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NEPHROLOGY - REVIEW

Kidney–liver pathophysiological crosstalk: its characteristics and importance

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Abstract

The kidney plays a crucial role in controlling the blood volume and pressure, electrolyte and acid–base balance, erythropoietin secretion, as well as renin–angiotensin–aldosterone system activity. All these renal activities have important repercussion in the organism, explaining why morbidity and mortality rates are high in patients with significant renal dysfunction. In this sense, there are renal-induced liver damages in acute kidney injury, as well as liver-induced renal damages in hepatic disease. Ischemia, reperfusion, cytokine outflow, pro-inflammatory cascades, metabolic acidosis, oxidative stress, and changes in enzymatic and metabolic pathways provide the bases for this bidirectional kidney–liver damage. In conclusion, knowing the characteristics of this kidney–liver crosstalk is crucial for handling the complications induced by this vicious circle.

Keywords Kidney · Liver · Crosstalk

Introduction

The concept of 'organ crosstalk' aroused in the 1980s from the growing concern about the non-target effects of drug administrations. The definition of this entity establishes that signals are passed from organ to organ via neural pathways, paracrine interactions within cells of the same tissue, and through the endocrine system. In this way, it reinforces the concept that neurons and bloodstream allow perfect interaction between the organs for maintaining an adequate homeostasis, but this communication also facilitates the spread of damage mediators [1].

Acute kidney injury (AKI), defined as an absolute increase in serum creatinine ≥ 0.3 mg/dl (≥ 26.4 micromol/L) in less than 48 h, or as a percentage increase in serum creatinine ≥ 50% (1.5-fold from baseline) in less than 7 days, can per se lead to multiorgan dysfunction (MOF) or be one of the initial manifestations of a bigger clinical picture. The study performed by the Rocky Mountain Regional Trauma Center, which established the Denver score for MOF, revealed that the indices which related AKI with MOF and death in critical care patients were higher than those observed in patients suffering from an organ failure different from the kidney, and that AKI appeared 48 h after MOF installation in 98% of the critical care patients [1, 2].

The studies elicited to approach this issue agree that AKI is not an isolated event, but rather has repercussions in other vital organs, such as heart, lungs, liver, intestine, and brain due to the chain reaction of the inflammatory cascade activated during AKI [3]. Neutrophil migration and infiltration, cytokine expression, and its subsequent activation of pro-inflammatory and pro-apoptotic pathways, oxidative stress, and changes in acid–base and blood volume correlated with ischemia lead to organ dysfunction and increased mortality in 50% of cases [3]. Moreover, different meta-analysis studies reveal that the other half which survives has also 50% probabilities of developing chronic kidney disease (CKD), as lesions exceed the regenerative capacities [4].

The purpose of this review article is to analyze the kidney–liver crosstalk damaging mechanisms and their consequences (Figs. 1, 2).

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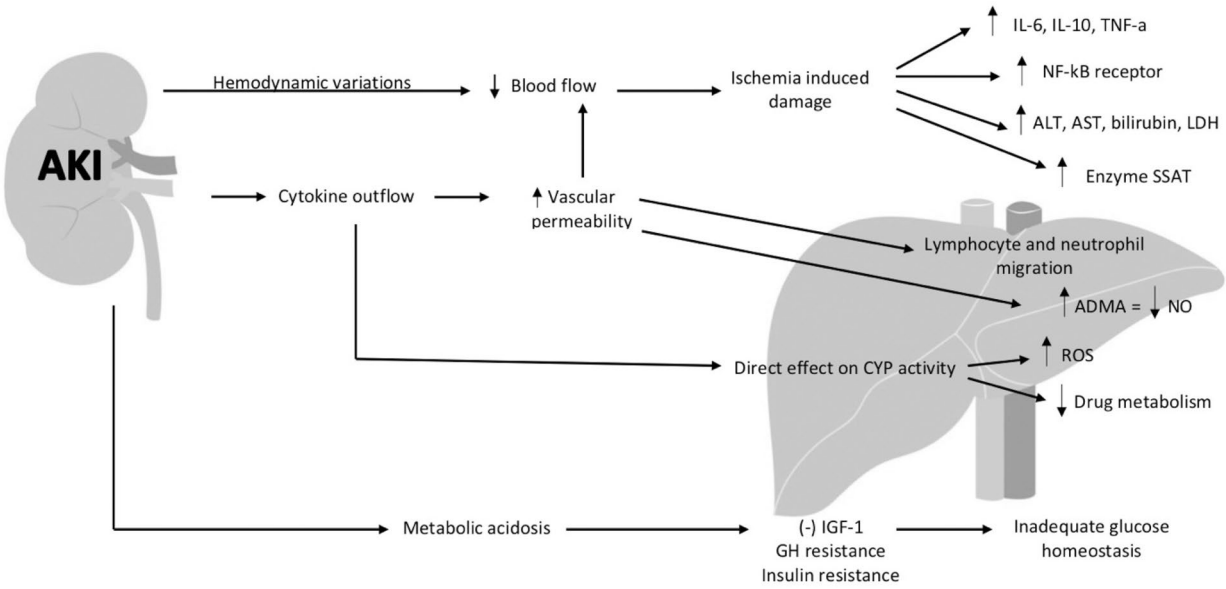

