

REVIEW ARTICLE

Anti-diabetic effect in patients with hypertension and liver disease: An integrated therapeutic perspective

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Abstract

Comorbidity, defined as the coexistence of multiple chronic diseases, has become a major concern in global healthcare. Among the clinically significant comorbid conditions, diabetes mellitus, hypertension, and liver disease, particularly non-alcoholic fatty liver disease (NAFLD), represent a complex and interrelated pathological triad. These disorders share common etiological factors and contribute substantially to the increasing burden on healthcare systems worldwide. The prevalence of type 2 diabetes mellitus (T2DM) continues to rise globally, with insulin resistance being a major underlying mechanism contributing to metabolic abnormalities and disease progression. Hypertension is one of the most common complications associated with diabetes and significantly increases the risk of cardiovascular disease, cerebrovascular events, renal impairment, and premature mortality. Similarly, NAFLD is highly prevalent among individuals with T2DM and may progress from simple steatosis to non-alcoholic steatohepatitis, fibrosis, cirrhosis, and liver failure. The coexistence of these metabolic disorders further increases morbidity and complicates therapeutic management. This review aims to provide an integrated overview of the pathophysiological association between diabetes mellitus, hypertension, and liver disease, with emphasis on shared mechanisms including insulin resistance, inflammation, oxidative stress, and metabolic dysfunction. Additionally, this article discusses current anti-diabetic therapeutic strategies, their cardiovascular and hepatic benefits, clinical evidence, treatment challenges, and future perspectives for improving outcomes in patients with these comorbid conditions. Overall, early preventive interventions involving lifestyle modification, weight management, and appropriate pharmacological approaches are essential for reducing disease progression and improving long-term clinical outcomes. A personalized and multidisciplinary treatment strategy may provide better therapeutic benefits in individuals affected by this complex metabolic disease combination.

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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% 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 Therefore, this review aims to provide an integrated overview of the relationship between DM, hypertension, and liver disease, highlighting the underlying pathophysiological mechanisms, current anti-diabetic therapeutic approaches, clinical evidence, treatment challenges, and future perspectives for improving patient outcomes.

2. Literature search strategy

This narrative review was conducted to summarize the current evidence regarding the relationship between DM, hypertension, and liver disease, with particular emphasis on pharmacological management strategies for T2DM in patients with associated comorbidities.

A comprehensive literature search was performed using electronic databases including PubMed, Scopus, Web of Science, and Google Scholar. The search included articles published from 2000 to 2025 using keywords and

combinations of terms such as “diabetes mellitus,” “type 2 diabetes,” “hypertension,” “non-alcoholic fatty liver disease,” “metabolic dysfunction-associated steatotic liver disease,” “SGLT2 inhibitors,” “GLP-1 receptor agonists,” “anti-diabetic therapy,” and “cardiovascular outcomes.”

Studies were selected based on their relevance to the topic, including clinical trials, systematic reviews, meta-analyses, observational studies, and important mechanistic studies. Articles focusing on pathophysiological mechanisms, therapeutic efficacy, cardiovascular outcomes, hepatic effects, and safety considerations were included.

Studies unrelated to diabetes-associated comorbidities, non-peer-reviewed sources, duplicate publications, and articles lacking sufficient clinical or mechanistic information were excluded.

As this manuscript represents a narrative review, no formal systematic review protocol or meta-analysis was performed. The available evidence was critically evaluated to summarize therapeutic benefits, limitations, safety concerns, and future perspectives.

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 DM, hypertension, and NAFLD.¹¹ 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.¹² 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.¹³ Figure 1 depicts the pathophysiological interplay between diabetes, hypertension and liver disease.

