

# Renal Hypertrophy in Liver Failure



**To the Editor:** The relationship between kidney function and liver function has been investigated largely in the context of pathologic changes in advanced liver failure, and little is known about any physiologic responses to hepatic failure. Because both organs are responsible for clearing metabolic by-products, there may be renal compensation for decreased hepatic clearance. This possibility is supported by the fact that both kidney size and glomerular filtration rate vary with other alterations in metabolic demand, such as changes in body size or protein intake.<sup>1,2</sup> Our frequent finding of large kidneys during sonography in patients with end-stage liver disease supported the possibility that renal hypertrophy was occurring. This was investigated by measuring renal parenchymal volume (RPV) on computed tomography scans and examining autopsy findings in patients with or without end-stage liver disease and no clinical or radiologic evidence of intrinsic renal disease.

## METHODS

See [Supplementary Methods](#).

## RESULTS

We identified 30 patients with ESLD and no evidence of intrinsic renal disease. One patient with argininosuccinate lyase deficiency had very large kidneys and was excluded as an outlier (RPV > 4 SD above the mean). The characteristics of the patients and the controls with normal liver function are shown in [Table 1](#). There were no significant differences in age, gender, body weight, or serum creatinine between the groups. The ESLD diagnoses are shown in [Table 2](#). Because RPV varies with body size,<sup>1</sup> the data for both

**Table 1.** Patient characteristics

Parameter	ESLD cases	Control group	P
n	29	30	NS
Age, yr	50 ± 3 (20–68)	53 ± 3 (22–73)	NS
Weight, kg	85 ± 6 (51–170)	83 ± 3 (60–134)	NS
Gender, female	15	16	NS
Race, % Caucasian	59	60	NS
Creatinine, mg/dl	0.8 (0.4–1.2)	0.9 (0.5–1.2)	NS
eGFR, ml/min per 1.73 m <sup>2</sup>	105 ± 8 (47–220)	90 ± 5 (52–161)	NS
Ascites, %	59		
MELD score	27 (17–41)		

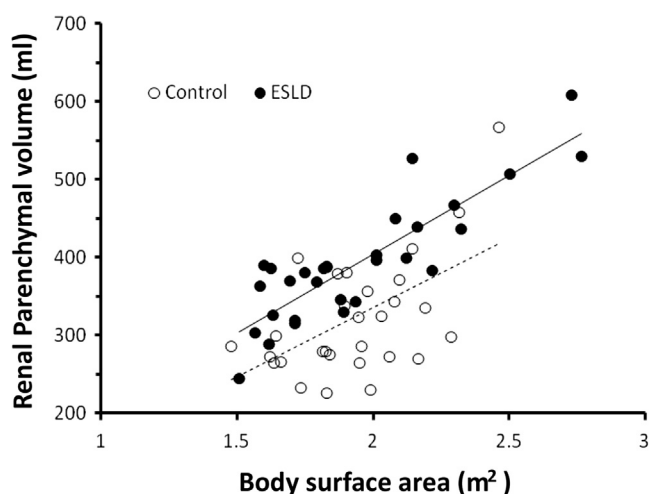
Data are means ± SEM, with ranges in parentheses. eGFR, estimated glomerular filtration rate; MELD, Model for End-Stage Liver Disease; NS, not significant.

**Table 2.** Causes of end-stage liver disease

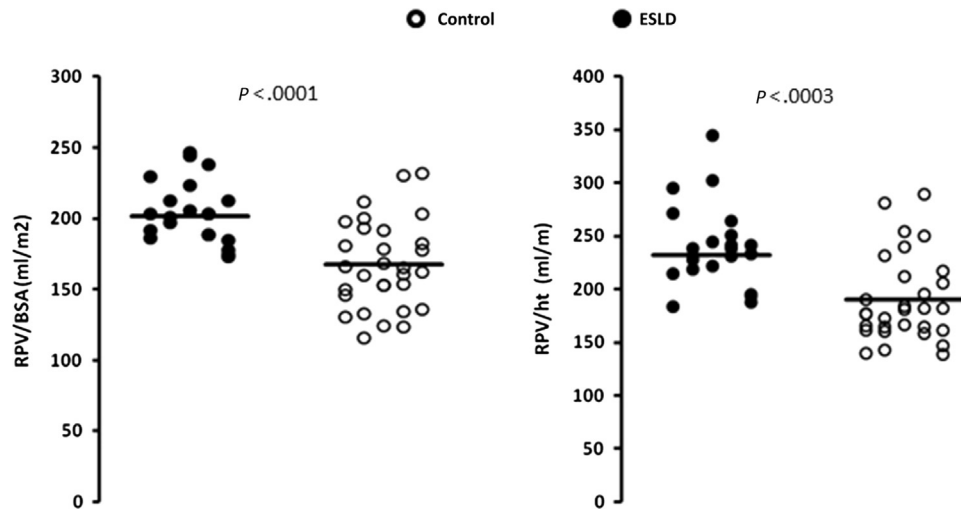
Diagnosis	n	%
Hepatitis C	12	43
Hepatitis B	2	7
NASH	2	7
Alcoholic	4	14
Biliary disease	3	10
Congestive hepatopathy	2	7
Cryptogenic cirrhosis	1	3.5
Autoimmune hepatitis	4	14
Metastatic cancer (neuroendocrine tumor)	1	3.5

