Pseudonormal Corticomedullary Differentiation of the Kidney Assessed on T1-weighted Imaging for Chronic Kidney Disease Patients with Cirrhosis

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Purpose: We investigated whether corticomedullary differentiation (CMD) increased to a pseudonormal appearance on T1-weighted magnetic resonance (MR) images in patients with chronic kidney disease (CKD) with cirrhosis compared with patients with CKD without chronic liver disease.

Methods: We assessed CMD on T1-weighted MR images of 32 patients with CKD with liver cirrhosis and 32 age-matched patients with CKD without liver cirrhosis, grading CMD visualization as good, moderate, or poor. We calculated quantitative CMD by the ratio of the signal intensity of the cortex to that of the medulla.

Results: The proportions of patients in each of the good, moderate, and poor groups differed significantly between those with and without liver cirrhosis ($P = 0.048$). In patients with CKD with liver cirrhosis, the estimated glomerular filtration rate (eGFR) differed between those with poor CMD and those with good or moderate CMD ($P < 0.01$) but not between those with good and those with moderate CMD. In patients with CKD without cirrhosis, the eGFR differed significantly among the good, moderate, and poor CMD groups ($P < 0.05$). We observed no significant correlation between CMD and eGFR in patients with and without cirrhosis ($P < 0.05, r = 0.62$).

Conclusion: CMD of the kidney had a pseudonormal appearance on T1-weighted MR imaging in patients with CKD with cirrhosis.

Keywords: chronic kidney disease, corticomedullary differentiation, liver cirrhosis, magnetic resonance imaging, T1-weighted imaging

Introduction

Magnetic resonance (MR) imaging, including sequences such as T1-weighted, dynamic contrast-enhanced, and diffusion-weighted imaging and arterial spin labeling, is useful in assessing renal morphology as well as function.1 Of these sequences, T1-weighted imaging is routinely used with abdominal MR imaging examination regardless of the presence or absence of renal insufficiency. In the normal kidney, corticomedullary differentiation (CMD) is clearly visualized on T1-weighted images.2–9 CMD reflects the differences in T1 values between the cortex and medulla; with a shorter T1 relaxation time, the cortex appears hyperintense compared with the medulla.2 Loss of CMD is observed in renal insufficiency induced by a variety of etiologies, including glomerulonephritis, acute tubular necrosis, end-stage chronic renal failure, obstructive hydronephrosis, and acute allograft rejection.2–9 In patients with renal insufficiency, reduced CMD is primarily attributable to an increase in the T1 value of the cortex.8 Thus, in daily practice, T1-weighted imaging is useful for identifying renal insufficiency because the estimated glomerular filtration rate (eGFR), the clinical marker of renal function, depends largely on patient gender, hydration status, and exercise level.8

Recently, Lee and associates described an increase in CMD of the kidneys in patients with cirrhosis with normal renal function compared with...
We also evaluated the correlation between CMD and eGFR in patients with or without liver cirrhosis. If these pathological conditions also occur in patients with cirrhosis with chronic kidney disease (CKD), the severity of renal insufficiency can be underestimated by T1-weighted MR imaging because of an increased value of CMD to pseudonormal CMD in the kidney. Normal CMD on T1-weighted images generally indicates normal or mildly impaired renal function, but may not necessarily reflect the renal function in patients with cirrhosis.

We investigated whether CMD in patients with CKD with cirrhosis increased to a pseudonormal appearance by comparing these patients with patients with CKD without chronic liver disease. We also evaluated the correlation between CMD and eGFR in patients with and without liver cirrhosis.

Materials and Methods

Study population

We enrolled 32 patients with CKD with cirrhosis (24 men, 8 women; aged 57 to 85 years, mean, 74.7 years) who underwent MR imaging of the abdomen from June 2012 to July 2013. Cirrhosis was diagnosed based on the patient’s clinical, laboratory, and radiological data. The etiologies of the cirrhosis were viral hepatitis C in 21 patients, alcohol in six, nonalcoholic fatty liver disease in three, hepatitis B in one, and autoimmune hepatitis in one. CKD was defined by an eGFR of less than 60 mL/min/1.73 m² for 3 months or longer. The time between MR imaging examination and eGFR evaluation was less than 3 months in all patients. Exclusion criteria were acute renal impairment, history of renal carcinoma, polycystic kidney disease, presence of hydronephrosis, history of nephrectomy, and atrophy of a unilateral kidney. The etiologies of CKD of the patients with cirrhosis were diabetes mellitus in 4 patients, nephrosclerosis in two, drug-induced renal failure in one, hepatorenal syndrome in one, and unknown in 24.

We recruited 32 age-matched patients with CKD without known liver disease (16 men, 16 women; aged 59 to 87 years, mean, 72.9 years) as our comparative group. They underwent abdominal MR imaging mainly for the observation of pancreaticobiliary diseases. We excluded patients with hepatic findings suspicious for malignancy in addition to the exclusion criteria noted above. The etiologies of CKD in the comparative group were diabetes mellitus in 5 patients, nephrosclerosis in three, IgA nephropathy in one, and unknown in 23.