2.1.2. Inflammation

Inflammation has been proved as playing a central role between diabetes, hypertension and hepatic pathology.¹⁴ 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.¹⁵ 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.¹⁶ 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.¹⁷ 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.¹⁸

2.1.3. 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 autooxidation by glucotoxicity and mitochondrial dysfunction.¹⁹ Likewise, hypertension causes oxidative stress by elevating the vascular shear forces, as well as activating the NADPH oxidase pathways.²⁰ 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.²¹ 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

2.2. Mechanistic connections

2.2.1. Renin–angiotensin–aldosterone system

Renin–angiotensin–aldosterone system (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.²⁴ The angiotensin II promotes vasoconstriction, sodium retention, and remodelling 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

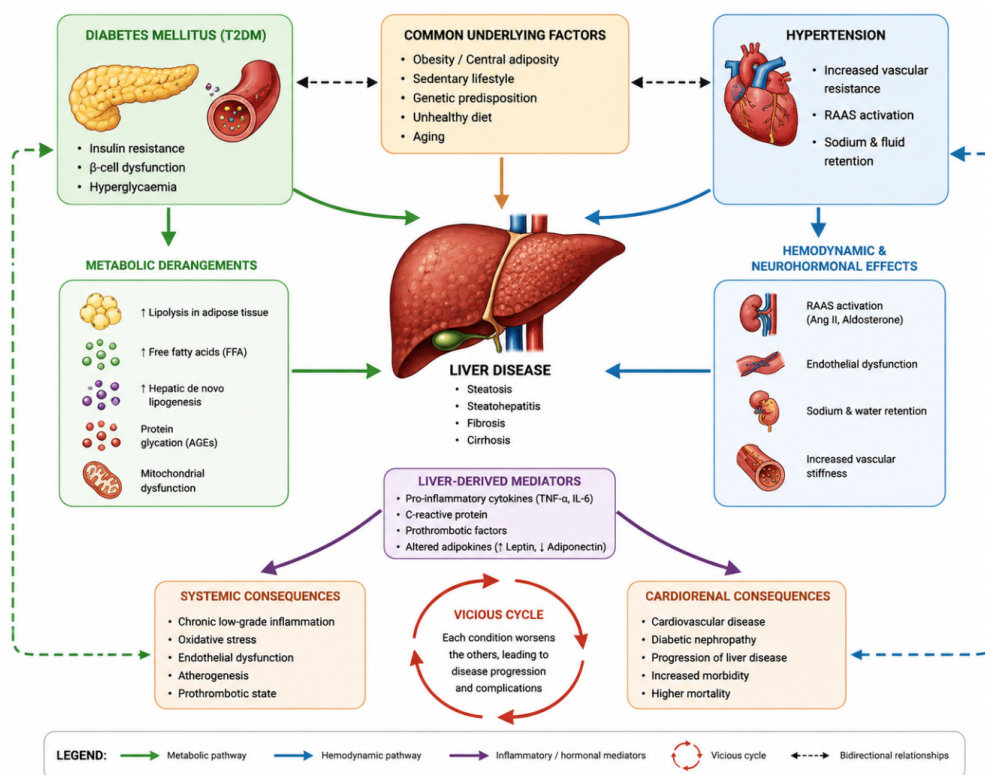


Figure 1. Pathophysiological interplay between diabetes, hypertension and liver disease

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 DM, hypertension and hepatic diseases, and therefore significantly contributes to the development of diseases.²⁷ Insulin resistance disrupts lipid homeostasis, leading to hypertriglyceridaemia, reduced high-density lipoprotein cholesterol (HDL-C), and the formation of small, dense low-density lipoprotein (LDL) particles. These atherogenic lipid abnormalities promote endothelial dysfunction and accelerate the progression of atherosclerosis, thereby increasing the risk of 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 lipotoxicity, 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 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 hyperglycaemia and insulin resistance that is found in DM reduces the nitric-oxide bioavailability and reduces vasodilatory function.³⁰ In the hypertensive milieu, sustained vascular shear's stress and activation of the RAAS cause endothelial injury and occurrence of vascular remodelling. 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 NAFLD.³²

Figure 2 presents mechanistic connections of diabetes and hypertension with RAAS, dyslipidaemia, and endothelial dysfunction.

