drugs and Their Impact on Hypertension.

Drug Class	Effect on Blood Pressure	Cardiovascular Outcomes	References
Metformin	Mild reduction	Neutral/beneficial	[49]
SGLT2 inhibitors	Moderate reduction	Strongly beneficial	[45]
GLP-1 receptor agonists	Mild reduction	Beneficial	[50]
DPP-4 inhibitors	Neutral	Neutral	[51]
Insulin	May increase BP	Neutral/variable	[52]
TZDs	May increase BP	Mixed/concern	[53]

4. Anti-Diabetic Therapies in Patients with Liver Disease

4.1 Metformin

Metformin is safe in patients with NAFLD and early fibrosis, improving hepatic steatosis and insulin sensitivity. However, it is contraindicated in advanced cirrhosis due to lactic acidosis risk. Metformin is the first-line oral pharmacologic therapy of type 2 diabetes mellitus and is considered safe in patients with non-alcoholic fatty liver disease (NAFLD) and in early hepatic fibrosis [54]. The medication enhances the insulin response, suppresses hepatic glucose synthesis, and has been shown to such an extent as to reduce hepatic steatosis, the effect of which provides metabolic and hepatic benefits. Its weight-neutral nature, together with a proven safety in cardiovascular use, make it a popular choice among the patients with metabolic syndrome [55]. However, caution is necessary in severe hepatic disease or in cirrhosis, in which the possibility of lactic acidosis is highly pronounced. As a result, metformin has advantages in NAFLD, although its consumption is contraindicated in people with decompensated cirrhosis or intense hepatic dysfunction [56].

4.2 Thiazolidinediones (TZDs)

Pioglitazone improves insulin sensitivity and histological outcomes in NAFLD/NASH but may cause weight gain and fluid retention, limiting use in cirrhotic patients. Thiazolidinedione, especially the use of pioglitazone, is one of the most potent insulin sensitizers via peroxisome proliferator-activated receptor gamma (PPAR7) [57]. They increase the uptake of peripheral glucose and reduce hepatic insulin resistance. The ability of pioglitazone to ameliorate histological parameters including steatosis, inflammatory activity

and fibrosis regression has been supported in clinical trials in patients with non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) [58]. However, its clinical use is limited by its side effects, which include weight gain, fluid retention, and increased likelihood of edam that can lead to the worsening of heart failure, or even worsening cirrhosis. Therefore, although pioglitazone has therapeutic effects in the initial phases of NAFLD/NASH, thiazolidinediones are to be used carefully and must be avoided in severe hepatic disease [37].

4.3 GLP-1 Receptor Agonists

GLP-1 agonists demonstrate hepatoprotective effects by reducing steatosis, inflammation, and fibrosis. Ongoing trials suggest their role in NASH management. The glucagon-like peptide-1 (GLP-1) receptor agonists represent an incretin-based therapeutic group that does not only improve glycaemic homeostasis and leads to substantial adiposity loss, but also presents hepatoprotective effects [59]. Recent literature shows that GLP -1 agonists lower hepatic steatosis, inflammation, and fibrogenesis, mainly by mechanisms that enhance insulin sensitivity, weight loss, and lip toxicity. They have shown promising results in clinical studies on patients with non-alcoholic fatty liver disease (NAFLD), as well as non-alcoholic steatohepatitis (NASH), and therefore have a higher purpose than merely managing diabetes [60]. Even though the NASH is yet to be approved, on-going studies are shaping the therapeutic potential of the molecules and a promising future in the treatment of metabolic liver disease is expected [61].

4.4 SGLT2 Inhibitors

These agents show promise in improving hepatic steatosis and reducing liver fat content while offering cardiovascular protection. Sodium-glucose-co-transporter-2 (SGLT2) inhibitors like empagliflozin and dapagliflozin are antidiabetic drugs that promote glycosuria and improve the insulin sensitivity [62]. Besides their well-reported cardiovascular and renal efficacy, the drugs have demonstrated possible hepatic health benefits as well, especially in patients with non-alcoholic fatty liver disease (NAFLD) [63]. Research studies performed in a clinical setting reveal that, SGLT2 inhibitors lower hepatic steatosis, fat content in liver and ameliorate body weight and fatty adiposities. These positive impacts are majorly owed to elevated lipid oxidation and reduced fat build up in the liver. Despite the fact that long-term data are still awaited, SGLT2 inhibitors are a potential helpful strategy [57].

