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Review on Kidney-Liver Crosstalk: Pathophysiology of Their Disorders

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Abstract

Kidney-liver crosstalk plays a crucial role in normal and certain pathological conditions. In pathologic states, both renal-induced liver damage and liver-induced kidney diseases may happen through these kidney-liver interactions. This bidirectional crosstalk takes place through the systemic conditions that mutually influence both the liver and kidneys. Ischemia and reperfusion, cytokine release and pro-inflammatory signaling pathways, metabolic acidosis, oxidative stress, and altered enzyme activity and metabolic pathways establish the base of this interaction between the kidneys and liver. In these concomitant kidney-liver diseases, the survival rates strongly correlate with early intervention and treatment of organ dysfunction. Proper care of a nephrologist and hepatologist and the identification of pathological conditions using biomarkers at early stages are necessary to prevent the complications induced by this complex and potentially vicious cycle. Therefore, understanding the characteristics of this crosstalk is essential for better management. In this review, we discussed the available literature concerning the detrimental effects of kidney failure on liver functions and liver-induced kidney diseases.

Keywords: Cirrhosis, Hepatitis, Liver Failure, Nephropathy, Renal Failure

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Introduction

The kidneys and liver are the major organs for detoxifying and body homeostatic maintenance. Kidneys have vital roles in regulating blood volume and pressure, electrolyte and pH balance, erythropoietin, and calcitriol (1,25-dihydroxycholecalciferol) secretion. In addition, prostaglandin secretion and the regulation of renin-angiotensin-aldosterone system (RAAS) activity are other vital activities of the kidneys (1). All these functions are crucial for the human body, explaining increased morbidity and mortality rates in patients with severe renal dysfunction. Accordingly, kidney dysfunction affects many organs, including the liver. Liver is a complex organ, which is responsible for a considerable part of the metabolism of proteins, fats, and carbohydrates (2). The kidney and liver are two pivotal organs in the human body, each with distinct functions but also deeply interconnected in various physiological processes. Disorders affecting one can significantly impact the other, leading to complex clinical scenarios. Moreover, while interactions between the liver and other organs are undoubtedly important, the complexity of kidney-liver interactions warranted a dedicated review. The intricate web of pathways and mechanisms involved in these interactions, including metabolic processes, immune responses, and hormonal regulation, necessitated an in-depth investigation to better understand the pathophysiology of related disorders. Hepato-renal crosstalk is active in both physiological and pathological conditions (Fig.1). Ischemia-reperfusion, cytokine release and pro-inflammatory signaling, metabolic acidosis, oxidative stress, and altered enzymes activities establish the base of these reciprocal cross-talks between kidneys and liver (3, 4).

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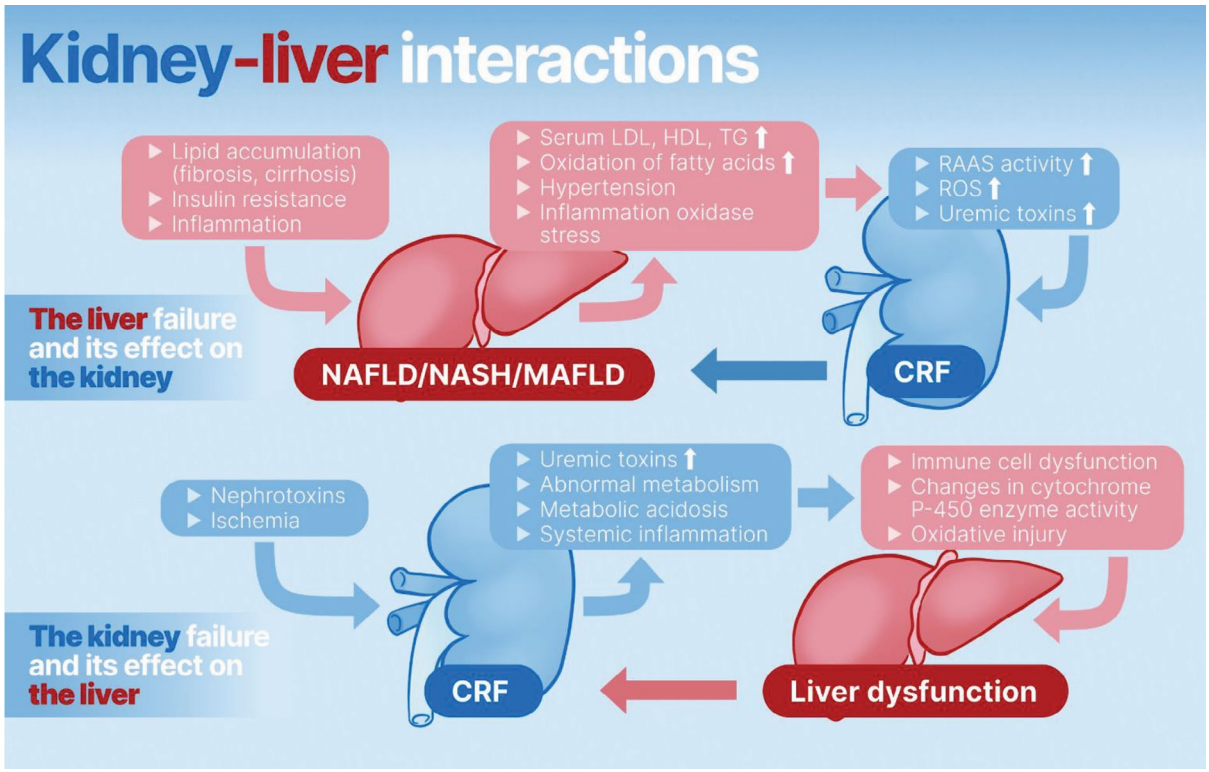

Fig.1: Kidney-liver crosstalk. Kidney-liver crosstalk is a dynamic, two-way communication that occurs due to systemic factors influencing both organs. Various factors, such as ischemia and reperfusion, cytokine release, pro-inflammatory signaling pathways, metabolic acidosis, oxidative stress, and changes in enzyme activity and metabolic pathways, form the foundation of this interaction between the kidneys and liver. ARF can evolve into CRF, marked by a gradual and persistent decline in renal clearance and glomerular filtration over time. ARF; Acute renal failure, CRF; Chronic renal failure, NAFLD; Nonalcoholic fatty liver disease, NASH; Non-alcoholic steatohepatitis, MAFLD; Metabolic associated fatty liver diseases, LDL; Low-density lipoprotein, HDL, High-density lipoprotein, TG; Triglycerides, RAAS; Renin-angiotensin-aldosterone system, and ROS; Reactive oxygen species.

The bidirectional kidney-liver crosstalk is affected in many renal-induced liver diseases due to acute renal failure (ARF) and liver-induced renal injuries following liver diseases (4). Major pathophysiological states of ARF-induced liver dysfunction are proinflammatory cytokines release, oxidative stress, hepatocellular necrosis, apoptosis, and fatty degeneration (5). On the other hand, several liver diseases, such as cirrhosis, nonalcoholic fatty liver disease (NAFLD), and hepatitis contribute to kidney diseases (6, 7). Proper care of a nephrologist and the identification of pathological conditions, using biomarkers in the early stages, are necessary to prevent renal deterioration in these patients. Therefore, knowing the characteristics of this crosstalk is crucial for handling the complications induced by this vicious cycle (8). In this review, we discuss bidirectional kidney-liver crosstalk, its role in kidney disease and its impact on liver function.