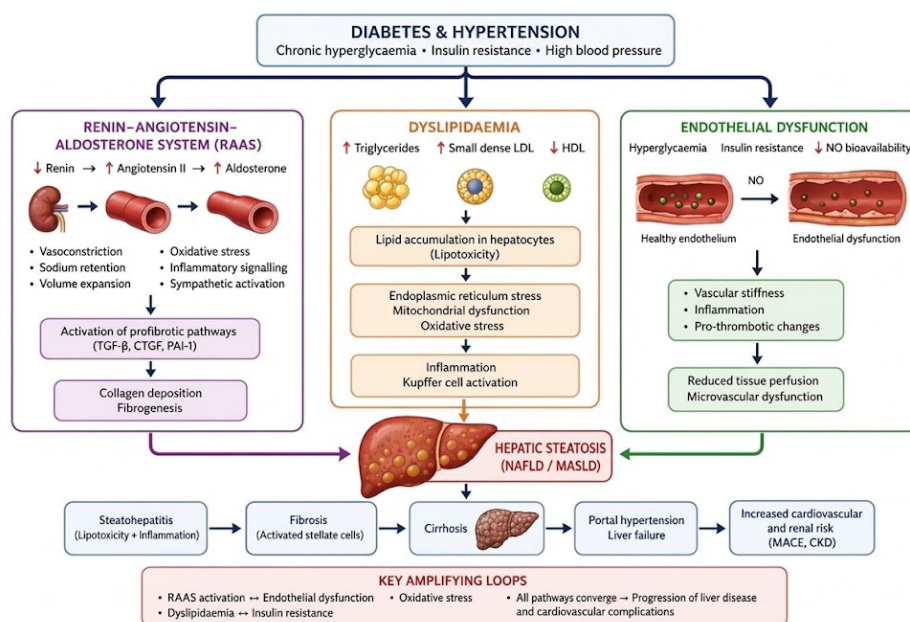


Figure 2. Mechanistic connections with renin-angiotensin-aldosterone system (RAAS), dyslipidaemia, and endothelial dysfunction

Abbreviations: CKD: Chronic kidney disease; CTGF: Connective tissue growth factor; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; MACE: Major adverse cardiovascular events; MASLD: Metabolic dysfunction-associated steatotic liver disease; NO: Nitric oxide; PAI-1: Plasminogen activator inhibitor-1; TGF-β: Transforming growth factor beta.

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 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 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

Sodium-glucose cotransporter-2 (SGLT2) inhibitors (*e.g.*, empagliflozin, dapagliflozin) reduce hyperglycaemia 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 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 SGLT2 inhibitors are particularly beneficial in patients with coexisting T2DM and hypertension because of their favorable effects on glycaemic control, blood pressure, and cardiovascular outcomes. However, their use may increase the risk of genital mycotic infections, volume depletion, and, rarely, diabetic ketoacidosis. Therefore, careful patient selection and regular clinical monitoring are essential during therapy.³⁹

3.3. GLP-1 receptor agonists

Glucagon-like peptide-1 (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 T2DM.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 GLP-1 and glucose-dependent insulinotropic polypeptide (GIP), while inhibiting the release of glucagon in a glucose-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 DM, 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

4. Genetic and protein-level mechanisms underlying the T2DM–hypertension–NAFLD triad

The coexistence of T2DM, hypertension, and NAFLD represents a complex metabolic phenotype involving interconnected alterations in glucose homeostasis, lipid metabolism, inflammation, oxidative stress, vascular function, and neurohormonal regulation.⁴² Although these disorders share conventional risk factors such as obesity and insulin resistance, increasing evidence indicates that their progression is also influenced by alterations in genes, proteins, and intracellular signalling pathways. Understanding these molecular interactions may provide a mechanistic explanation for the simultaneous development of hepatic, metabolic, and cardiovascular abnormalities and may facilitate the identification of molecular biomarkers and therapeutic targets.

4.1. Genetic and protein regulators of insulin signalling

Insulin resistance represents a central molecular feature linking T2DM and NAFLD and may also contribute to the development and progression of hypertension. The physiological actions of insulin are initiated following binding of insulin to the insulin receptor (INSR), a transmembrane tyrosine kinase receptor. Activation of INSR promotes phosphorylation of insulin receptor substrate proteins, particularly insulin receptor substrate-1 (IRS1), followed by activation of phosphoinositide 3-kinase (PI3K) and protein kinase B (AKT). This signalling cascade regulates glucose uptake, glycogen synthesis, lipid metabolism, and cellular growth.

Impairment of the INSR–IRS1–PI3K–AKT signalling axis can reduce insulin-mediated glucose utilization and promote compensatory hyperinsulinemia. In hepatic tissue, impaired insulin signalling may simultaneously coexist with continued activation of lipogenic pathways, thereby promoting hepatic triglyceride accumulation and progression of NAFLD.⁴⁹ Alterations in IRS1 and downstream AKT signalling have therefore been implicated

in the development of systemic insulin resistance and metabolic dysfunction.