4.5 DPP-4 Inhibitors

DPP-4 inhibitors exhibit hepatoprotective effects in preclinical models but clinical benefits remain inconclusive. Dipeptidyl peptidase-4 (DPP-4) inhibitors are oral antidiabetic agents

that enhance endogenous incretin effects by inhibiting the enzyme degradation of glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) and thereby improve glycaemic control with no clinically significant risk of causing hypoglycaemia [64]. All these agents have shown potential hepatoprotective properties in preclinical studies, such as reducing oxidative stress and hepatic inflammation, and fibrogenesis. The potential to therapeutically apply these observations to non-alcoholic fatty liver disease (NAFLD) and related metabolic hepatic disorders is raised [65]. Nevertheless, the existing clinical evidence is limited and inconclusive, and randomized controlled trials on the topic have produced inconsistent findings in the context of hepatic enzyme and histopathological parameter improvement. Theoretical potential therefore is present, but more intensive long-term clinical studies are justified to ascertain irrefutable hepatic advantages [64].

4.6 Insulin

While effective for glycaemic control, insulin therapy may worsen NAFLD progression due to its anabolic effects on lipid metabolism. Insulin still forms the basis of treatment approaches to diabetes especially when the patient portrays a high level of hyperglycemia or lack of responsiveness to oral pharmacotherapies [66]. It successfully lowers the level of glycaemic through the insulin-like uptake of glucose to the cells, and lowers gluconeogenesis in the liver. Nevertheless, its impact on hepatic activity is of concern. Insulin anabolic effects can lead to lipogenesis, which might worsen hepatic steatosis and may further initiate the progression of non-alcoholic fatty liver disease (NAFLD) [67]. In addition, insulin administration is often accompanied by the gain of weight which further worsens the metabolic control. Nevertheless, insulin has become an unavoidable tool in the therapy of many patients due to these constraints, which is why close attention and the use of unique intervention plans should be used to stabilize its benefits and harms [68].

Table 2. Anti-Diabetic Drugs and Their Impact on Liver Disease.

Drug Class	Effect on Liver Disease	Safety Considerations	References
Metformin	Improves steatosis	Contraindicated in advanced cirrhosis	[69]
SGLT2 inhibitors	Reduces steatosis, hepatoprotection	Good safety profile	[70]
GLP-1 receptor agonists	Reduces steatosis and fibrosis	Generally safe	[71]
DPP-4 inhibitors	Possible hepatoprotection	Inconclusive benefits	[72]
Insulin	May worsen steatosis	Risk of weight gain	[72]
TZDs	Improves NASH, fibrosis	Risk of fluid retention, heart failure	[73]

5. Clinical Evidence

Several randomized controlled trials and meta-analyses have evaluated the efficacy of anti-diabetic drugs in patients with hypertension and liver disease. The EMPA-REG OUTCOME and CANVAS trials highlighted the dual benefit of SGLT2 inhibitors on cardiovascular and hepatic endpoints. Similarly, GLP-1 receptor agonists such as liraglutide have shown beneficial effects in NASH resolution and blood pressure reduction [74]. A number of randomized controlled trials and meta-analyses have been conducted to find out the effectiveness of antidiabetic treatment in patients with concomitant liver disease and hypertension. The works like the EMPA-REG OUTCOME and CANVAS trials proved that SGLT2 inhibitors do not only enhance the glycaemic control but also cause extensive cardiovascular protection and it might have other advantages that can be an improvement in hepatic steatosis [75]. Similarly, GLP-1 receptor agonists, such as liraglutide and similitude, have demonstrated themselves as effective in improving non-alcoholic steatohepatitis (NASH) resolution, weight loss, and a minor decrease in blood pressure. In spite of these positive results, additional, large-scale, long-term research is needed to confirm their hepatoprotective benefits and to explain their new place in clinical practice [76].