Fig. 1 Kidney–liver crosstalk. *AKI* Acute kidney injury, *ALT* alanine transaminase, *AST* aspartate transaminase, *LDH* lactate dehydrogenase, *ADMA* asymmetric dimethylarginine, *NO* nitric oxide, *ROS* oxygen reactive species, *CYP* cytochrome P450, *GH* growth hormone, inhibited [(–)], *TNF-α* tumor necrosis factor alpha, nuclear factor KB (NF-kB)

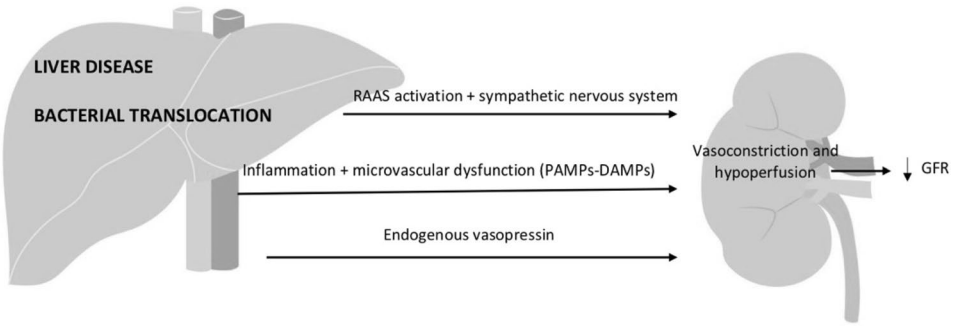

Fig. 2 Liver–kidney crosstalk. Renin–angiotensin–aldosterone system (RAAS) and glomerular filtration rate (GFR)

Kidney–liver damaging mechanisms

Ischemia and ischemia–reperfusion-induced damage

Distant organs during AKI are extremely susceptible to oxygen and nutrients deprivation derived from poor blood supply secondary to not only the central role the kidney has on managing blood pressure and volume, but also because of the changes in vascular tone and permeability triggered by cytokine outflow. In addition, kidney ischemia leads itself to an increase in mediators that induce hepatocyte apoptosis via activation of the nuclear factor κ-light-chain-enhancer of activated B-cell (NF-kB) receptor, especially after organ reperfusion. Besides, AKI specifically leads to an interleukin-6 (IL-6) increase in the liver, which leads to interleukin-10 (IL-10) production by Kupffer cells [5]. It is known that these interleukins have an essential role in liver regeneration, but they have also been related with hepatocellular carcinoma development, and they have also been found elevated in cirrhotic patients [6]. In fact, it was seen that in knock-out mice for tumor necrosis factor-α (TNF-α), IL-6, and interleukin-17A (IL-17A), there was less liver damage after kidney ischemia. Animal models are widely used to delve deeply in the pathophysiology of these mechanisms. Different AKI experimental prototypes have been created to approximate all possible clinical scenarios: bilateral nephrectomy, bilateral or unilateral ischemia–reperfusion injury models, and it has been seen an increase in hepatic enzymes (alanine transaminase, aspartate transaminase, and lactate dehydrogenase) and bilirubin, reflecting hepatocyte damage and/or inflammation in these three AKI experimental models. Further biopsies have revealed increase in liver necrosis and vascular congestion [7]. Ischemia–reperfusion

produces an increase in pro-inflammatory cytokines which activates the pro-apoptotic pathways by stimulating the NF-kB receptors causing liver-damage amplification, as has been stated before. Particularly in the cases of reperfusion, the TNF-α has been found elevated, and can lead to a dramatic increase in the myeloperoxidase (MPO) activity. It has also been documented under this condition a reduction of superoxide dismutase and catalase enzymes, together with an increase in glutathione levels, leading to damage by oxidative stress. Studies revealed a raise in the spermidine/spermine N^1-acetyltransferase (SSAT) enzyme, involved as a limiting factor in the polyamine metabolism, which is responsible for the production of oxygen reactive species that add up to the ones brought by the reperfusion itself [5].