Research Question/Objective:

To discuss the best available literature concerning the detrimental effects of kidney failure on liv-er functions and liver-induced kidney diseases.

Keywords:

" Cirrhosis " " Hepatitis " " Liver failure " " Nephropathy" "Organ crosstalk" "Renal failure"

Search Strings:

1. Cirrhosis: ("Cirrhosis" OR "Cirrhotic Liver")
2. Hepatitis: ("Hepatitis " OR "viral Hepatitis")
3. Liver failure: ("Liver failure " OR "hepatic failure")
4. Nephropathy: ("Nephropathy" OR "Kidney Disorder" OR "Renal Disorder")
5. Organ Crosstalk: ("Organ crosstalk" "Kidney–Liver Crosstalk" OR "Liver- Kidney Crosstalk")
6. Renal failure: ("Renal Failure", "Kidney Failure")

Combined Search String:

(1 OR 2 OR 3) AND (4 OR 5)

Databases:

PubMed, Web of Science, and discipline-specific databases in the life sciences.

Filters and Limits:

Publication date, (<40 recent years).

Documentation:

Maintain a record of the search strategy, including search strings, databases searched, and applied filters for transparency and reproducibility. In the initial search, we retrieved 210 potentially rele-vant records, out of which 48 were duplicates. After screening the papers by reading the title and abstract, we included 162 studies in our review.

Kidney failure and its effect on liver metabolism

Acute renal failure

ARF is a growing healthcare concern worldwide, which affects over half of critically ill patients, and leads to a 25% mortality rate during hospitalization. ARF is related to several adverse health outcomes including increased duration of intensive care unit (ICU) and hospital stay, and the development of chronic renal failure (CRF). When accompanied by liver injury (which is present in 28% of these patients), the ARF-related mortality rate (84%) can be markedly higher (9). The primary causes of ARF in this setting are ischemia/hypoxia (10) and nephrotoxicity due to multiple drug consumption and septicemia (11). The common signs and symptoms of ARF include volume overload, uremia, hyperkalemia, systemic inflammation, and metabolic acidosis. Major pathophysiological mechanisms of ARF-induced liver dysfunction (Fig.2) consist of proinflammatory cytokines outflow, oxidative stress, hepatocellular necrosis, apoptosis, and fatty degeneration (12).

Cytokine secretion

Several studies have indicated that ARF induces low-grade systemic inflammation. Inflammatory cytokines released in ARF [IL-6, IL-17A, and tumour necrosis factor-alpha (TNF-α)] result in hepatic vascular permeability and endothelial dysfunction, which leads to immune cell migration and initiation of inflammatory response to hepatic cells (13). The activity of CYP is reduced in ARF. Indoxyl sulfate is a prototypical protein-bound uremic toxin. Its serum concentration increases during ARF, causing further inflammation and also reducing CYP activity (3). Furthermore, IL-6 specifically reduces the activity of the isoform CYP3A4. It also increases the expression of serum amyloid A, C-reactive protein, alpha-1-antitrypsin, fibrinogen, and haptoglobin. Additionally, it downregulates the production of albumin, fibronectin, and transferrin (14). IL-10 and TNF-α reduce the activity of CYP enzymes (15). Moreover, the activity of CYP3A1/2 and CYP2E1 enzymes seems to be notably affected by AKI. Simvastatin metabolism by CYP3A4 is enhanced when exposed to the IL-6-targeting monoclonal antibody, tocilizumab. This underscores the importance of AKI-induced changes in liver drug metabolism on a clinical level (3). Following the systemic inflammation, the liver produces acute-phase proteins. Moreover, asymmetric dimethylarginine (ADMA) is accumulated during ARF and eliminated by the liver, hence being a marker of damage. It is a competitive inhibitor of nitric oxide synthase and its elevation leads to endothelial dysfunction. As a result, the deficiency of intrahepatic nitric oxide plays a key role in the pathophysiology of portal hypertension (3).

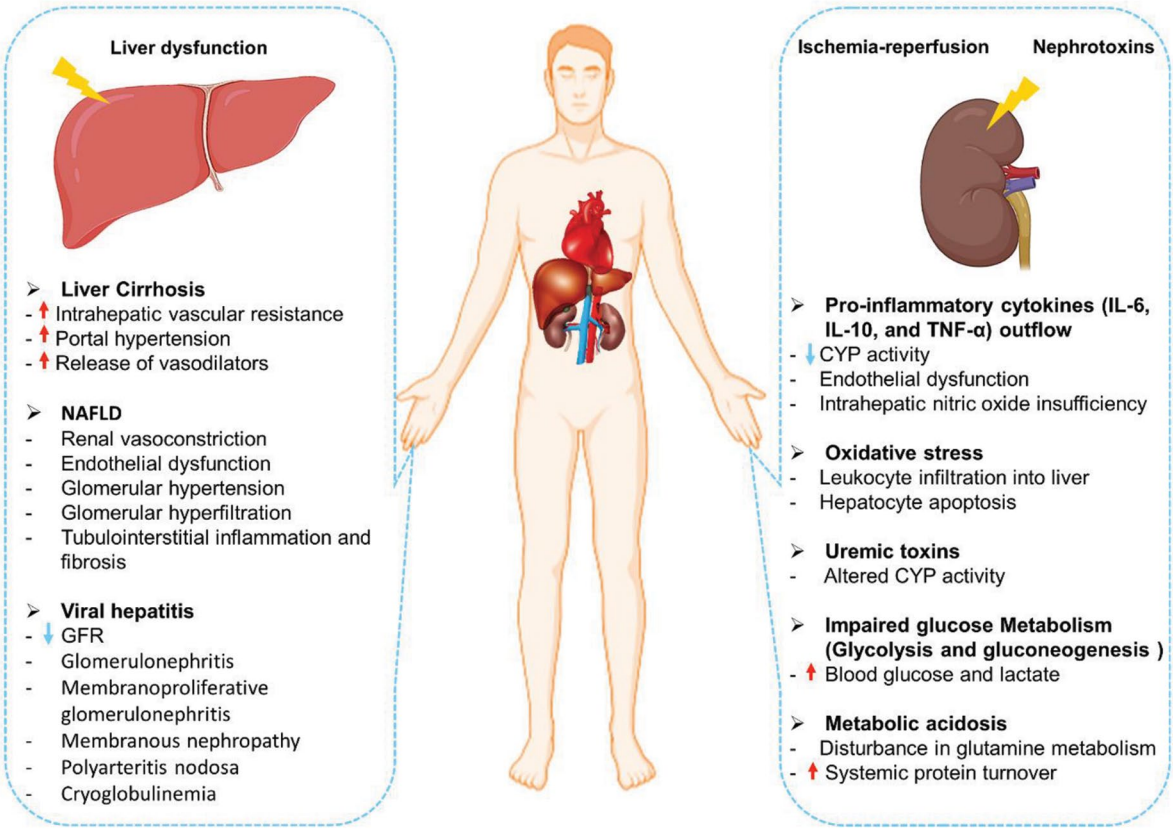

Fig.2: Overview of pathophysiological mechanisms involved in bidirectional kidney–liver crosstalk. CYP; Cytochrome P450, GFR; Glomerular filtration rate, IL; Interleukin, NAFLD; Nonalcoholic fatty liver disease, and TNF-α; Tumor necrosis factor-alpha.

