**Name of Journal:** *World Journal of Hepatology*

**Manuscript NO:** 39860

**Manuscript Type:** LETTER TO THE EDITOR

**Protecting kidneys in liver transplant patients: A pathway to preventive interventions**

Sibulesky L *et al.* Protecting kidneys in liver transplant patients

Lena Sibulesky, Scott W Biggins, Raimund Pichler

**Lena Sibulesky,** Division of Transplant Surgery, Department of Surgery, University of Washington, Seattle, WA 98195, United States

**Scott W Biggins,** Division of Gastroenterology and Hepatology, Department of Medicine, University of Washington, Seattle, WA 98195, United States

**Raimund Pichler,** Division of Nephrology, Department of Medicine, University of Washington, Seattle, WA 98195, United States

**ORCID number:** Lena Sibulesky ([0000-0001-5435-737X](http://orcid.org/0000-0001-5435-737X)); Scott W Biggins (0000-0002-3081-4668); Raimund Pichler (0000-0002-7685-9415).

**Author contributions:** Sibulesky L, Biggins SW and Pichler R wrote this letter.

**Conflict-of-interest statement:** There are no conflicts of interest.

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

**Manuscript source:** Unsolicited manuscript

**Correspondence to: Lena Sibulesky, MD, Assistant Professor, Surgeon,** Division of Transplant Surgery, Department of Surgery, University of Washington, 1959 NE Pacific Street, Box 356410, Seattle, WA 98195, United States. lenasi@uw.edu

**Telephone:** +1-206-5987797

**Fax:** +1-206-5984287

**Received:** May 16, 2018

**Peer-review started:** May 16, 2018

**First decision:** May 24, 2018

**Revised:** May 30, 2018

**Accepted:** June 28, 2018

**Article in press:**

**Published online:**

**Abstract**

Acute kidney injury (AKI) is a frequent postoperative complication after liver transplantation. The etiology is multifactorial, including perioperative renal status, surgery related events, and postoperative immunosuppression therapy. The role of renal hypoperfusion and hepatic ischemia-reperfusion injury as causes of early AKI are now being increasingly recognized. Further studies should focus on therapies that would attenuate this injury.

**Key words:** Acute kidney injury; Liver transplantation; Hepatic ischemia-reperfusion injury; Marginal grafts; Small interfering ribonucleic acid

**© The Author(s) 2018.** Published by Baishideng Publishing Group Inc. All rights reserved.

**Core tip:** Acute kidney injury early post liver transplantation is a major cause of morbidity and mortality. The etiology is multifactorial. The renal hypoperfusion and hepatic ischemia-reperfusion injury are being increasingly recognized. Further studies need to focus on therapies that would attenuate this injury.

Sibulesky L, Biggins SW, Pichler R.Protecting kidneys in liver transplant patients: A pathway to preventive interventions. *World J Hepatol* 2018; In press

**To the Editor**

Acute kidney injury (AKI) is a frequent and serious postoperative complication in the early period after liver transplantation (LT) and is believed to be a major cause of morbidity and mortality. The incidence of postoperative AKI varies widely, from 17% to 95% of the recipients, with some requiring renal replacement therapy. The etiology is suggested to be multifactorial and related to almost all aspects of perioperative management. The factors that have been widely discussed in the literature concentrate on the recipient factors including their preoperative renal status, surgery-related events, including blood loss, hypotension, and postoperative immunosuppression therapy effects, such as calcineurin inhibitor–induced vasoconstriction. Based on these independent risk factors, many preventive interventions to reduce the risk of renal injury have been instituted.

Renal hypoperfusion during liver transplantation has been recognized as an important cause of AKI for a long time and studies have estimated, that ischemic and hypovolemic acute tubular necrosis are the cause for AKI in more than a third of liver transplant recipients[1].Recent progress has been made in the field of open heart surgery, another surgical procedure, with a high incidence of ischemic and hypovolemic AKI. A small interfering ribonucleic acid (siRNA) targeting p53 developed by Quark Pharmaceuticals, has been developed for prevention of Delayed Graft Function following renal transplantation but we now have evolving evidence that use of this siRNA during cardiac surgery results in a 26% relative risk reduction in the incidence of AKI[2]. Consideration should be given to also study the use of this siRNA in liver transplantation.