Cytokine damage

It has been documented that some cytokines released in AKI (IL-6, IL-17A, and TNF-α) can modify hepatic clearance, since they target its main regulators such as hepatic blood supply, liver intrinsic clearance, and unbound drug fraction. In addition, liver blood flow is also affected by an increased in hepatic vascular permeability, which even favors neutrophil and lymphocyte migration, leading to an inflammatory cascade on liver cells [6].

Endothelial dysfunction can also be attributed to the increase in asymmetric dimethylarginine (ADMA), a competitive inhibitor of the nitric oxide synthase, which is accumulated during AKI and eliminated by the liver, being hence also a marker of damage. Consequently, the intrahepatic nitric oxide deficiency plays a pathophysiological role in portal hypertension [6, 7].

With regards to the liver intrinsic clearance, both membrane transporters and hepatic enzymes are affected during AKI. The activity of the hepatic cytochrome (CYP) is reduced in many inflammatory conditions, such as bacterial infections, and cancer and autoimmune diseases, and considering the central role the cytokine IL-6 plays in these scenarios, it may explain the reason why they are also reduced in AKI, as the cytokine is markedly increased, although the specific mechanisms remains unclear. Moreover, IL-6 specifically reduces the activity of the isoform CYP3A4 [5–7]. Indoxyl sulfate, a substance derived from tryptophan, is 90% protein-bound, but its serum concentrations increase during AKI causing further inflammation and also reducing the drug metabolism by the same mechanism of lessening the CYP activity [7]. It is worth pointing out that urea has also an effect in hepatic clearance, as when it has been administered in mice it has induced an increase in the expression of the CYP2E1, as it also happens in AKI [2]. This isoform is responsible for the metabolism of xenobiotics and endogenous substances such as acetol and acetone. Studies with knock-out mice compared with wild-type revealed that the latter had accentuated toxicity to certain chemicals such as acetaminophen, and considerably more damage by oxidative stress, as byproducts of its metabolic activities lead to lipid peroxidation [8].

Metabolic acidosis damage

The lactic acid generated as a metabolic waste product from cell anaerobic respiration is usually eliminated by the liver and the kidney. When the kidneys undergo major dysfunction as it happens in AKI, lactic acid that cannot be removed in urine is captivated by the liver, which increases the hepatic enzyme phosphoenolpyruvate carboxykinase activity to maintain an adequate serum pH value [9].

When this mechanism becomes oversaturated, a lactic metabolic acidosis is consequently installed. Metabolic acidosis is associated with an increase in mortality in AKI patients, since it produces an increase in insulin resistance causing changes in glucose homeostasis and secondary changes in hepatic metabolism, such as insulin-like growth factor-1 (IGF-1) synthesis inhibition, which causes growth hormone (GH) resistance [9].

Liver–kidney damaging mechanisms: hepato-renal syndrome

Hepato-renal syndrome (HRS) should be accounted in clinical pictures with patients who have acute liver failure, chronic liver disease, or biliary surgery, and develop kidney failure in the absence of another evident etiology [5]. In fact, AKI should be considered a prognostic entity in cirrhotic patients, since it has been documented that in this case, an increase in creatinine levels is related to low survival forecast. As blood flow is altered progressively as cirrhosis advances, the greater the hemodynamic alteration, the greater susceptibility to develop kidney failure [10]. It was noticed a triggering event in 50% of patients that developed an hepato-renal syndrome, these being a bacterial infection, consumption of diuretics, episodes of diarrhea and/or vomits, bleeding varicose veins (specially in cirrhotic), any gastrointestinal hemorrhage, or after paracentesis performed with inadequate management of blood volume [9]. The mechanisms that trigger this outcome include the compensatory activation of the RAAS and sympathetic nervous system due to the increased splanchnic hyperemia and vasodilation (as this happens almost exclusively in patients with ascites). The RAAS mechanism as well aggravates furthermore the liver as it causes hepatic fibrosis. Simultaneously, there is a non-osmotic secretion of endogenous vasopressin, that contributes to the further vasoconstriction of intra-renal

vessels and hypoperfusion that unleashes a decrease in the glomerular filtrate rate [11, 12].