Peroxisome proliferator-activated receptor gamma (PPAR γ), encoded by the *PPARG* gene, represents another important regulator of insulin sensitivity and lipid metabolism. PPAR γ regulates adipocyte differentiation, lipid storage, and glucose homeostasis. Altered PPAR γ activity may influence the distribution of fatty acids between adipose tissue and the liver and consequently contribute to hepatic lipid accumulation. The involvement of PPAR γ in insulin sensitization also provides a molecular basis for the therapeutic effects of thiazolidinediones.

In addition, AMP-activated protein kinase (AMPK) functions as an important cellular energy sensor and regulates glucose uptake, fatty acid oxidation, and hepatic energy metabolism. Reduced AMPK activity may contribute to impaired metabolic flexibility, increased hepatic lipogenesis, and insulin resistance.⁴⁹ Thus, the interaction between insulin signaling and cellular energy-sensing pathways represents an important molecular link among T2DM, NAFLD, and cardiometabolic dysfunction.

4.2. Molecular regulation of hepatic lipid metabolism

Dysregulated lipid metabolism is a major molecular characteristic of NAFLD and an important contributor to cardiovascular risk in individuals with T2DM and hypertension. Insulin resistance increases the delivery of free fatty acids to the liver and promotes alterations in *de novo* lipogenesis, fatty acid oxidation, triglyceride synthesis, and lipoprotein metabolism.

Sterol regulatory element-binding protein-1c (SREBP-1c), encoded by *SREBF1*, is a major transcriptional regulator of hepatic fatty acid synthesis. Increased SREBP-1c activity promotes the expression of lipogenic enzymes, including fatty acid synthase (FASN) and acetyl-CoA carboxylase (ACC). Consequently, enhanced SREBP-1c/FASN/ACC signalling may increase *de novo* lipogenesis and contribute to hepatic triglyceride accumulation.

In contrast, peroxisome proliferator-activated receptor alpha (PPAR α), encoded by *PPARA*, regulates genes involved in mitochondrial and peroxisomal fatty acid oxidation. Altered PPAR α activity may reduce hepatic fatty acid utilization and facilitate lipid accumulation. Carnitine palmitoyltransferase 1A (CPT1A), an important regulator of mitochondrial fatty acid transport, also participates in hepatic fatty acid oxidation.

Therefore, an imbalance between hepatic lipid synthesis and lipid oxidation can result in excessive intracellular lipid deposition. In the setting of insulin resistance, this

metabolic imbalance may promote lipotoxicity, oxidative stress, inflammation, and progression from simple hepatic steatosis toward more advanced forms of metabolic liver disease.

4.3. Inflammatory Proteins and Molecular mediators

Chronic low-grade inflammation represents another major molecular mechanism connecting T2DM, hypertension, and NAFLD. The current manuscript already identifies inflammatory activation as an important component of the shared pathophysiology of these diseases. At the molecular level, inflammatory cytokines and transcription factors may interfere with insulin signalling while simultaneously promoting vascular and hepatic injury.

Tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6), and interleukin-1 β (IL-1 β) are important inflammatory mediators associated with metabolic dysfunction.⁴² Increased inflammatory signalling may impair insulin receptor signalling through alterations in IRS proteins and downstream pathways. Persistent activation of nuclear factor kappa B (NF- κ B) further promotes transcription of pro-inflammatory genes and establishes a positive feedback loop between metabolic stress and inflammation.

In hepatic tissue, persistent inflammatory activation can promote hepatocellular injury and fibrogenic responses. In the vascular system, inflammatory signalling contributes to endothelial dysfunction, vascular remodelling, and increased cardiovascular risk. Thus, inflammatory mediators may represent common molecular intermediates through which metabolic abnormalities influence both hepatic and cardiovascular outcomes.

4.4. Oxidative stress and antioxidant signalling

Oxidative stress represents an additional molecular bridge among T2DM, hypertension, and NAFLD. Hyperglycaemia, mitochondrial dysfunction, lipid overload, and activation of vascular NADPH oxidase pathways can increase the production of reactive oxygen species (ROS). The current manuscript already describes excessive ROS formation, endothelial injury, reduced nitric oxide bioavailability, lipid peroxidation, and hepatic injury as important consequences of oxidative stress.