NASH, nonalcoholic steatohepatitis.

groups were plotted as a function of body surface area. As shown in [Figure 1](#), there was a clear separation between the groups and, when normalized to body surface area ([Figure 2a](#)), RPV was 21% greater in ESLD subjects (202 ml/m<sup>2</sup> vs. 167 ml/m<sup>2</sup>, *P* = 0.0001). To account for the possible effect of fluid retention in ESLD on body surface area, RPV was instead normalized to height ([Figure 2b](#)), which also showed a 21% increase in ESLD subjects (230 ml/m vs. 190 ml/m). Renal parenchymal volume also varies with gender, independent of body size,<sup>1</sup> and, as shown in [Figure 3](#), the increase in RPV was seen in both males and females. There was no difference in RPV between ESLD subjects with (200 ± 5 ml/m<sup>2</sup>; *n* = 17) or without (205 ± 6 ml/m<sup>2</sup>; *n* = 12) ascites. In the combined cohort of ESLD and controls, serum creatinine showed a significant negative correlation with RPV (*r* = -0.42, *P* < 0.001). In a multivariable model including subjects with and without ESLD ([Table 3](#)), ESLD remained significantly



**Figure 1.** Renal parenchymal volume as a function of body surface area (BSA) in patients with end-stage liver disease (ESLD) and controls without liver disease. Linear regressions are shown and have the following equations: controls, 178 × BSA – 21; ESLD, 202 × BSA – 0.1.



**Figure 2.** Renal parenchymal volume (RPV) in patients with end-stage liver disease (ESLD) and in controls without liver disease, normalized to either body surface area (BSA) or body height (ht).

associated with RPV, together with gender and serum creatinine. There was no correlation between RPV and Model for End-Stage Liver Disease (MELD) score.

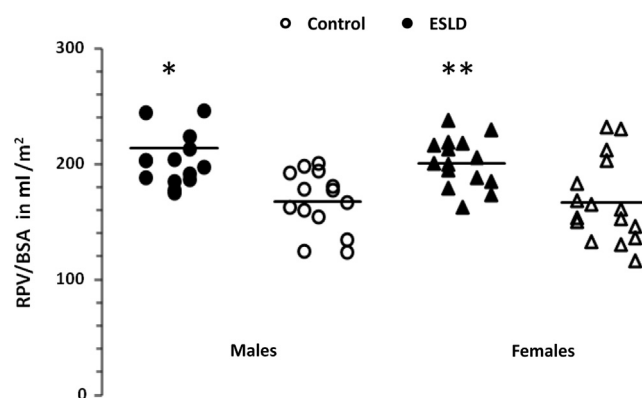
To determine whether edema could explain the increase in RPV, attenuation of the parenchyma was measured on the computed tomography scans. Measurements were possible in 20 of the ESLD patients and 28 of the control subjects. The mean Hounsfield units was actually greater in the ESLD patients ( $35.3 \pm 1.0$ ; range, 26.2–42.3) than in the controls ( $29.5 \pm 0.7$ ; range, 20.7–36.2), inconsistent with edema ( $P < 0.0001$ ). The cause of the increased attenuation is unclear.

Because of the inability to obtain kidney tissue prospectively, histologic confirmation was limited to autopsies. However, only 15 cases with ESLD and 16 cases with normal liver function could be identified that had no clinical evidence of intrinsic renal disease and were performed within 24 hours *postmortem*. Of these, 8 with ESLD and 8 with normal liver function

were excluded because of histologic evidence of significant autolysis. The characteristics of the remaining patients are shown in Table 4, and representative histology is shown in Figure 4. Of note, kidney weight was 38% greater in the ESLD subjects when normalized to height but with borderline significance ( $P = 0.062$ ) and possibly due to the gender disparity. Estimated glomerular volume was 22% greater in ESLD kidneys ( $3.72 \pm 0.38$  vs.  $3.05 \pm 0.37 \text{ m}^3 \times 10^6$ ), but again this difference was not significant ( $P = 0.23$ ).

