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Review

Anti-Diabetic Therapy in Patients with Hypertension and Liver Disease: A Narrative Review of Integrated Therapeutic Perspectives

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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, Non-alcoholic fatty liver disease, Pharmacotherapy, Cardiovascular risk, Hepatotoxicity

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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]. This article is a narrative review that aims to provide an integrated overview of the pathophysiological interactions among DM, hypertension, and liver disease, with particular emphasis on shared molecular mechanisms, therapeutic strategies, and cardiovascular outcomes.

2. Methodology

This narrative review was conducted to provide an integrated overview of the pathophysiological interactions, clinical implications, and therapeutic management of DM, hypertension, and liver disease. Relevant literature was identified through searches of electronic databases including PubMed, Scopus, Google Scholar, and Web of Science.

The literature search focused on articles published between 2010 and 2025 using combinations of the following keywords: “diabetes mellitus,” “type 2 diabetes,” “hypertension,” “liver disease,” “non-alcoholic fatty liver disease,” “metabolic dysfunction-associated steatotic liver disease,” “insulin resistance,” “cardiovascular risk,” “anti-diabetic therapy,” “GLP-1 receptor agonists,” and “SGLT2 inhibitors.”

Original research articles, clinical trials, meta-analyses, systematic reviews, narrative reviews, and clinical practice guidelines published in English were considered for inclusion. Articles with limited relevance to the topic, duplicate publications, and studies lacking sufficient scientific quality were excluded.

The selected literature was critically reviewed and synthesized narratively to summarize current evidence regarding the interconnected mechanisms linking diabetes, hypertension, and liver disease, as well as contemporary therapeutic approaches and their implications for cardiovascular and hepatic outcomes.

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

3.1 Shared Risk Factors

3.1.1 Obesity and Insulin Resistance

Central obesity is one of the major causes of insulin resistance, which serves as a common mechanistic interplay between DM, hypertension, and 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 T2DM, hypertension exacerbation, and the hepatic steatosis onset, The results of these changes are hyperglycaemia, increased blood pressure (BP), 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].

3.1.2 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 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]. Recent clinical investigations have further highlighted the importance of inflammatory biomarkers in metabolic disorders, demonstrating altered inflammatory marker profiles in conditions associated with insulin resistance and metabolic dysfunction. These findings support the role of inflammation as a key contributor to disease progression and metabolic complications [20,21].

3.1.3 Oxidative Stress

Oxidative stress is a life-threatening mechanistic pathway between DM, hypertension, and hepatic pathology. Prolonged hyperglycaemia facilitates the formation of surplus reactive oxygen species (ROS) by means of autoxidation by glucotoxicity and mitochondrial dysfunction [22]. Likewise, hypertension causes oxidative stress by elevating the vascular shear forces, as well as activating the NADPH oxidase pathways [23]. The ensuing increase of ROS 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 [24]. This chronic oxidative stress perpetrates a vicious cycle of metabolic imbalance, vascular damage and chronic liver disease [25]. Figure 1 shows the pathophysiological interplay between DM, hypertension, and liver disease. Obesity-induced insulin resistance promotes hyperglycemia and hepatic lipid accumulation. Chronic inflammation and oxidative stress further contribute to hepatic steatosis and disease progression.