Table3 Case studies.

Category	**Case 1**[96] [97]	**Case 2** [98]	**Case 3**[99] [100]	**Case 4**[101] [102]
Symptoms	Fatigue, polyuria, mild RUQ pain, weight gain	Weakness, ankle edema, headaches	Ascites, jaundice, muscle wasting, confusion	Post-meal fatigue, bloating, snoring, weight gain
Duration	6–8 months	1 year	3 months worsening	2 years
Severity	Moderate	Moderate–severe	Severe	Mild–moderate
Culture Report	Urine culture: *No growth*	HBV DNA positive, high viral load	Ascitic fluid: *E. coli* (SBP)	Stool culture: Normal
Imaging / Scan Findings	USG: Fatty liver grade II; no fibrosis	FibroScan: F2 fibrosis; mild splenomegaly	CT: Nodular liver, ascites, portal HTN	MRI-PDFF: Moderate steatosis; no fibrosis
Treatment Plan	Continue metformin; add SGLT2 inhibitor and GLP-1 RA; increase	Start tenofovir; adjust antihypertensives; switch to DPP-4 inhibitor	Stop metformin; insulin therapy; treat SBP; lactulose; cautious diuretics	Start GLP-1 RA; continue metformin; add ACE inhibitor; weight-loss

	losartan			program
Complications	Mild nausea from GLP-1 RA	Mild hyperkalemia	Recurrent ascites; hypoglycemia risk	Mild injection-site reactions
Outcome	HbA1c improved, BP controlled, ALT/AST improved, weight −5%	Viral load suppressed, LFTs improved, BP controlled	Stabilized; requires transplant evaluation	Weight loss 9%; liver fat reduced; HbA1c 6.7%; BP normalized

6. CHALLENGES AND LIMITATIONS

Drug Safety: The risk of hepatotoxicity of specific agents (e.g., thiazolidinediones). The safety profile of the antidiabetic drugs is a critical issue in patients with diabetes mellitus, hypertension, and liver disease. Although many agents have metabolic and cardiovascular advantages, there are issues of hepatotoxicity. [77]. Thiazolidinediones (TZDs), for example, have been associated with fluid retention, weight gain, and rare instances of drug-induced liver injury, necessitating careful monitoring of hepatic function during therapy [78]. Similarly, some older antidiabetic medications have demonstrated adverse hepatic effects, limiting their use in patients with pre-existing liver disease. Conversely, newer agents such as GLP-1 receptor agonists and SGLT2 inhibitors appear safer, though long-term hepatic safety data remain under evaluation [79].

Comorbidities: Polypharmacy increases drug-drug interaction risk. A combination of comorbidities is common to patients diagnosed with diabetes mellitus, hypertension, and hepatic pathology, including obesity, dyslipidaemia, and cardiovascular disease [80]. Polypharmacy is often essential to the therapeutic treatment of these comorbid conditions and significantly increases the risk of drug-drug interactions and adverse pharmacological events. Concomitant use of antihypertensive drugs, lipid-lowering drugs, and antidiabetic drugs can make the treatment regimens complicated, hence reduce the adherence of patients and increase the chances of toxicity [81]. In addition, impaired hepatic metabolism in liver disease may modify drug clearance, and hence increase the chances of drug retention. As a result, the rational choice of pharmacotherapeutic agents, correct dose adjustment, and systematic observation are all that is needed to reduce complications and ensure the best safety and treatment outcomes [82].

Individualized Therapy: Varying severity of hypertension and liver disease demands personalized treatment strategies. Many comorbid conditions (obesity, dyslipidaemia, and

cardiovascular disorders) are common in patients with diabetes mellitus, hypertension, and hepatic disease [83]. The co-occurring nature of these interrelated disorders is a factor that has significantly increased the risk of drug-drug interactions and adverse events due to polypharmacy. The therapeutic regimens are complicated by simultaneous use of antihypertensives, lipid-lowering, and antidiabetic drugs, which may reduce adherence and result in toxicity [84]. In addition, the lower hepatic metabolic rate in liver disease may modify the drugs clearance, increasing the risk of accumulation. As a result, there is a strong need to carefully choose pharmacologic agents, properly titrate doses, and conduct regular follow-up to reduce possible complications and ensure the highest level of patient safety and treatment efficacy [85].