At the molecular level, excessive ROS can impair insulin signalling, promote lipid peroxidation, activate inflammatory pathways, and damage cellular proteins and membranes. Persistent oxidative stress may therefore intensify insulin resistance and hepatic lipotoxicity while simultaneously promoting vascular dysfunction.

The nuclear factor erythroid 2-related factor 2 (NRF2), encoded by *NFE2L2*, represents an important transcriptional

regulator of cellular antioxidant responses. Activation of NRF2 induces the expression of several antioxidant and cytoprotective proteins. Impairment of antioxidant defense mechanisms in conditions characterized by metabolic stress may increase susceptibility to oxidative injury. Therefore, the balance between ROS generation and antioxidant defense may influence the progression of both metabolic and vascular complications.

4.5. RAAS-associated genes and proteins

The RAAS represents an important molecular pathway connecting hypertension with metabolic and hepatic dysfunction. At the molecular level, the pathway involves angiotensinogen (AGT), renin (REN), angiotensin-converting enzyme (ACE), angiotensin II, and the angiotensin II type 1 receptor (AGTR1).⁴⁹ Increased angiotensin II-AGTR1 signalling promotes vasoconstriction, sodium retention, oxidative stress, inflammatory signalling, and vascular remodelling, thereby contributing to hypertension.

Beyond its vascular effects, excessive angiotensin II signalling may influence hepatic inflammation, oxidative stress, and fibrogenic pathways. Consequently, dysregulated RAAS activity may contribute to the simultaneous progression of hypertension and metabolic liver disease. The ACE/ACE2 balance may also influence the activity of angiotensin II-dependent and counter-regulatory pathways, providing an additional molecular layer linking cardiovascular and hepatic pathology.

4.6. Endothelial dysfunction and nitric oxide signalling

Endothelial dysfunction is an important molecular and functional consequence of metabolic and hypertensive stress. The manuscript currently describes reduced nitric oxide bioavailability, vascular stiffness, inflammation, and vascular remodelling in the context of diabetes and hypertension.

Endothelial nitric oxide synthase (eNOS), encoded by *NOS3*, is responsible for the production of nitric oxide in vascular endothelial cells. Under physiological conditions, nitric oxide promotes vasodilation and maintains vascular homeostasis. Insulin resistance, oxidative stress, and excessive angiotensin II signalling can impair eNOS activity and reduce nitric oxide bioavailability.

The resulting endothelial dysfunction can promote vasoconstriction, platelet activation, vascular inflammation, and atherosclerotic processes. Because T2DM and hypertension are major cardiovascular risk factors and NAFLD is increasingly recognized as a component of cardiometabolic disease, impaired endothelial signalling

may represent an important molecular interface between hepatic metabolic dysfunction and cardiovascular complications.

4.7. Shared genes, proteins and molecular pathways

The molecular abnormalities described above demonstrate that T2DM, hypertension, and NAFLD do not represent completely independent disease processes. Instead, they share several genes, proteins, and signalling pathways that regulate glucose metabolism, lipid homeostasis, inflammation, oxidative stress, and vascular function.

Table 1 presents representative genes and proteins involved in the molecular interplay among T2DM, hypertension, and NAFLD.

4.8. Molecular interconnection of insulin resistance, lipid metabolism and vascular dysfunction

The coexistence of T2DM, hypertension, and NAFLD

can therefore be conceptualized as a molecular network rather than three independent disease entities. Insulin resistance initiates disturbances in glucose and lipid metabolism, while increased free fatty acid flux and hepatic lipogenesis promote lipid accumulation. Lipotoxicity and mitochondrial dysfunction increase oxidative stress, which activates inflammatory pathways involving TNF- α , IL-6, NF- κ B, and related mediators. Concurrent activation of the RAAS further amplifies oxidative and inflammatory signalling and promotes endothelial dysfunction.