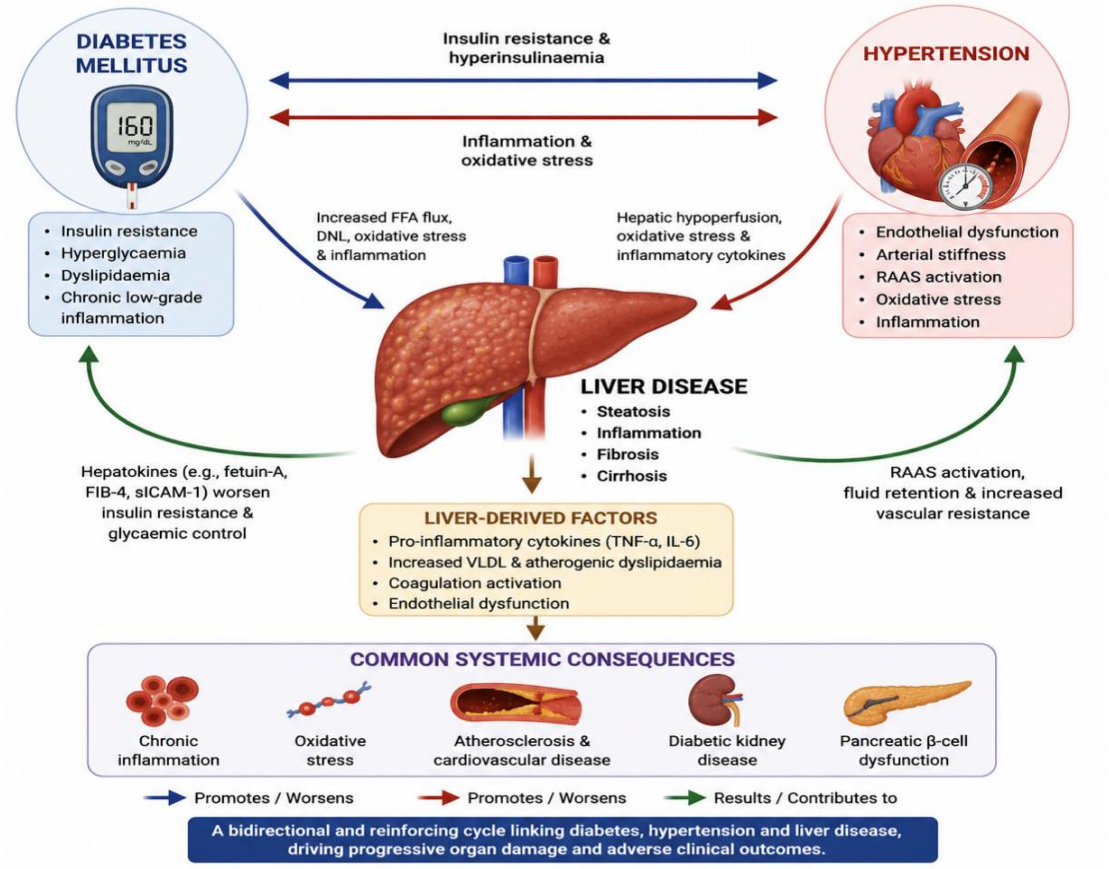

Figure 1. Pathophysiological interplay between DM, hypertension, and liver disease. Obesity-induced insulin resistance promotes hyperglycemia and hepatic lipid accumulation. Chronic inflammation and oxidative stress further contribute to hepatic steatosis and disease progression.

3.2 Mechanistic Connections

3.2.1 Renin-Angiotensin-Aldosterone System (RAAS)

RAAS is a key factor in the nexus of DM, hypertension and hepatic disease. RAAS activity is upregulated in states with hyperinsulinemia and insulin resistance, thus increasing angiotensin 2 and aldosterone biosynthesis [26]. 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 [27]. In hepatic tissue, RAAS stimulation enhances hepatic stellate cell activity and collagen deposition, and stimulates fibrogenesis in NAFLD and non-alcoholic steatohepatitis (NASH). The ultimate result of dysregulation of the RAAS is, therefore, overlapping cardiovascular and hepatic sequelae [28].

3.2.2 Dyslipidaemia

Abnormal lipid metabolism exacerbates fatty liver progression and cardiovascular risk. Dyslipidaemia is a common metabolic imbalance in people with DM, hypertension and hepatic diseases, and therefore significantly contributes to the development of diseases [29]. 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 [30]. 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 NASH and eventual fibrosis. Subsequently, a state of dyslipidaemia not only worsens the hepatic damage, but also cardiovascular sequels, creating a dual-organ pathology [31].

3.2.3 Endothelial Dysfunction

The presence of DM 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 DM, hypertension, and hepatic pathology. Prolonged hyperglycemia and insulin resistance that is found in DM reduces the nitric-oxide bioavailability and reduces vasodilatory function [32]. In the hypertensive milieu, sustained vascular shear's stress and activation of the RAAS 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 [33]. 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 NAFLD [34]. Figure 2 shows the mechanistic connections among the RAAS, dyslipidemia, endothelial dysfunction, and hepatic steatosis. Activation of RAAS, altered lipid metabolism, and vascular dysfunction collectively contribute to liver injury and cardiometabolic complications.