7. Future Perspectives

Precision medicine approaches, integrating pharmacogenomics, biomarkers, and nanotechnology-based drug delivery, are promising. Novel agents targeting inflammation and fibrosis pathways could revolutionize management. Nutraceuticals and herbal formulations are also being investigated [86]. Precision medicine is becoming the new way forward of managing diabetes with comorbid hypertension and liver disease. The pharmacogenomic profiling and biomarker-based methodology could be used to forecast the response to therapy and reduce the adverse effects and to ensure that the best type of drug is selected to use in a particular patient [87]. New nanotechnology-based drug delivery systems have potential to enhance bioavailability and targeted delivery to the liver thereby improving efficacy and decreasing toxicity. Also, there are emerging pharmacological interventions against major inflammatory and fibrotic pathways and which may revolutionize the treatment of non-alcoholic fatty liver disease (NAFLD) and NASH [88]. Similar studies of nutraceuticals and herbal preparations offer complementary approaches to integrated and patient-cantate concept of precision medicine is becoming an optimal change in paradigm in the treatment of diabetes mellitus on top of hypertension and hepatic disease. The integration of biomarker-driven and pharmacogenomic approach could potentially allow clinicians to make predictions on how patients will react to a drug, minimize toxicity, and tailor treatment to patient profiles [87]. Nanotechnological drug delivery models are under investigation in order to enable hepatic targeting, and thus optimization of therapeutic efficacy. In addition, emerging pharmacotherapeutic agents with the ability to modulate inflammatory, oxidative stress, and fibrotic pathways [89]. could have the potential to change the treatment of a non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH). Concomitantly, the growing attention to nutraceuticals and herbal preparations expands further the range of

propositions related to treatment offering more holistic and complementary modalities, which is consistent with patient-centred care models [89].

8. CONCLUSION

Treatment of diabetes in hypertensive liver disease individuals demands a fine balance between efficacy, safety and tolerability of treatment. A combination of these three comorbidities produces overlapping metabolic and vascular impairments that make the choice of treatment difficult [90]. Of all the existing types of therapy, sodium-glucose co-transporter 2 (SGLT2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists should be identified as particularly advantageous [91]. These drug classes can not only increase glycaemic control, but can also play a role in lowering blood pressure, improved cardiovascular protection and hepatoprotective effects, such as non-alcoholic fatty liver disease (NAFLD) [91]. Clinical trials are invariably associated with decreased risk of heart failure, enhanced renal outcomes, and amelioration of hepatic steatosis and fibrosis, which render them appealing treatment alternatives in high-risk groups. Conventional agents, such as insulin, metformin, and sulfonylureas still play a crucial role in the treatment of diabetes [92]. Nevertheless, they should be used with care in the presence of major liver dysfunction since the hypoglycaemia, lactic acidosis, or hepatotoxicity risks are likely to occur. Individual dosing and close observation are thus necessary in order to maximize the outcomes and reduce the harm [93]. In the future, cardiometabolic and hepatoprotective effects are more likely to be combined in a holistic manner in future therapeutic approaches. This could be facilitated by additional developments in the field of precision medicine, such as pharmacogenomics, biomarkers, and new drug delivery methods, which could facilitate truly individualized treatment [94]. This is not only to attain glycaemic control but also to decrease the cardiovascular disease, complications of high blood pressure, and progressive liver damage. An increased, patient-cantered care approach has a potential to help in improving clinical outcomes and quality of life in this high-risk and complicated population [95].

Ethical Statement

This article does not contain any studies with human participants or animals performed by any of the authors. All the information presented in this review is compiled from previously published and ethically approved studies.

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Conflict of Interest

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