Ischemia and ischemia-reperfusion-induced injury

Renal ischemia-reperfusion injury is linked to heightened levels of pro-inflammatory cytokines, triggering hepatocyte apoptosis. Additional information regarding ischemia and ischemia-reperfusion-induced injury has been moved to the supplementary data and Table S1 (See Supplementary Online Information at www.celljournal.org).

Oxidative stress

Ischemic and non-ischemic ARF has been shown to activate oxidative stress, leading to liver injury. Ischemic ARF induces activation of oxidative stress in the early stages of acute renal damage, which leads to leukocyte infiltration into liver tissue, hepatocyte apoptosis, and decreased concentrations of hepatic antioxidants (16, 17). Leukocyte infiltration has an important role in stimulating hepatic oxidative stress after renal ischemia-reperfusion. Leukocyte infiltration reduces hepatic antioxidants, including superoxide dismutase (SOD) and catalase, and increases malondialdehyde, an index of lipid peroxidation (17). Twenty-four hours after renal ischemia-reperfusion injury, hepatoprotective and antioxidant markers including nuclear factor erythroid 2- related factor 2 (Nrf2), hepatic hemoxygenase-1 (Hmox-1), and thioredoxin (TRx) are overexpressed in liver tissue. These antioxidants attenuate hepatic inflammation and injury (18).

Studies have indicated that treatment with antioxidants offers beneficial therapeutic effects in oxidative stress liver injury in ARF (16, 19, 20). ARF causes a significant depletion of the antioxidant glutathione (GSH) and increases the expression of malondialdehyde in liver tissue. It has been indicated that intravenous administration of GSH markedly attenuates plasma ALT levels and liver lipid peroxidation in a rat ARF model. Therefore, it protects the liver against reperfusion injury (16). Fadillioglu and colleagues investigated the therapeutic potential of an antioxidant, melatonin, on liver injury in a renal ischemia-reperfusion injury rat model. They observed that treatment with melatonin attenuated the increased activities of CAT, SOD, xanthine oxidase, and MPO, which are responsible for hepatic oxidative stress and inflammation (19). Vitamin E is a phenolic antioxidant that helps in maintaining glutathione activity. Vitamin E supplementation decreases aspartate aminotransferase (AST), ALT, and MDA concentrations in plasma, as well as attenuated GSH activity and liver injury caused by ischemia-reperfusion in ARF (20). Mallow (Malva sylvestris L.) extract, having CAT activity, decreases the expression of pro-inflammatory cytokines in the kidney and the level of leukocyte infiltration into the liver. Mallow extract reduces lipid peroxidation improves the total antioxidant capacity, and subsequently attenuates liver damage (21). Another study showed that this antioxidant extract protects the liver against damage following cisplatin-induced kidney injury, purportedly by anti-inflammatory and antioxidant effects (11). The antioxidant properties of black pepper or piperine (1-peperoylpiperidine) significantly improve the activity of glutathione-S-transferase (GST), SOD, CAT and glutathione peroxidase (GPx), and reduce GSH activity in kidney and liver tissues. It has been shown that these agents protect rat liver from the effects of renal ischemia-reperfusion and high-fat diet injury (22). Several studies have investigated the therapeutic effects of pioglitazone, a peroxisome proliferator activator receptor gamma (PPARγ) agonist, in renal failure-induced liver injury. They showed that it reduces the mRNA expression of MDA and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase while enhancing the synthesis and activity of SOD, and improving CAT activity. Furthermore, prophylactic administration of pioglitazone results in lower TNF-α levels, and hepatocyte necrosis and apoptosis. Therefore, it could be used as an antioxidant and liver and kidney-protective drug for patients with renal IR injury (18). A recent study assessed the harmful effects of low-level lead (Pb) exposure on the liver and kidneys in rats. It found that Pb exposure led to toxicity in these organs, primarily through mechanisms such as decreasing copper levels in the liver, increasing advanced oxidation protein products (AOPP) levels in the liver, and inhibiting SOD activity in the kidneys. The study also calculated benchmark doses (BMD), with the most sensitive effect being the decrease in liver copper levels. This research sheds light on the mechanisms of Pb toxicity at low exposures (23).

Glucose metabolism

Glycolysis and gluconeogenesis are two metabolic processes responsible for endogenous glucose production. Gluconeogenesis occurs mainly in the liver and partly in the renal cortex. Major enzymes of renal gluconeogenesis are located within the renal proximal tubular cells, while enzymes responsible for glycolysis are often active in distal tubular cells. Renal gluconeogenesis maintains the appropriate concentration of blood glucose levels by releasing glucose into the circulation during fasting and under stress states (24). Hypoglycemia stands as the most prevalent endocrine factor contributing to mortality in diabetic patients with kidney diseases and can lead to multiple organ injury including liver. Hypoglycemia increases inflammation markers and leads to severe liver injury markers (AST, ALT, ALP, and γ-GTP) (25). Furthermore, almost 50% of patients hospitalized with hypoglycemia develop CRF in future. On the other hand, nondiabetic kidney disease is a predisposing factor for developing hypoglycemia. Renal gluconeogenesis, glucose production and lactate clearance are deteriorated in proximal tubular cells during ARF (26). Normally, the kidney and liver work together to remove lactate. Increasing lactate concentration elevates hepatic phosphoenolpyruvate carboxykinase activity, which stimulates hepatic lactate absorption (3).

On the other hand, increased blood glucose and lactate concentrations are also associated with a significant increase in markers of liver injury (AST, ALT, AP, GGT, and prothrombin) and mortality rate (27). Thiamine (vitamin

B1) is a crucial cofactor in carbohydrate metabolism. One study showed that it reduced glycolysis rate, and increased lactate clearance and glucose production. Therefore, thiamine rescues cell metabolism in renal proximal tubule cells and reduces the mortality rate in ARF patients (28). Acute renal damage depletes cortical pyruvate by increasing pyruvate-to-lactate conversion. Pyruvate has antioxidant and anti-inflammatory effects and also plays an important role in energy metabolism. Therefore, pyruvate therapy attenuates the severity of ARF via increasing the expression of renoprotective heme oxygenase 1 and IL-10 and decreasing pro-inflammatory cytokines, such as MCP-1 and TNF-a (29).

Chronic renal failure

ARF may progress to CRF, characterized by gradual and constant deterioration in renal clearance or glomerular filtration over time, caused by irreversible renal tissue remodelling and fibrosis (30). 10% of the world's population suffers from CRF. 10-20% of these patients experience a progressive loss of kidney function over time, eventually leading to end-stage renal disease (ESRD), which generally means that glomerular filtration rate (GFR) drops to less than 10% and the patient needs hemodialysis (31). CRF is related to a decline in many members of drug-metabolizing enzymes and drug transporters in liver tissue, including the cytochrome P450 enzyme (CYP) family and the ATP-binding cassette (ABC) and solute carrier (SLC) families (Table 1). Understanding the impacts of renal failure on liver function could offer attractive opportunities for future medicine (32).