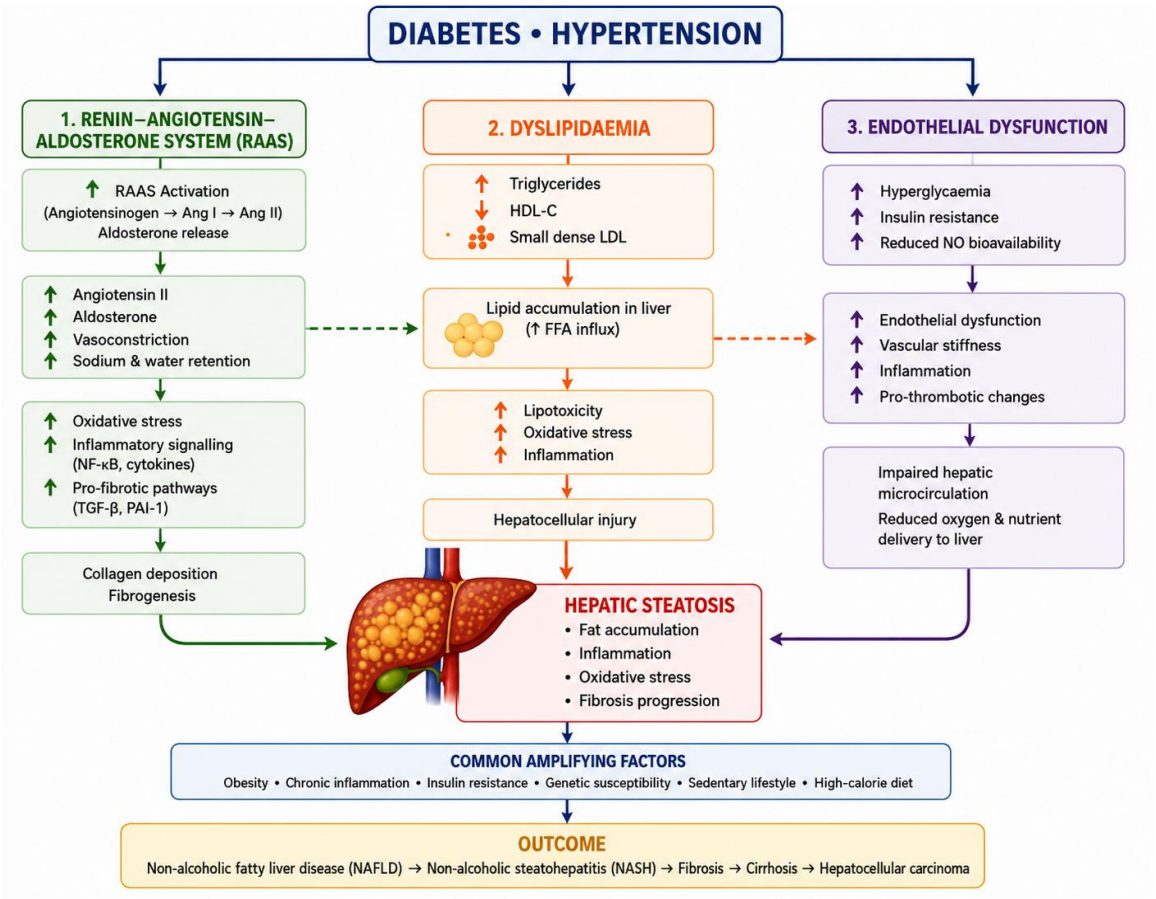

Figure 2. Mechanistic connections among the RAAS, dyslipidemia, endothelial dysfunction, and hepatic steatosis. Activation of RAAS, altered lipid metabolism, and vascular dysfunction collectively contribute to liver injury and cardiometabolic complications.

4. Anti-Diabetic Therapies in Patients with Hypertension

4.1 Metformin

Metformin improves insulin sensitivity and is associated with modest BP 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 [35]. Metformin is the first drug treatment option in the management of 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 BP in the arteries and positive lipid profile changes [36]. 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 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 [37].

4.2 SGLT2 Inhibitors

SGLT2 inhibitors (e.g., empagliflozin, dapagliflozin) reduce hyperglycemia by promoting glucosuria. They also lower BP via osmotic diuresis and natriuresis. Clinical trials demonstrate cardiovascular and renal benefits, making them attractive in hypertensive diabetics [38]. 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 BP of the bodies and body weight decrease [39]. 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 [40]. 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 [41].