## DISCUSSION

The results demonstrate that the kidneys enlarge in advanced liver failure without clinical evidence of intrinsic kidney disease. This is unlikely to be due to edema, as there was no correlation with the presence or absence of ascites, and as the attenuation of the renal parenchyma was not decreased in the ESLD patients. These findings indicate that the renal enlargement most likely represents hypertrophy. However, histologic confirmation is problematic due to the inability to obtain tissue prospectively and is possible only in autopsy specimens, with their inherent limitations. Although only 7 suitable autopsy specimens could be identified, they consistently showed normal histology, with the exception of some mild autolysis, and no other cause for enlargement such as interstitial edema,



**Figure 3.** Comparison of renal parenchymal volume (RPV) by gender in patients with end-stage liver disease (ESLD) and in controls without liver disease. BSA, body surface area. Circles represent males; triangles represent females. \* $P = 0.0007$ ; \*\* $P = 0.003$ .

**Table 3.** Multivariable model of renal parenchymal volume normalized to height (n = 59)

Parameter	Coefficient	P
ESLD	30	0.001
Age, yr	-0.004	0.9
Gender, female	-25	0.04
Creatinine, mg/dl	-97	0.009

ESLD, end-stage liver disease.

**Table 4.** Characteristics of the autopsy cases

Parameter	ESLD cases (n = 7)	Control cases (n = 8)	P
Age, yr	49 ± 3 (35–58)	48 ± 3 (31–56)	NS
Height, cm	174 ± 5	163 ± 4	NS
Gender, female	1	6	0.04
Creatinine, baseline	0.8 (0.5–1)	0.7 (0.5–1.1)	NS
Kidney weight, g	488 ± 71	325 ± 21	0.04
Kidney weight/height, g/m	276 ± 36	200 ± 15	0.06

ESLD, end-stage liver disease; NS, not significant. Ranges are given in parentheses.

vascular congestion, or hemorrhage. This is consistent with previous studies of renal histology in patients with advanced liver failure without kidney injury<sup>3–6</sup> in which there is no mention of significant interstitial edema or vascular congestion. The increases in kidney weight and glomerular volume are consistent with hypertrophy, but the differences were not significant due to the small sample sizes and could be explained by the substantial gender disparity. Thus, additional data will be needed to demonstrate increased kidney weight or glomerular hypertrophy. Hypertrophy was not addressed in previous histologic studies.

Clinical data also provide evidence for hypertrophy. Specifically, creatinine clearance is increased in patients with liver failure despite reduced glomerular filtration and reduced serum creatinine levels,<sup>7,8</sup> with similar findings for uric acid,<sup>8</sup> consistent with increased renal tubular mass and function. The mechanism underlying this hypertrophy is unknown but it is likely to be compensatory in response to decreased clearance of metabolic products by the liver. Previous studies have shown that kidney size is dynamic and responds to changes in metabolic demand. Renal parenchymal volume varies closely with body surface area or lean body mass,<sup>1</sup> decreases after weight loss,<sup>1</sup> and increases with protein intake.<sup>2</sup> Among metabolites cleared by both the liver and kidney that might be

responsible, ammonia is a likely candidate, because circulating levels increase in liver failure and it is a stimulus for renal tubular hypertrophy.<sup>9</sup> In fact, the patient with extremely large kidneys who was excluded from analysis suffered from argininosuccinate lyase deficiency, which is associated with extremely high ammonia levels. Unfortunately, ammonia levels were not available for most of the subjects with ESLD, and this will require future study.

In summary, renal enlargement consistent with hypertrophy occurs in advanced liver failure. Because parameters of glomerular filtration can be unreliable in liver failure, kidney size is also used as a parameter of intrinsic renal disease and the need for combined liver and kidney transplantation. This physiologic renal enlargement must therefore be taken into account, as absence of hypertrophy could represent underlying renal disease. Furthermore, the increased metabolic demand represented by the hypertrophy may predispose the kidneys to acute tubular necrosis. Additional studies are needed to determine the mechanism of the hypertrophy and its prognostic significance.

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## DISCLOSURE

All the authors declared no competing interests.

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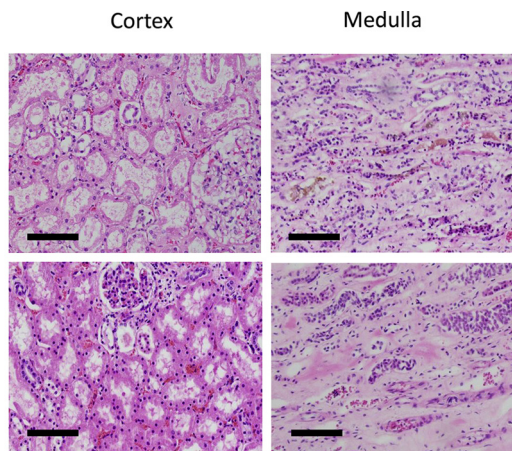
## SUPPLEMENTARY MATERIAL

### Supplementary Methods.

Supplementary material is linked to the online version of the paper at [www.kireports.org](http://www.kireports.org).