Uremic toxins

Uremic toxins produced during CRF impair the expression of certain enzymes and transporters predominantly found located in hepatic tissue (32). The cytochrome P-450 (CYP) enzyme system, is primarily located in hepatic cells and is responsible for approximately 70-75% of the body's drug metabolism and bioactivation of drugs (33). Liver damage has been observed in rodent models of uremia and, to a lesser degree, in patients with acute and chronic renal failure. Drug clearance involves both bile and urine. Uremic toxins have a key role in this process. CRF contributes to a decline in the level of hepatic transporters associated with drug absorption and an increase in those involved in drug excretion (32). CYP enzymes have a crucial role in the activation of clopidogrel, an antiplatelet agent. Therefore, its metabolism may be altered in CRF patients. Activation of clopidogrel occurs in two steps involving CYP1A2, CYP2C19, and CYP2B6 in the first step, and CYP2C9, CYP2C19, CYP3A, and CYP2B6 in the second step (34). Jain and colleagues indicated that patients with CRF have lower clopidogrel-induced platelet aggregation inhibition (34% less) and higher residual platelet aggregation (47.7% more) compared to patients without CRF. However, there was no association between the presence of cytochrome P450 2C19 polymorphisms for platelet aggregation and CRF (35). Advanced CRF induces the accumulation of uremic toxic metabolites and the influx of them into the gastrointestinal lumen that leads to the disruption of intestinal epithelial tight junctions, dysbiosis, and the transport of lipopolysaccharide and other toxic substances into the circulatory system. These events result in systemic inflammation and promote nonalcoholic fatty liver disease (NAFLD) and insulin resistance (36).

Renal failure also alters the clinical response to medications that are typically metabolized by the liver, such as eribulin, doxorubicin, paclitaxel and cyclophosphamide. A key player in this mechanism is a molecular transporter expressed particularly on the sinusoidal side of hepatocytes named Organic Anion Transport Protein 1B1 (OATP1B1). Acute and chronic renal dysfunctions, via producing uremic toxins, repress the activity of OATP1B1 and consequently impair the liver's ability to uptake the above-mentioned oncologic agents (37).

Table 1: Investigations into the impact of acute AKI on the transcription and translation of drug metabolism enzymes in animal/human studies

AKI model / experimental model	Targeted enzyme	Important findings	Ref
Glycerol-induced acute renal failure/Rat	P-glycoprotein	P-glycoprotein function was globally suppressed in acute renal failure, possibly due to the accumulation of endogenous P-glycoprotein substrates/modulators in the plasma during disease states.	(38)
IRI/Rat	CYP3A1	IRI led to an 8-fold increase in CYP3A1 mRNA transcription, a response mitigated by the antioxidant thymoquinone. Additionally, thymoquinone alleviated hepatic inflammation induced by IRI.	(39)
AKI induced by uranyl nitrate/Rat	CYP1A1/2, 2B1, 2D1 and 3A1/2	The metabolism of mirodenafil in the liver escalated during AKI, mainly driven by an increase in CYP3A1 expression.	(40)
AKI in critically ill adults/Human	CYP3A4, CYP3A5	A correlation between the severity and duration of AKI and reduced midazolam elimination in critically ill patients was observed. This suggests impaired CYP3A activity as a potential cause, with preliminary data indicating a mitigating effect in patients expressing functional CYP3A5.	(41)

AKI; Acute kidney injury and IRI; Ischaemia-reperfusion injury.

Metabolic acidosis

Both the kidneys and liver are vital modulators of acid-base balance (5). Lactic acid is a known metabolic waste product, which is usually eliminated by the kidneys and liver. In CRF, lactic acid that cannot be excreted through urine becomes sequestered by the liver, resulting in metabolic acidosis. This, in turn, prompts an increase in the activity of the hepatic enzyme phosphoenolpyruvate carboxykinase to maintain a secure serum pH (42). Acute acidosis may result in an intense disturbance in glutamine metabolism, which consequently leads to an acute increase in circulatory glutamine concentrations and a decline in total hepato-splanchnic glutamine concentrations (43). Studies have indicated that chronic acidosis decreases glutamine extraction and albumin synthesis in the liver while increasing renal glutamine extraction and ammonia production (44). Besides, acidosis is correlated with the elevated rate of systemic protein turnover, encompassing both protein synthesis and proteolysis (45).

Liver dysfunction and its effect on the kidney

The liver has many crucial functions, including the production of several important proteins such as albumin and clotting factors, storage and activation of vitamins, carbohydrate and lipid metabolism, immunomodulation, as well as the activation, inactivation, modulation, and elimination of drugs and toxins. Several liver diseases, such as liver failure due to cirrhosis, NAFLD, and hepatitis are associated with kidney diseases.

Cirrhosis

Cirrhosis may be developed as a result of an exogenous infectious, immunopathological condition, vascular impairments, or inborn metabolic diseases. Viral hepatitis (B and C types), alcoholic and non-alcoholic fatty liver diseases, and obesity are the main causes of cirrhosis. Furthermore, genetic risk factors have critical roles in determining the risk that an individual could be predisposed to early liver cirrhosis (46). The majority of genetic factors are brought on by an enzyme or transport protein deficiency, which changes a metabolic pathway and particularly affects the liver (47). Cirrhosis is a liver chronic disease with multi-system (kidneys, heart, lungs, the immune systems, and other organ systems) complications (46). ARF is relatively frequent among patients with liver cirrhosis, and 20% of patients hospitalized with cirrhosis develop ARF. In addition, CRF occurs in about 1% of liver cirrhosis patients (7). As most of the renal failure in patients with cirrhosis is related to either prerenal azotemia or hepatorenal syndrome (HRS), physicians often consider renal impairment in cirrhotic patients primarily as HRS. HRS is a severe and sometimes reversible renal impairment in patients with baseline liver disease. It is defined as decreased renal blood flow and GFR most probably in a cirrhotic patient or cases with fulminant hepatic failure. Its main pathophysiological hallmark is severe renal vasoconstriction (48). In patients with cirrhosis, biglycan is secreted by the cirrhotic liver tissue transported through the circulation to the kidney and plays a part in hepatorenal crosstalk. Biglycan interacts with TLR2/TLR4-CD14 on macrophages and induces the production of inflammatory cytokines. Biglycan stimulates Beclin-1 secretion and autophagosome formation in M1 macrophages. Increased levels of soluble biglycan play an important role in hepatorenal inflammation and autophagy. Therefore, biglycan serum levels could be used as a novel non-invasive biomarker for HRS (49).

HRS is a specific form of ARF that typically occurs in advanced cirrhosis with portal hypertension. The circulatory impairment in HRS, at least to a certain extent, is due to cardiac dysfunction before the functional impairment of the kidney (50). Cirrhotic cardiomyopathy describes a certain type of heart dysfunction characterized by weakened contractile responsiveness to stress, altered diastolic relaxation, and impaired contractility in patients without any recognized cardiac disease. Among patients with nonalcoholic cirrhosis, a broad range of cirrhotic cardiomyopathy manifestations has been reported, including right ventricular systolic dysfunction, left and right atrial enlargement, biventricular diastolic dysfunction, systolic pulmonary arterial pressure elevation and left ventricular mass (51). These conditions may be associated with portal hypertension, increased vasodilator mediators, peripheral vasodilatation and the consequent reduction of systemic vascular resistance. In its advanced stages, liver cirrhosis may cause increased cardiac output due to splanchnic arterial vasodilation and hyperdynamic circulation (52). Although the cardiac output is higher in these patients, this higher cardiac output cannot ensure sufficient arterial blood pressure and renal perfusion (53). Circulatory dysfunction leads to cardiac inotropic and chronotropic dysfunction and consequent type 1 HRS. The major pathophysiologic mechanism of HRS is the maladaptive activation of neurohormones and consequent vasoconstriction due to low cardiac output and the use of diuretic drugs. This results in GFR reduction, defective water and electrolyte excretion, and further deterioration of renal function (50). Therapeutic options in these patients are non-selective beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, and finally, liver transplantation (6).