4.3 GLP-1 Receptor Agonists

GLP-1 agonists improve glycaemic control and induce weight loss. Evidence suggests modest BP reductions, mediated by improved endothelial function and natriuresis.GLP-1 receptor agonists are a group of antidiabetic agents that resemble the activity of endogenous GLP-1, and they augment insulin secretions and inhibit glucagon releases in a glucose-dependent fashion [42]. 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 BP reduction [43]. 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 T2DM [44].

4.4 Dipeptidyl Peptidase-4 (DPP-4) Inhibitors

These agents exert neutral effects on BP but are valuable for glycaemic control in patient's intolerant to other drugs. Their cardiovascular safety profile supports their use in hypertensive diabetics [45]. DPP-4 inhibitors are oral antidiabetic agents, which stimulate insulin secretion by preserving the activity of GLP-1 and glucose-dependent insulinotropic polypeptide (GIP), while inhibiting the release of glucagon in a glucagon-dependent manner [46]. 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 BP; 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 BP is not a treatment priority [47].

4.5 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 DM, especially when oral hypoglycaemic agents or new injectable preparations are unable to achieve preset goals of glycaemic control [48]. 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 [49]. 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 [50]. The effects of different anti-diabetic drug classes on BP and cardiovascular outcomes are summarized in Table 1.

Table 1. Anti-diabetic drugs and their impact on hypertension.

Drug Class	Effect on BP	Cardiovascular Outcomes	References
Metformin	Mild reduction	Neutral/beneficial	[51]
SGLT2 inhibitors	Moderate reduction	Strongly beneficial	[47]
GLP-1 receptor agonists	Mild reduction	Beneficial	[52]
DPP-4 inhibitors	Neutral	Neutral	[53]
Insulin	May increase BP	Neutral/variable	[54]
TZDs	May increase BP	Mixed/concern	[55]

5. Anti-Diabetic Therapies in Patients with Liver Disease

5.1 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 T2DM and is considered safe in patients with NAFLD and in early hepatic fibrosis [56]. 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 [57]. 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 [58].

5.2 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) [59]. 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 NAFLD and NASH [60]. However, several adverse effects, including weight gain, fluid retention, and an increased risk of edema, which may exacerbate heart failure and worsen hepatic cirrhosis, limit its clinical use. Therefore, although pioglitazone has therapeutic effects in the initial phases of NAFLD/NASH, TZDs are to be used carefully and must be avoided in severe hepatic disease [39].

5.3 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 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 [61]. 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 NAFLD, as well as NASH, and therefore have a higher purpose than merely managing diabetes [62]. 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 [63].

5.4 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 [64]. Besides their well-reported cardiovascular and renal efficacy, the drugs have demonstrated possible hepatic health benefits as well, especially in patients with NAFLD [65]. 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 [59].

5.5 DPP-4 Inhibitors

DPP-4 inhibitors exhibit hepatoprotective effects in preclinical models but clinical benefits remain inconclusive. DPP-4

inhibitors are oral antidiabetic agents that enhance endogenous incretin effects by inhibiting the enzyme degradation of GLP-1 and GIP and thereby improve glycaemic control with no clinically significant risk of causing hypoglycaemia [66]. 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 NAFLD and related metabolic hepatic disorders is raised [67]. 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 [66].

5.6 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 [68]. 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 NAFLD [69]. 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 [70]. The effects of different anti-diabetic drugs on liver disease, including their therapeutic benefits and safety considerations, are summarized in Table 2.

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	[71]
SGLT2 inhibitors	Reduces steatosis, hepatoprotection	Good safety profile	[72]
GLP-1 receptor agonists	Reduces steatosis and fibrosis	Generally safe	[73]
DPP-4 inhibitors	Possible hepatoprotection	Inconclusive benefits	[74]
Insulin	May worsen steatosis	Risk of weight gain	[74]
TZDs	Improves NASH, fibrosis	Risk of fluid retention, heart failure	[75]

5.7 Cardiovascular Benefits of Contemporary Anti-Diabetic Therapies

Recent cardiovascular outcome trials have demonstrated that certain anti-diabetic therapies provide benefits beyond glycemic control. Sodium-glucose cotransporter-2 (SGLT2) inhibitors and GLP-1 receptor agonists have been shown to reduce major adverse cardiovascular events (MACE), heart failure hospitalization, and cardiovascular mortality in patients with T2DM. Landmark clinical trials such as EMPA-REG OUTCOME, LEADER, and DECLARE-TIMI 58 highlighted the cardioprotective effects of these agents, supporting their use in patients at high cardiovascular risk. These findings are particularly relevant in individuals with coexisting diabetes, hypertension, and liver disease, where reduction of cardiovascular complications is a major therapeutic objective.