These interconnected processes create a self-reinforcing cycle in which metabolic dysfunction promotes hepatic injury, vascular dysfunction, and hypertension, while vascular and inflammatory abnormalities further worsen insulin resistance and hepatic metabolic disturbances. Identification of shared molecular targets within this network may therefore provide opportunities for biomarker discovery and development of therapies capable

Table 1. Representative genes and proteins involved in the molecular interplay among T2DM, hypertension, and NAFLD

Gene	Protein	Major pathway/function	Relevance to T2DM	Relevance to hypertension	Relevance to NAFLD
<i>INSR</i>	Insulin receptor	Insulin signalling	Insulin sensitivity	Metabolic/vascular signalling	Hepatic insulin resistance
<i>IRS1</i>	Insulin receptor substrate-1	PI3K/AKT signaling	Glucose metabolism	Metabolic dysfunction	Insulin resistance
<i>AKT1</i>	Protein kinase B	PI3K/AKT pathway	Glucose uptake and metabolism	Vascular signaling	Hepatic metabolic regulation
<i>PPARG</i>	PPAR- γ	Glucose and lipid metabolism	Insulin sensitization	Cardiometabolic regulation	Hepatic lipid homeostasis
<i>SREBF1</i>	SREBP-1c	<i>De novo</i> lipogenesis	Lipid dysregulation	Indirect cardiometabolic effects	Hepatic lipogenesis
<i>FASN</i>	Fatty acid synthase	Fatty acid synthesis	Dyslipidemia	Cardiometabolic risk	Hepatic steatosis
<i>PPARA</i>	PPAR- α	Fatty acid oxidation	Lipid metabolism	Cardiometabolic effects	Hepatic lipid oxidation
<i>CPT1A</i>	CPT1A	Mitochondrial fatty acid oxidation	Energy metabolism	Metabolic regulation	Hepatic lipid oxidation
<i>TNF</i>	TNF- α	Inflammatory signalling	Insulin resistance	Vascular inflammation	Hepatic inflammation
<i>IL6</i>	IL-6	JAK/STAT signalling	Metabolic inflammation	Vascular inflammation	Hepatic inflammation
<i>NFE2L2</i>	NRF2	Antioxidant response	Oxidative stress	Vascular protection	Hepatic oxidative stress
<i>AGT</i>	Angiotensinogen	RAAS	Metabolic/RAAS interaction	Blood-pressure regulation	Hepatic inflammation/fibrosis
<i>ACE</i>	ACE	RAAS	Cardiometabolic effects	Angiotensin II formation	Hepatic RAAS signalling
<i>AGTR1</i>	AT1 receptor	Angiotensin II signalling	Metabolic dysfunction	Vasoconstriction	Oxidative/inflammatory signalling
<i>NOS3</i>	eNOS	Nitric oxide signalling	Endothelial dysfunction	Vascular tone	Cardiometabolic interface

of simultaneously addressing metabolic, hepatic, and cardiovascular abnormalities.

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.⁵⁰ 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.⁵¹ 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.⁵²

5.2. Thiazolidinediones

Pioglitazone improves insulin sensitivity and histological outcomes in NAFLD/NASH but may cause weight gain and fluid retention, limiting use in cirrhotic patients. Thiazolidinediones, particularly pioglitazone, are among the most effective insulin-sensitizing agents and exert their therapeutic effects through activation of the PPAR- γ .⁵³ 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.⁵⁴ However, the clinical use of pioglitazone is limited by adverse effects such as weight gain, fluid retention, and edema, which may exacerbate heart failure and can be particularly problematic in patients with advanced or decompensated 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

5.3. GLP-1 receptor agonists

Glucagon-like peptide-1 (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.⁵⁵ Recent literature shows that GLP-1 agonists lower hepatic steatosis, inflammation, and fibrogenesis, mainly by mechanisms that enhance insulin sensitivity, weight loss, and lipotoxicity. 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.⁵⁶ 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.⁵⁷

5.4. SGLT2 inhibitors

These agents show promise in improving hepatic steatosis and reducing liver fat content while offering cardiovascular protection. SGLT2 inhibitors like empagliflozin and dapagliflozin are antidiabetic drugs that promote glycosuria and improve the insulin sensitivity.⁴⁹ Besides their well-reported cardiovascular and renal efficacy, the drugs have demonstrated possible hepatic health benefits as well, especially in patients with NAFLD.⁵⁸ 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 mainly attributable 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.⁵³