Liver cirrhotic patients often experience a decline in cholesterol synthesis, leading to insufficient substrate for steroid generation in the adrenal gland (54). Relative adrenal insufficiency is a syndrome characterized by the inadequate synthesis or activity of cortisol, which leads to an increased cardiac output and vascular tonus in severe liver cirrhosis. Furthermore, low cortisol levels in these patients result in a deficiency of activated glucocorticoids, failing to suppress the transcription of inflammatory cytokines, which leads to aggravation of immunological incompetence (55). Relative adrenal insufficiency is frequent in liver cirrhosis patients, and 15.23% of non-hospitalized stable cirrhotic patients develop relative adrenal insufficiency. In these patients, the survival rate decreases, the and risk of complications such as bleeding and HRS increases in comparison to those without adrenal

insufficiency (56). Deficient adrenal cortisol production gives rise to disturbances of the vascular tonus, cardiac output, and renal perfusion (55). Adrenal insufficiency and low levels of glucocorticoids result in a decreased number of beta-adrenergic receptors in the heart and consequently lower cardiac contractility and impaired circulatory and kidney functions (57). Corticosteroid therapy is a beneficial therapeutic option in severe cirrhotic patients, contributing to improved hospital survival rates (56).

Cirrhotic patients are also exposed to renal damage due to infections, hypovolemia and the accumulation of bile acids and nephrotoxic drugs for the treatment of their infections (58). The pathogenesis of HRS is thought to consist of concurrent mechanisms, including functional renal vasoconstriction and non-hemodynamic tubulo-toxic factors, like endotoxins and bile acids. Portal hypertension and maladaptive arterial vasodilation in these patients lead to the over-stimulation of the sympathetic nervous system and the renin-angiotensin system (RAS), resulting in renal vasoconstriction. These events reduce GFR and mediate the occurrence of acute tubular necrosis (ATN), acute glomerulonephritis (AGN), and acute interstitial nephritis (AIN) in cirrhotic patients. HRS is associated with ominous clinical outcomes and a high mortality rate (59). In the case of severe hypotension and low output state, vasoconstrictor therapy to raise mean arterial pressure could be necessary to achieve the restoration of renal blood flow and improve renal function. However, this therapeutic approach has a low efficiency in severe ARF and contributes to cholestasis. While liver transplantation is the preferred treatment in such cases, it may not be an appropriate option for all patients (60).

CRF may be initiated by cirrhosis-associated IgA nephropathy (IgAN) or HRS in these patients. On the other hand, ARF can also occur in the presence of pre-existing CRF in patients with cirrhosis (58). A comprehensive understanding of all potential relevant mechanisms of renal dysfunction in cirrhotic patients is crucial for clinicians to effectively manage cases of acute, chronic or acute-on-chronic renal dysfunction in cirrhotic patients with or without HRS.

Nonalcoholic fatty liver disease

NAFLD stands as the most common chronic liver disease and may lead to cirrhosis and end-stage liver disease (61). Among patients with NAFLD, a broad range of renal dysfunction manifestations have been reported, including abnormal GFR (5%), proteinuria (18%), and impaired renal function(28%) (62).

Adipose tissue, liver, and kidneys, express all RAS components. Studies have indicated that the activation of both systemic and local (renal and hepatic) Angiotensin II-type 1 receptor significantly contributes to the development of obesity-related disorders such as NAFLD and CRF (61). Activation of the renin-angiotensin II type 1 receptor axis is related to insulin resistance, inflammation, hepatic steatosis and fibrosis. In kidneys, these processes result in renal vasoconstriction, endothelial dysfunction, and glomerular hypertension, glomerular hyperfiltration, tubulointerstitial inflammation and fibrosis (63). In a clinical trial study, the therapeutic potential of telmisartan or losartan in the treatment of NAFLD was examined. The results showed that telmisartan ameliorated necroinflammation, NAFLD activity score, and fibrosis stage in nonalcoholic steatohepatitis, as well as microalbuminuria (64).

5'-AMP-Activated protein kinase plays a vital role as a cellular metabolism regulator. Adenyl monophosphate-activated protein kinase (AMPK) is inhibited in calorie-excess conditions, such as obesity. Pharmacological AMPK activators are being developed to decrease hepatic inflammation and fibrosis along with providing endothelial protection (6, 61). Furthermore, AMPK plays a vital role at the intersection of energy metabolism, water and ion transport and suppression of inflammation in renal cells. AMPK activators reduce toxic lipid deposition in renal tubular cells, endothelium, podocytes, and mesangial cells and ameliorate the progression of CRF (65).

Sirtuin-1 (SIRT1) is an NAD^+-dependent histone/protein deacetylase and acts as a cellular and whole-body nutrient/energy sensor (66). Calorie restriction and elevated intracellular NAD^+ levels upregulate SIRT1, leading to chromatin silencing and transcriptional repression, and improvements in lipid and glucose homeostasis in the liver, adipose tissue, and muscles. Moreover, SIRT-1 activation is associated with anti-inflammatory effects, mitochondrial biogenesis regulation and suppression of oxidative stress in the liver and adipose tissue (67), and the promotion of autophagy (68). Since SIRT expression is markedly decreased in NAFLD, SIRT1 activators could be used as therapeutic agents for the treatment of fatty liver diseases (67). One study showed that SIRT1 increases cell survival and controls cellular senescence by inhibiting p53-dependent apoptosis in response to DNA damage and oxidative stress. Therefore, it exerts renoprotective effects in renal tubular cells and podocytes (69). SIRT-1 deacetylates key transcriptional regulators involved in kidney pathogenesis, such as FOXO, p53, STAT3, RelA/p65NF-κB, and PGC1α/PPARγ, and consequently represses their activity. SIRT-1 improves glucose and lipid metabolism. Due to its critical role in the kidney, promoting SIRT-1 activity helps in controlling kidney diseases including diabetic nephropathy and CRF. SIRT-1 expression in renal cells decreases before the occurrence of albuminuria in diabetic kidney disease. Hasegawa and colleagues indicated that SIRT-1 directly downregulates the tight junction protein claudin-1. Furthermore, it induces synaptopodin and podocin expression in podocytes and preserves glomerular barrier integrity (70). One study showed that SIRT1 agonist (BF175) was significantly protective against high glucose-mediated mitochondrial injury, and ameliorated albuminuria and glomerular injury. Therefore, it could be a potential novel therapeutic agent against diabetic nephropathy (71).

In NASH and CRF patients, free cholesterol accumulates in liver and kidney cells. This leads to altered metabolism of lipids, nitric oxide (NO) depletion, oxidative stress, hyperhomocysteinemia, endothelial dysfunction, inflammation, and fibrosis in these patients (6, 72).