Furthermore, in specific cases of cirrhotic cardiopathology, there is a greater hemodynamic instability as vasodilators such as endothelin, nitric oxide, and prostacyclin are released. In this sense, it has been documented a declined cardiac output as a preceding event for HRS [12].

However, according to the new theory that has been developed on the pathophysiology of decompensated cirrhosis, the view on HRS has been changed in recent years, moving from the idea that it was only related to renal hypoperfusion due to macrocirculatory dysfunction (i.e., splanchnic arterial vasodilation and reduction of cardiac output) [13–15]. The new theory proposes that a systemic inflammatory response due to translocation of intestine bacteria acts as the precipitator of overexpression of tubular TLR4 and pro-inflammatory cytokine outflow responsible for microvascular changes and arterial vasoconstriction [12, 16].

The new theory is that the increased circulating levels of pro-inflammatory cytokines and chemokines may exercise a direct relevant role in the development of HRS [17, 18]. Such cytokines have been associated with renal impairment in patients and in animal models of cirrhosis with infection [19, 20]. Moving from the concept that AKI and HRS-AKI are often precipitated by bacterial infection, the new hypothesis on the pathogenesis of sepsis-induced AKI should also be considered [21–23]. This theory proposes that a synergic interplay of inflammation and microvascular dysfunction is responsible for the amplification of the signal that the pathogen-associated molecular pattern molecules (PAMPs), which are derived from microorganisms, and the damage-associated molecular pattern molecules (DAMPs), which are derived from cells, exert on proximal epithelial tubular cells. The recognition of this signal and its subsequent spread to all the other proximal tubular epithelial cells cause a mitochondria-mediated metabolic downregulation [24].

The International Ascites Club established in 2007 the following HRS diagnosis criteria, which consist of:

- Cirrhosis with ascites.
- Serum creatinine levels > 1.5 mg/dL.
- No creatinine improvement after 2 days without diuretics or volume expansion with albumin.
- Absence of shock.
- Absence of regular or recent consumption of nephrotoxic drugs.
- Absence of signs that denote injury of the renal parenchyma (proteinuria > 500 mg/day and hematuria > 50 erythrocytes per field) and/or abnormal renal ultrasound.

It is worth mentioning that creatinine clearance values are currently no longer used for diagnosis, and unless there is a septic shock, the diagnosis of a bacterial infection does not exclude HRS diagnose. Oliguria is not included in the criterions, but is a sensitive marker for AKI with adverse outcomes. Biomarkers such as neutrophil gelatinase-associated lipocalin, IL-18, and liver fatty-acid binding protein are being studied. They are non-specific of kidney injury nor have cut-off values with respect to tubular necrosis, but are markers of early kidney ischemia events. Further analysis of these criteria appoints the limitation of the exclusion for the coexistence with another form of AKI or CDK from other glomerular pathologies that may as well be associated with liver disease [3]. In addition, HRS can be classified in two types: HRS type 1 is defined as when serum creatinine levels duplicate to more than 2.5 mg/dL in a lapse of time no more than 2 weeks (accounting as a specific type of AKI), while HRS type 2 accounts for a progressive increase in serum creatinine levels to more than 1.5 mg/dL (considered as a form of CKD), and is usually associated with refractory ascites resistant to diuretics [7, 12].

Conclusion

There is usually a kidney–liver crosstalk in health and certain pathological states. In this sense, there are renal-induced liver damages in acute kidney injury, as well as liver-induced renal damages in hepatic disease. Ischemia, reperfusion, cytokine outflow, pro-inflammatory cascades, metabolic acidosis, oxidative stress, and changes in enzymatic and metabolic pathways provide the bases for this bidirectional kidney–liver damage. Thus, knowing the characteristics of this crosstalk is crucial for handling the complications induced by this vicious circle.

Compliance with ethical standards

Conflict of interest All the authors declare that they have no conflict of interest.

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