5.5. DPP-4 inhibitors

Dipeptidyl peptidase-4 (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 glucose-dependent insulinotropic polypeptide (GIP) and thereby improve glycaemic control with no clinically significant risk of causing hypoglycaemia.⁵⁹ 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.⁶⁰ 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.⁵⁹

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 hyperglycaemia or lack of responsiveness to oral pharmacotherapies.⁶¹ 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.⁶² 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 is needed and the use of unique intervention plans should be used to stabilize its benefits and harms.⁶³

Although GLP-1 receptor agonists and SGLT2 inhibitors have demonstrated significant cardiovascular and metabolic benefits, their clinical application requires consideration of several limitations. The effectiveness and response may vary among individual agents within the same drug class. Factors such as treatment cost,

accessibility, patient adherence, renal and hepatic status, and comorbid conditions may influence real-world outcomes. In addition, clinical trials often involve selected patient populations, which may limit generalizability to patients with multiple comorbidities. Safety considerations, including gastrointestinal adverse effects with GLP-1 receptor agonists and risk of genitourinary infections with SGLT2 inhibitors, should be carefully evaluated during clinical decision-making. Therefore, personalized treatment selection based on patient characteristics remains essential.

Table 2 tabulates several classes of anti-diabetic drugs and their impact on liver disease.

6. Clinical evidence

Several randomized controlled trials and systematic reviews have evaluated the efficacy and safety of antidiabetic therapies in patients with T2DM, hypertension, and liver disease. Among SGLT2 inhibitors, the EMPA-REG OUTCOME trial, a randomized, double-blind, placebo-controlled study involving patients with T2DM and established cardiovascular disease, demonstrated significant reductions in major adverse cardiovascular events, cardiovascular mortality, and hospitalization for heart failure. However, hepatic outcomes were not

Table 2. Anti-diabetic drugs and their impact on liver disease

Drug class	Effect on liver disease	Safety considerations	Ref.
Metformin	May improve steatosis	Contraindicated in advanced cirrhosis	64
SGLT2 inhibitors	Reduces steatosis; potential hepatoprotective effects	Good safety profile	64
GLP-1 receptor agonists	Reduces steatosis; may improve fibrosis	Generally safe	65
DPP-4 inhibitors	Potential hepatoprotective effects	Inconclusive benefits	66
Insulin	May contribute to steatosis through weight gain	Risk of weight gain	66
TZDs	Improves NASH; may improve fibrosis	Risk of fluid retention, heart failure	66

Abbreviations: DPP-4: Dipeptidyl peptidase-4; GLP-1: Glucagon-like peptide-1; NASH: Non-alcoholic steatohepatitis; SGLT2: Sodium-glucose cotransporter 2; TZDs: Thiazolidinediones.

predefined primary endpoints, and evidence regarding improvement in hepatic steatosis and liver enzymes was derived mainly from secondary analyses and smaller clinical studies rather than the primary trial outcomes.⁶⁷

Similarly, the CANVAS Program confirmed the cardiovascular and renal benefits of canagliflozin while

also reporting favorable metabolic effects, including weight reduction and improved glycemic control. Although some studies have suggested improvements in liver enzyme levels and hepatic steatosis with SGLT2 inhibitor therapy, these observations remain secondary findings, and further large-scale studies specifically evaluating liver-related endpoints are required.⁶⁸

Among GLP-1 receptor agonists, clinical trials such as the LEAN trial demonstrated that liraglutide promoted resolution of NASH and reduced progression of liver fibrosis in selected patients. More recently, studies evaluating semaglutide have reported significant improvements in weight reduction, glycaemic control, and NASH resolution. Nevertheless, consistent improvement in liver fibrosis has not yet been conclusively established, and additional long-term randomized clinical trials are necessary before definitive conclusions regarding hepatoprotective efficacy can be drawn.⁶⁹

Overall, current evidence strongly supports the cardiovascular and renal benefits of SGLT2 inhibitors and GLP-1 receptor agonists. In contrast, evidence for liver-specific benefits remains promising but comparatively limited, as most hepatic outcomes have been reported from secondary analyses or dedicated liver disease studies rather than cardiovascular outcome trials. Future well-designed randomized controlled trials focusing on liver-specific clinical endpoints are needed to establish their precise role in patients with coexisting diabetes, hypertension, and liver disease.^{67,69}