Liver fat accumulation in NAFLD patients results in lower levels of high-density lipoprotein cholesterol (HDL-C) and elevated circulating levels of triglycerides and small dense low-density lipoprotein (LDL) (6). In CRF patients, there is an increase in triglyceride-rich lipoproteins such as VLDL due to decreased levels of endothelium-bound lipoprotein lipase (LPL). LPL is an extracellular enzyme, that is present on the endothelial surface of extrahepatic capillaries and catalyzes the hydrolysis of circulating triglycerides and phospholipids within VLDL and chylomicrons (72). In CRF, increased circulating VLDL promotes atherosclerosis (73). VLDL has a charge affinity for glycosaminoglycans in the GBM, and subsequently increases its permeability and promotes persistent albuminuria. Persistent albuminuria induces excess hepatic lipoprotein synthesis, which continues a lipid-mediated damage cycle. Additionally, VLDL binds to certain receptors on renal tubular cells, glomerular capillary cells, mesangial cells, and interstitial macrophages, promoting mesangial cell proliferation and foam cell emergence (74).

Sterol regulatory element-binding protein-2 (SREBP-2), nuclear transcription factors, and farnesoid X receptor (FXR) are major regulators of cholesterol metabolism. They are expressed in hepatic cells and renal proximal tubule and glomerular cells (6). In NASH and CRF models, upregulation of SREBP-2 results in an inappropriate increase in cholesterol synthesis, accumulation of cytotoxic free cholesterol, impaired bile acid synthesis, and reduced bile acid-induced FXR activation. These events lead to intracellular cholesterol overload and finally cell death, inflammation, and fibrosis in the hepatic and renal cells. Wang and colleagues showed that in a mouse who is fed a high-fat diet, expression of the transcriptional factor sterol-regulatory element-binding protein-1 (SREBP-1) in kidney cells is increased. This protein has an essential role in kidney lipid accumulation and promotes the activation of proinflammatory cytokines, oxidative stress, fibrosis, and proteinuria in the kidneys. Treatment of diet-induced experimental CRF mice with the highly selective and potent FXR-activating ligand, 6-ethyl-chenodeoxycholic acid (INT-747), modulated SREBP-1 activity and reversed renal lipid accumulation by controlling fatty acid synthesis. INT-747 treatment ameliorated proteinuria, and prevented podocyte loss, mesangial expansion, oxidative stress, inflammation, and fibrosis in the kidneys (75). In another study, Neuschwander-Tetri and colleagues assessed the therapeutic effects of bile acid derivative 6-ethylchenodeoxycholic acid (obeticholic acid), an activator of the farnesoid X nuclear receptor, in patients with non-cirrhotic non-alcoholic steatohepatitis. They indicated that FXR activation improves the NAFLD activity score and fibrosis in the diseased liver (76). Epidemiological evidence suggests that NAFLD is linked to chronic kidney disease (CKD), but the mechanism is unclear. A recent study using mouse models found that overexpressing PDE4D in the liver led to NAFLD, while its inhibition improved liver and kidney health in high-fat diet-fed diabetic mice. The study uncovered that PDE4D in the fatty liver increased TGF-β1 production, which triggered kidney injury. These findings suggest that PDE4D is a crucial link between NAFLD and CKD, with potential therapeutic implications using the PDE4 inhibitor roflumilast (77).

Metabolic-associated fatty liver disease

The most common reason for liver transplantation is metabolic-associated fatty liver diseases (MAFLD), which are the leading global causes of liver diseases. MAFLD is a situation of fat accumulation in the liver accompanied by metabolic dysfunction. It's also associated with obesity, insulin resistance, and cardiovascular and kidney diseases (78). MAFLD is a potential risk factor for CRF. The association between MAFLD and CRF is still unknown. However, insulin resistance could be a mechanism in the association between CKD and MAFLD. Through several processes, including salt retention, and downregulation of the natriuretic peptide system, insulin resistance facilitates the progression of CKD. Furthermore, insulin resistance accelerates the CKD progression through indirect processes such as atherosclerosis, vascular dysfunction, and left ventricular hypertrophy (79).

Viral hepatitis

Viral hepatitis is a major global public health issue and is linked with significant mortality and morbidity. The hepatotropic viruses A, B, C, D, and E, are most frequently associated with liver and kidney diseases (80). Renal injury in viral hepatitis is associated with the generation of immune complexes and antibody synthesis against infected cells (6). ARF develops in 1.5-4.7% of patients with non-fulminant hepatitis A (81). Nephrotic syndrome is also a rare complication of HAV infection (82).

HBV may be associated with a wide variety of renal diseases including membranoproliferative glomerulonephritis, membranous nephropathy, and polyarteritis nodosa. The HBe antigen (HBeAg) -IgG complexes have been observed in both the blood and kidney tissue of membranous nephropathy patients. Since HBeAg has a positive electrical charge, and HBeAg-IgG complexes have a low molecular weight, immune deposition takes place under the glomerular epithelium. These complexes are the most common cause of immunologic injury in HBV-associated membranous nephropathy (7). In the impaired kidney tissue, HBV DNA and HBV RNA are distributed in both the nucleus and cytoplasm of the glomerular and tubular epithelial cells (83). A large cohort study of 299,913 adults free of CRF at baseline, showed a prospective association between HBsAg positive serology and a higher risk of developing CRF (84). The study provided novel evidence about this

association, observing a higher occurrence of proteinuria in chronic HBV-infected patients. Adults with HBV-induced membranous nephropathy usually experience hypertension and kidney dysfunction, which, if left untreated will lead to an increased risk of ESRD (85). An *in vitro* study showed that HBV can directly induce the proliferation of human glomerular mesangial cells and the expression of type IV collagen and fibronectin (86). In addition, HBx protein predominantly deposits in renal tubular cells, macrophages, and $CD4^+$ T cells infiltrated into the renal interstitium. HBV increases the inflammation in renal tubules with these cells acting as antigen-presenting cells (87). Renal damage in HBV-induced polyarteritis nodosa predominantly manifests as microscopic hematuria, hypertension, and proteinuria. Circulating HBeAg-IgG complexes deposit in the vessels of these patients. The kidney injury may be limited to medium-sized arteries and the proximal part of interlobular arteries. These arterial injuries lead to ischemic renal parenchyma and glomeruli (88). Immunosuppressive therapy and antiviral therapy are therapeutic options for the treatment of HBV-induced renal impairments (6).

A robust causal link exists between chronic HCV infection and glomerular injuries including membranous nephropathy, polyarteritis nodosa, and mixed cryoglobulinemia syndrome. Less common complications of long-term HCV infection include focal segmental glomerulosclerosis, proliferative glomerulonephritis, and fibrillary and immunotactoid glomerulopathies. Moreover, Elevated serum levels of HCV RNA are associated with an increased risk of ESRD (89). CRF patients undergoing hemodialysis have a higher risk of HCV infection. Furthermore, the prevalence of CRF is higher in HCV-infected patients. Antiviral therapy and immunosuppressive therapy (in patients with severe and progressive polyarteritis nodosa, and mixed cryoglobulinemia syndrome) are therapeutic options for the treatment of HCV-associated renal impairments (90).

Hepatitis E virus (HEV) infection is also commonly associated with renal complications including decreased eGFR, glomerulonephritis, cryoglobulinemia, membranous glomerulonephritis, membranoproliferative glomerulonephritis, IgA nephropathy, and nephroangiosclerosis. Ribavirin is an attractive therapeutic option for rapid viral clearance and the recovery of kidney function in these patients (91). In a case-control study, Scotto et al. (92) examined the sero-virological prevalence and clinical characteristics of HEV infection in ESRD patients. Their results showed elevated serum levels of HEV in hemodialysis patients compared to a healthy population.