6. 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 BP reduction [76]. 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 [77]. Similarly, GLP-1 receptor agonists, such as liraglutide and similitude, have demonstrated themselves as effective in improving (NASH) resolution, weight loss, and a minor decrease in BP. 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 [78]. Illustrative clinical scenarios demonstrating the integrated management approach for patients with diabetes, hypertension, and liver disease are presented in Table 3.

Table 3. Illustrative clinical scenarios demonstrating integrated management of diabetes, hypertension, and liver disease.

Category	**Case 1** [79,80]	**Case 2** [81]	**Case 3** [82,83]	**Case 4** [84,85]
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 Hypertension	MRI-PDFF: Moderate steatosis; no fibrosis
Treatment Plan	Continue metformin; add SGLT2 inhibitor and GLP-1 RA; increase losartan	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 Angiotensin-converting enzyme (ACE) inhibitor; weight-loss program
Complications	Mild nausea from GLP-1 RA	Mild hyperkalemia	Recurrent ascites; hypoglycemia risk	Mild injection-site reactions
Outcome	Glycated hemoglobin (HbA1c) improved, BP controlled, alanine aminotransferase (ALT) / aspartate aminotransferase (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

7. Challenges and Limitations

Drug Safety: The risk of hepatotoxicity of specific agents (e.g., TZDs). The safety profile of the antidiabetic drugs is a critical issue in patients with DM, hypertension, and liver disease. Although many agents have metabolic and cardiovascular advantages, there are issues of hepatotoxicity [86]. 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 [87]. 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 [88].

Comorbidities: Polypharmacy increases drug-drug interaction risk. A combination of comorbidities is common to patients diagnosed with DM, hypertension, and hepatic pathology, including obesity, dyslipidaemia, and cardiovascular disease (CVD) [89]. 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 [90]. 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 [91].

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 DM, hypertension, and hepatic disease [92]. 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 [93]. 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 [94].

8. 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. 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. 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 NAFLD and NASH. 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 DM 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. 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. could have the potential to change the treatment of a NAFLD and 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 model.

9. 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. Of all the existing types of therapy, sodium-glucose co-transporter 2 (SGLT2) inhibitors and GLP-1 receptor agonists should be identified as particularly advantageous. These drug classes can not only increase glycaemic control, but can also play a role in lowering BP, improved cardiovascular protection and hepatoprotective effects, such as NAFLD. 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. 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. 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. This is not only to attain glycaemic control but also to decrease the CVD, complications of high BP, 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.

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Ethics Statement

This article is a review article and does not involve any studies with human participants or animals performed by the authors.

Data Availability Statement

No new data were generated or analyzed in this study. All data discussed in this review are derived from previously published literature.

Author Contributions

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Conflict of Interest

The authors declare no conflict of interest.

Generative AI Statement

The authors declare that no generative artificial intelligence technologies were used in the preparation of this manuscript.

Abbreviations

ACE: Angiotensin-converting enzyme

ALT: Alanine aminotransferase

AST: Aspartate aminotransferase

BP: Blood pressure

CVD: Cardiovascular disease

DM: Diabetes mellitus

DPP-4: Dipeptidyl peptidase-4

GIP: Glucose-dependent insulinotropic polypeptide

GLP-1: Glucagon-like peptide-1

HbA1c: Glycated hemoglobin

MACE: Major adverse cardiovascular events

NAFLD: Non-alcoholic fatty liver disease

NASH: Non-alcoholic steatohepatitis

RAAS: Renin-angiotensin-aldosterone system

ROS: Reactive oxygen species

SGLT-2: Sodium-glucose co-transporter-2

T2DM: Type 2 diabetes mellitus

TZDs: Thiazolidinediones

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