Presently, the role of hepatic ischemia- reperfusion injury (IRI) in the pathogenesis of AKI early after liver transplantation is being increasingly recognized. IRI is defined as cellular damage after the reperfusion of the previously viable ischemic tissues, *i.e.,* liver allograft. Reperfusion of the liver allograft is associated with increased reactive oxygen species production and inflammation, resulting in renal tubular cell injury and death. The severity of the IRI and the postoperative systemic inflammatory response, which is the common pathway in organ dysfunction, including kidney injury, has been linked to the use of the marginal organs, including liver grafts from older donors, liver grafts with prolonged cold ischemia time, graft steatosis, split liver allografts, and donation after circulatory death (DCD). Leithead *et al*[3] demonstrated that in the immediate postoperative period DCD liver transplantation was associated with an increased incidence of AKI [DCD 53.4%; donor after brain death (DBD) 31.8%, *P* = 0.004]. In their study increased peak perioperative aspartate aminotransferase (AST), a surrogate marker of hepatic ischemia-reperfusion injury, was the only consistent predictor of renal dysfunction after DCD transplantation (OR 7.44, 95%CI: 2.78–19.88, *P* < 0.001). Rahman *et al*[4] showed that peak serum AST was the only consistent predictor of AKI in multivariate analysis (OR 1.001, 95%CI: 1.00-1.001, *P* = 0.02), suggesting that hepatic ischemia-reperfusion injury may play a critical role in the pathogenesis of post-transplant renal dysfunction. In various studies, AKI and IRI were associated with a longer time to extubation, increased length of intensive care unit stay and reduced patient and graft survival. AKI has also been shown to be a risk factor for chronic kidney disease[3,4].

Recently, the growing demand for organs, has necessitated the increased use of more marginal liver grafts, potentially leading to the increasing incidence of the IRI and AKI. Given the high incidence of post-LT AKI and its significant impact on recipient survival and complications, further research should be aimed at the attenuating hepatic ischemia-reperfusion injury, while investigating its effects on preventing post-LT AKI and eventually improving outcomes. Because preventive strategies are limited and the evidence is still lacking, further studies should focus on therapies, such as liver machine perfusion and pharmacologic therapies similar to siRNA approaches, that silence genes associated with ischemic AKI or ischemia-reperfusion injury, and participation in clinical trials would elucidate the translational research from the bench to the bedside.

**REFERENCES**

1 **McCauley J**, Van Thiel DH, Starzl TE, Puschett JB. Acute and chronic renal failure in liver transplantation. *Nephron* 1990; **55**: 121-128 [PMID: 2362625 DOI: 10.1159/000185938]

2 **American Society of Nephrology**. Kidney week. 2017. Available from: URL: https://www.asn-online.org/education/kidneyweek/2017/

3 **Leithead JA**, Tariciotti L, Gunson B, Holt A, Isaac J, Mirza DF, Bramhall S, Ferguson JW, Muiesan P. Donation after cardiac death liver transplant recipients have an increased frequency of acute kidney injury. *Am J Transplant* 2012; **12**: 965-975 [PMID: 22226302 DOI: 10.1111/j.1600-6143.2011.03894.x]

4 **Rahman S**, Davidson BR, Mallett SV. Early acute kidney injury after liver transplantation: Predisposing factors and clinical implications. *World J Hepatol* 2017; **9**: 823-832 [PMID: 28706581 DOI: 10.4254/wjh.v9.i18.823]

**P-Reviewer:** Abushady EAE, Ferraioli G **S-Editor:** Ji FF **L-Editor: E-Editor:**

**Specialty type:** Gastroenterology and hepatology

**Country of origin:** United States

**Peer-review report classification**

Grade A (Excellent): 0

Grade B (Very good): 0

Grade C (Good): C, C

Grade D (Fair): 0

Grade E (Poor): 0