Kidney biomarkers for clinical complications

In the context of diagnosing early-stage kidney-liver crosstalk disorders, physicians rely on a panel of specific biomarkers. These biomarkers serve as critical indicators, facilitating the early detection and assessment of pathological conditions affecting both the kidneys and the liver. In the realm of renal biomarkers and their critical role in diagnosing kidney-related conditions, it is important to acknowledge the limitations of creatinine as the prevailing parameter. While creatinine is widely accepted globally, there is growing anticipation regarding the emergence of novel renal biomarkers with potential clinical significance. Nevertheless, there's promising potential for the development of new renal biomarkers with clinical utility (93). One key advantage of urinary biomarkers is their ability to pinpoint the cause of renal failure, particularly in distinguishing between ATN and HRS-AKI. Among these biomarkers, neutrophil gelatinase-associated lipocalin (N-GAL) has been extensively studied and demonstrated its robustness in differentiating ATN from HRS-AKI, guiding vasoconstrictor therapy effectively (94). N-GAL's diagnostic capability for ATN is well-established, with a cutoff value of 220 μg/g. Approximately 86% of ATN cases exceed this threshold, while 88% and 93% of HRS-AKI and prerenal-AKI cases, respectively, fall below it (95). While these urinary biomarkers can discriminate effectively, they aren't widely available in everyday healthcare, emphasizing the need for easier-to-access diagnostic tools.

To distinguish between functional and structural damage, fractional excretion of sodium (FENa) plays a valuable tool. In instances of functional damage, the tubules typically remain intact, resulting in increased sodium reabsorption due to renal hypoperfusion. However, circulatory disorders, particularly in advanced cirrhosis, can lead to chronic renal hypoperfusion and FENa values <1%. Nevertheless, several studies in HRS-AKI have shown that FENa values <0.2% effectively differentiate HRS-AKI from ATN (96).

Furthermore, recent research has demonstrated the diagnostic potential of high levels of albuminuria in identifying ATN. Lastly, serum Cystatin C has gained significance, not only for its ability to identify patients at risk of renal events regardless of muscle mass or gender but also for its predictive value in the development of acute on chronic liver failure (ACLF) and mortality while awaiting a liver transplant (97). Emerging biomarkers show great potential and could potentially be incorporated into the standard evaluation protocol for renal function pending validation in forthcoming studies.

Therapeutic approaches in kidney-liver complications

Due to the identification of circulatory factors that are associated with remote organ injuries, cytokine hemoadsorption therapy could be a novel approach in patients with multiple organ dysfunction syndromes such as kidney-liver complications (Fig.3). This new technology removes all of the cytokines from the

circulatory system of patients and could be used in the treatment of renohepatic syndrome (98). Furthermore, inflammatory cytokine release is very common in renohepatic syndrome. Therefore, drugs with anti-inflammatory effects can be useful in this setting. Isoflurane, a potent anaesthetic agent, has beneficial effects in attenuating cytokine-mediated liver injury. Isoflurane is currently in widespread clinical use and its safety is approved. Kim et al. (99) indicated that isoflurane stimulates intestinal sphingosine kinase-1 (SK1) expression and reduces liver and intestine injuries after ischemia-reperfusion-induced ARF. This effect appears to be associated with decreased IL-6, TNF-a, and IL-17A expression in the hepatic tissue 24 hours following the injury.

In HRS, restoration of sufficient renal blood flow and GFR leads to improvement in kidney function and could be achieved by vasoconstrictor agents and liver transplantation. Pharmacological therapeutic approaches such as terlipressin, albumin, noradrenaline, midodrine, and octreotide have all been studied, alone and in combination, with varying efficacy (100). These pharmaceutical agents act by causing splanchnic vasoconstriction, which leads to improved renal blood flow and circulating blood volume. Meta-analysis studies indicated that intravenous infusion of terlipressin is the most common effective therapy for HRS (101). Intravenous infusion of noradrenaline is as effective as terlipressin and therefore an accepted alternative treatment in these patients (101). Table S2 (See Supplementary Online Information at www.celljournal.org) summarizes the clinical trials using vasoactive medications and their outcomes for the treatment of HRS. The functional identity of HRS implies that improvement in renal function is anticipated with liver transplantation, which remains the ideal therapeutic approach for renal failure whenever possible. However, kidney recovery is dependent on several factors, including the duration and type of kidney damage (102). In addition to vasoconstrictor drugs, therapies to treat systemic inflammation, such as pathogen-associated molecular patterns (PAMPs, that represent bacterial products), damage-associated molecular patterns (DAMPs, which represent intracellular components released from injured hepatocytes), and downstream signalling molecules could be investigated in HRS (103). Transjugular intrahepatic portosystemic shunt (TIPS) insertion is a method that could be used to decrease portal hypertension and its complications in HRS. Studies indicated that renal function improved in patients with cirrhosis and refractory ascites after TIPS insertion. This procedure leads to a decrease in serum creatinine level and increases in urine volume and a consequent decrease in mortality rate (104).

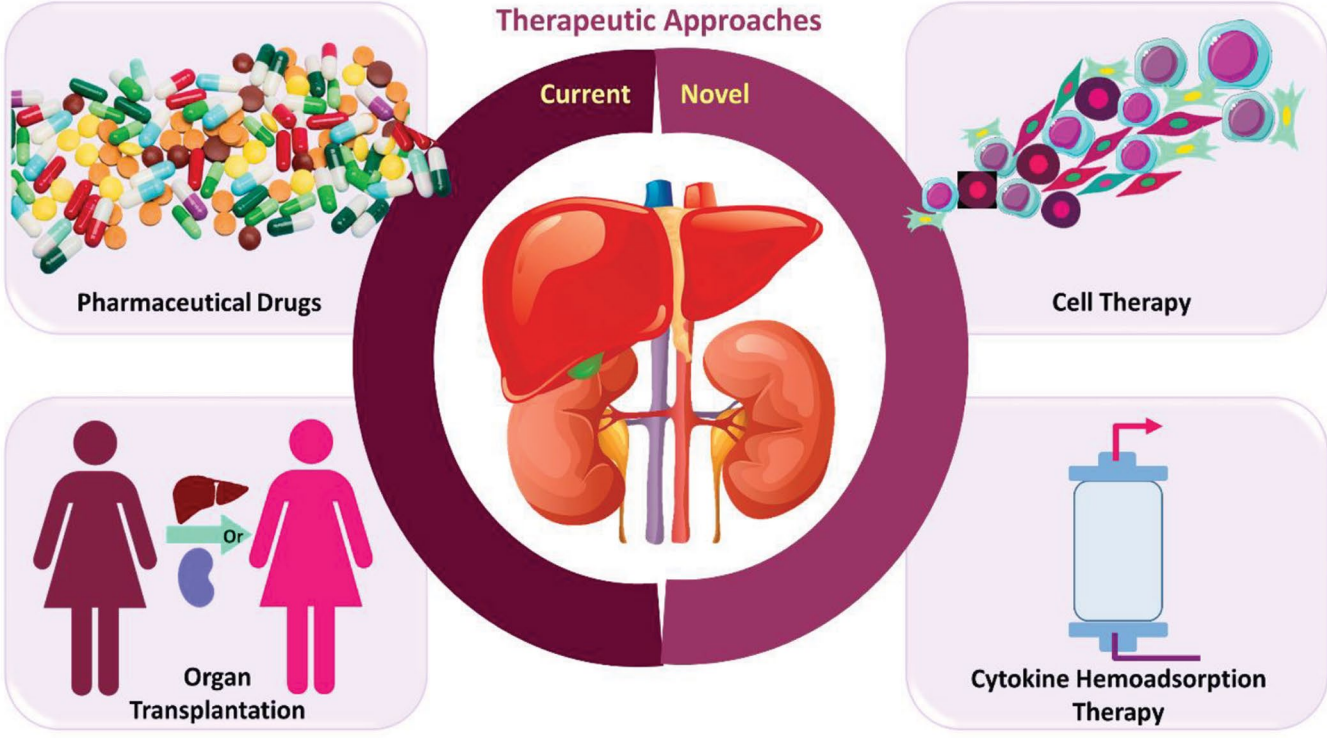

Fig.3: Current and novel therapeutic approaches for the treatment of kidney-liver complications.