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**Figure 4.** Renal histology from autopsies of patients with end-stage liver disease (ESLD) and control patients without clinical evidence of kidney disease. Bars = 100  $\mu$ m.

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## Multicenter Study Evaluating Intrarenal Oxygenation and Fibrosis Using Magnetic Resonance Imaging in Individuals With Advanced CKD



**To the Editor:** The chronic hypoxia theory states that hypoxia and interstitial fibrosis are key contributors to progression of chronic kidney disease (CKD).<sup>1</sup> Presence of fibrosis may further enhance the hypoxia by limiting oxygen transport, resulting in a perpetual cycle of hypoxic injury and progressive loss of kidney function. Blood oxygenation level dependent (BOLD)<sup>2</sup> and diffusion<sup>3</sup> magnetic resonance imaging (MRI) can provide information on renal oxygenation and fibrosis, respectively. The methods rely on endogenous contrast

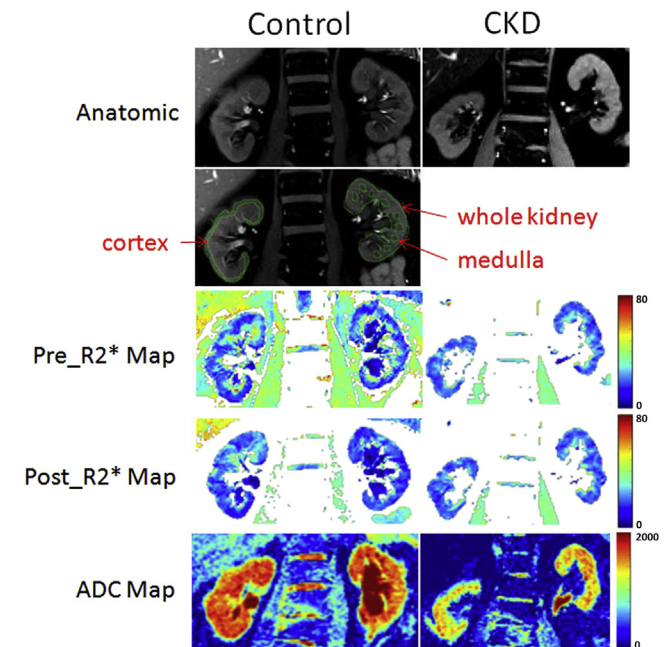
**Table 1.** Baseline characteristics of study population

Variable	CKD, n = 127	Control, n = 13
Age, yr	65 ± 12	59 ± 9
Male, n (%)	81 (64)	6 (46)
Race, n (%)		
White	73 (57)	7 (54)
African American	39 (31)	3 (23)
Other	15 (12)	3 (23)
Diabetes, n (%)	64 (50)	0 (0)
eGFR, ml/min per 1.73 m <sup>2</sup>	33.4 ± 7.2	90.7 ± 11.9
UACR, mg/g	161 (20–584)	n/a
HGB, g/dl	12.9 ± 1.7	n/a

eGFR, estimated glomerular filtration rate; HGB, serum hemoglobin; n/a, not available; UACR, urine albumin to creatinine ratio shown as median (interquartile range).

administration and that are widely available on major vendor platforms.

We report baseline MRI data in 127 individuals with advanced CKD (mean estimated glomerular filtration rate [eGFR] = 33.4 ± 7.2 ml/min per 1.73m<sup>2</sup>) who participated in the COMBINE (CKD Optimal Management with BInders and NicotinamidE) study, a multicenter clinical trial that aimed to test whether



**Figure 1.** Illustration of typical magnetic resonance imaging data from a representative subject from the control and chronic kidney disease (CKD) groups. Shown are anatomical images, pre- and post-furosemide R2\*, and apparent diffusion coefficient (ADC) maps. The maps are scaled similarly using the same color bar for both control and CKD. Note that changes in medullary regions in control, but not in CKD on the post-furosemide R2\* map compared with the pre-furosemide R2\* map. Also included is an illustration of sample regions of interest (ROIs) defined for the analysis of R2\* maps. Cortical ROIs (outlined in green) are defined as thin regions parallel to the outer boundary of the kidney covering the entire length of the kidney. Also shown are whole-kidney ROI and multiple small ROIs in the medulla.