7. Challenges and limitations

7.1. Drug safety and individualized treatment strategies

The safety profile of antidiabetic drugs is a critical consideration in patients with DM, hypertension, and liver disease. Although several therapeutic agents provide metabolic and cardiovascular benefits, potential safety concerns, particularly hepatotoxicity, require careful evaluation.⁷⁰ Thiazolidinediones (TZDs), for example, have been associated with adverse effects such as fluid retention, weight gain, and rare cases of drug-induced liver injury, emphasizing the importance of monitoring hepatic function during therapy.⁷¹ Similarly, some older antidiabetic medications may have limited applicability in patients with pre-existing liver dysfunction due to increased risk of adverse hepatic effects. In contrast, newer therapeutic classes, including GLP-1 receptor agonists and SGLT2 inhibitors, demonstrate favorable metabolic and cardiovascular profiles; however, their long-term hepatic safety in patients with advanced liver disease requires further investigation.⁷²

Patients with DM, hypertension, and hepatic disease often present with additional comorbidities such as obesity, dyslipidaemia, and cardiovascular disorders, making treatment management complex.⁷³ The requirement for multiple medications, including antihypertensive, lipid-lowering, and antidiabetic agents, increases the possibility of drug-drug interactions, adverse events, reduced adherence,

and therapeutic challenges.⁷⁴ Furthermore, impaired hepatic metabolism may alter drug clearance and increase the risk of drug accumulation and toxicity. Therefore, selection of appropriate pharmacological agents, dose adjustment, and regular clinical monitoring are essential to optimize safety and therapeutic outcomes.⁷⁵ Considering variations in disease severity and patient characteristics, individualized treatment strategies are necessary to achieve effective disease control while minimizing complications.⁷⁶ Personalized pharmacotherapy with careful assessment of comorbid conditions, medication burden, hepatic status, and patient response can improve treatment efficacy and safety.⁷⁷

7.2. Strengths and limitations of the review

The major strength of this review is the comprehensive discussion of the interconnected relationship between DM, hypertension, and liver disease, integrating their shared pathophysiological mechanisms with current therapeutic approaches. The review provides an overview of recent pharmacological advancements, including anti-diabetic agents with cardiovascular and hepatic benefits, and highlights their clinical relevance in managing complex metabolic disorders.

However, this review has certain limitations. As a narrative review, it does not involve quantitative analysis or meta-analysis, and the conclusions are based on the currently available published literature. Variations in study populations, treatment duration, disease severity, and clinical outcomes among different studies may contribute to differences in reported findings. Future systematic investigations and well-designed clinical studies are required to further validate therapeutic strategies and establish personalized treatment approaches.

8. Future perspectives

The future management of patients with DM, hypertension, and liver disease is expected to shift toward precision medicine, with increasing emphasis on individualized therapeutic strategies based on pharmacogenomic profiling and biomarker-guided treatment selection. Such approaches may improve therapeutic efficacy while minimizing adverse drug reactions by enabling clinicians to tailor treatment according to each patient's genetic and clinical characteristics.^{78,79}

Advances in nanotechnology-based drug delivery systems are expected to enhance targeted hepatic drug delivery, improve drug bioavailability, and reduce systemic toxicity. In parallel, several novel pharmacological agents targeting inflammatory, oxidative stress, and fibrotic pathways are currently under investigation and may

provide more effective therapeutic options for patients with metabolic dysfunction-associated steatotic liver disease (MASLD) and metabolic dysfunction-associated steatohepatitis (MASH).⁸⁰

In addition, increasing interest in nutraceuticals and herbal therapies offers complementary strategies for improving metabolic health and reducing disease progression. Although preliminary findings are encouraging, further large-scale randomized clinical trials are required to establish their long-term safety, efficacy, and role in routine clinical practice. Overall, integrating precision medicine, innovative drug delivery technologies, and emerging therapeutic approaches may significantly improve the management of patients with DM complicated by hypertension and liver disease.⁸¹

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.⁸² Of all the existing types of therapy, SGLT2 inhibitors and GLP-1 receptor agonists should be identified as particularly advantageous.⁸³ 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 NAFLD.⁸³ 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.⁸⁴ 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.⁸⁵ 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.⁸⁶ 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-centred care approach has a potential to help in improving clinical outcomes and quality of life in this high-risk and complicated population.⁸⁷

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