Future studies should explore the effects of therapeutic approaches for the clinical management of kidney-liver complications. Furthermore, exploring novel and sensitive biomarkers is important to avoid unnecessary delays in the diagnosis and more accurately guide treatment. In most cases, conventional techniques like urine output, and fractional sodium- or urea-excretion have been demonstrated to have severe limitations and poor association with biopsy results (105). Neutro-phil gelatinase-associated lipocalin (NGAL), tissue inhibitor of metalloproteinases 1 [TIMP-1], osteopontin, and cystatin C could be powerful prognostic biomarkers in patients with AKI in liver diseases due to their activity in the kidney after injury and renoprotective effects (106). Liver fat-ty acid-binding protein (L-FABP) is a mediator of lipid metabolism and has been associated with kidney/liver injury. Urinary L-FABP is a prognostic biomarker for liver and kidney injury (107). Furthermore, numerous novel biomarkers have been investigated recently, IL-18, liver fatty acid-binding protein, kidney injury molecule-1 (KIM-1), and glycated-albumin receiving the most attention in earlier detection and predicting the risk of worsening kidney-liver complications (108).

A recent study explored the effectiveness of vasoconstrictor treatments for type 1 HRS in cirrhosis patients. The analysis involved 16 studies with 1244 patients. Terlipressin was found to signif-icantly increase the odds of HRS reversal compared to placebo but was associated with a higher risk of adverse events. Norepinephrine (NE) showed similar outcomes to terlipressin. In contrast, the combination of midodrine and octreotide had a lower likelihood of HRS reversal. Overall, no treatment improved liver transplant (LT)-free patient survival. Patients with lower baseline serum creatinine and Model for End-stage Liver Disease (MELD) scores responded better to treatment, and the risk of adverse effects was similar between terlipressin and NE. Further research is needed to identify treatment responders with a favourable safety profile (109).

In addition to current methods, there is a fundamental need to establish novel therapeutic approaches. Recent studies have assessed the use of stem cells as a promising and advanced therapeutic approach for acute and chronic injuries to overcome the limited number of donors and end-stage organ failure (110). Furthermore, human pluripotent stem cell (hPSC)-derived cells provide new opportunities for understanding the physiology and treatment of renal and hepatic diseases (2).

Addressing therapeutic options for critically ill patients with both liver and kidney dysfunction is challenging due to their severe condition and high mortality rates. Diagnostic delays using serum creatinine hinder research targeting these patients. While extracorporeal hemoadsorption therapy, which filters out cytokines, has potential, its effectiveness remains uncertain. Targeting specific cytokines such as IL-6 using drugs like Tocilizumab and using Isoflurane anaesthesia may offer liver protection in specific cases, but further research is required to validate these approaches (111). Regenerative medicine and cell-based therapies also hold substantial potential in addressing kidney-liver crosstalk disorders. Stem cell transplantation, including mesenchymal stem cells (MSCs), has garnered attention due to its ability to modulate inflammation and promote tissue repair. Preclinical studies involving MSCs have demonstrated encouraging results in mitigating renal and hepatic damage in experimental models of crosstalk disorders. However, further research is needed to determine the optimal protocols and safety profiles for these therapies in clinical settings. Researchers are working to identify specific biomarkers and molecular pathways that can serve as targets for therapeutic interventions. By tailoring treatments to individual patient profiles and the underlying causes of their kidney-liver crosstalk disorders, it becomes possible to achieve more precise and effective outcomes (112). The registered randomized controlled clinical trials of vasoactive drugs for the treatment of hepatorenal syndrome are listed in Table S1 (See Supplementary Online Information at www.celljournal.org).

Conclusion

Bidirectional kidney-liver crosstalk plays an important role in the well-being maintenance and pathogenesis of certain disorders. In pathologic states, both renal-induced liver damage and liver-induced kidney diseases may happen through these kidney-liver interactions. Further research is crucial for better management of the complications induced by this complex and potentially vicious cycle that may lead to renal and liver dysfunction. In these concomitant kidney-liver diseases, survival rate correlates strongly with early diagnosis, appropriate intervention, and treatment of organ dysfunction; therefore, efforts to explore novel and sensitive biomarkers are important to avoid unnecessary delays in diagnosis and treatment. The kidneys and liver serve as the primary excretory organs in mammals, playing a crucial role in maintaining homeostasis. From a pathological perspective, these organs exhibit overlapping pathways that are interconnected. The bidirectional kidney–liver crosstalk is a complex and intricate interplay between these two vital organs, and it plays a crucial role in maintaining overall health and contributing to the development of specific disorders. In pathological conditions, these interactions can lead to two main scenarios: renal-induced liver damage and liver-induced kidney diseases. Renal-induced liver damage includes a range of issues, including the release of proinflammatory cytokines, oxidative stress, hepatocellular necrosis, apoptosis, and fatty degeneration. On the other side, liver diseases such as cirrhosis, NAFLD, and hepatitis can contribute to inducing kidney diseases. Understanding the mechanisms behind these interactions is essential for effective disease management.

To tackle the complications that arise from this

intricate cycle, further research is vital. Researchers must investigate deeper into the molecular and biochemical processes involved in kidney–liver crosstalk. This knowledge will aid in developing more precise diagnostic tools and therapeutic interventions. In the context of concomitant kidney-liver diseases, early diagnosis is a critical factor in improving patient survival rates. Timely and accurate intervention, coupled with the appropriate treatment of organ dysfunction, is essential. Therefore, researchers must prioritize efforts to explore novel and sensitive biomarkers. These biomarkers can help scientists identify these interconnected renal and liver dysfunctions at an early stage, allowing for quicker and more effective treatments. In conclusion, gaining a comprehensive understanding of bidirectional kidney-liver crosstalk is pivotal for advancing patient care and enhancing outcomes in the realm of renal and liver diseases. The ongoing pursuit of knowledge in this field holds the promise of improving the quality of life for countless individuals facing these complex medical challenges.

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Authors' Contributions

N.K.R., Z.H.; Performed the literature review and Drafted the manuscript. A.H.T., E.Z., A.S., M.B.; Reviewed and Edited manuscript. P.T., M.H., N.H.-K.; Criticlly edited and Reviwed the manuscript. M.V.; Proposed the concept Supported the project and edited and approved the final manuscript. All authors read and approved the final manuscript.

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