Our review of radiological and clinical data was consistent with our institutional ethics guidelines, and additional patient informed consent was waived because of the retrospective study design.

MR imaging protocol

All MR imaging examinations were performed on 1.5-tesla scanners (Signa HDx, GE Healthcare, Milwaukee, WI, USA) using an 8-channel multicoil. Breath-hold, transverse T1-weighted gradient-echo images were obtained with parameters: repetition time, 180 ms; echo time, 4.2 ms; flip angle, 90°; field of view, 360 × 360 mm; matrix size, 224 × 320 pixels, leading to an in-plane resolution of 1.6 × 1.1 mm²; and slice thickness, 8 mm with a 2-mm gap. A parallel imaging technique (array spatial sensitivity encoding technique [ASSET]) with a reduction factor of 1.75 to 2.0 was used to reduce the duration of breath-holding to 22 s for 20 slices.

Image analysis

Visual assessment of CMD

Two radiologists with one and 13 years’ experience in diagnostic radiology who were blinded to the underlying existence of liver cirrhosis and values of the eGFR graded the visualization of the CMD of both kidneys in each patient as good (CMD preserved and clearly visualized throughout the kidney), moderate (CMD less conspicuous or partly lost in the kidney), or poor (CMD completely lost). The 2 reviewers performed their assessments separately and resolved differences by consensus. Again, the senior observer assessed CMD visualization in 10 patients each with or without liver cirrhosis who were selected at random with an 8-month interval.

Quantitative assessment of CMD

Patients in whom the CMD was assessed as good or moderate were included in the quantitative analysis. Although Marotti and colleagues placed regions of interest (ROIs) on the renal parenchyma based on anatomic location in patients exhibiting loss of CMD, we excluded patients with poor CMD from this analysis. The junior observer placed ROIs with an average size of 10 mm² on the cortex and medulla at the upper, middle, and lower levels of both kidneys. Consequently, each patient had 6 ROIs in the cortex and 6 ROIs in the medulla. The mean signal intensity (SI) of the cortex or medulla was then calculated from the SI of the 6 ROIs in each patient. The CMD was quantitatively defined as the ratio of the mean SI of the cortex to that of the medulla.
Statistical analysis

We used kappa statistics to evaluate agreement between the 2 radiologists in the assessment of CMD visualization. A kappa coefficient of 0 to 0.4 was considered to represent poor agreement, 0.41 to 0.60, moderate agreement, 0.61 to 0.80, good agreement, and above 0.80, excellent agreement. We used estimated intraclass correlation coefficients (ICC) to assess intraobserver reliability. Reliability was considered slight with ICC of 0 to 0.20, fair with 0.21 to 0.40, moderate with 0.41 to 0.60, substantial with 0.61 to 0.80, and almost perfect above 0.80. We used the Yates-corrected chi-square test to assess the differences in the proportions of CMD visualization scores between patients with and without liver cirrhosis; the Kruskal-Wallis test to evaluate the differences in the eGFR among the good, moderate, and poor scores of the patients with or without liver cirrhosis; the nonparametric Mann-Whitney U test to evaluate the differences in quantitative CMD between the 2 patient groups graded good and moderate; and Spearman’s test to assess correlations between the quantitative CMD and eGFR in patients with and without liver cirrhosis.

For all analyses, results were considered significant when \( P < 0.05 \). An \( r \) value was described when a significant correlation was found. Statistical analysis was performed using SPSS Statistics version 20 (IBM, Armonk, NY, USA).

Results

The eGFR did not differ significantly between the patients with and without liver cirrhosis (\( P = 0.43 \), 45.7 ± 12.5 mL/min/1.73 m\(^2\) [range, 9.0 to 59.0 mL/min/1.73 m\(^2\)] vs. 42.7 ± 13.4 mL/min/1.73 m\(^2\) [range, 6.0 to 59.0 mL/min/1.73 m\(^2\)]. In addition, the number of patients using diuretics did not differ significantly between patients with (n = 12) and without cirrhosis (n = 8).

CMD visualization in patients with and without liver cirrhosis

For visual assessment of CMD on the T\(_1\)-weighted images, the interobserver agreement was excellent (k = 0.82), and the intraobserver reliability was almost perfect (ICC = 0.89).

After the visual assessment of CMD, 22 of the 32 patients with cirrhosis demonstrated good CMD, six demonstrated moderate CMD, and four with end-stage CKD (i.e., eGFR < 30 mL/min/1.73 m\(^2\)) demonstrated poor CMD. Twelve of the 32 patients without liver cirrhosis demonstrated good CMD, 12 demonstrated moderate CMD, and eight demonstrated poor CMD. The proportions of patients in the good, moderate, and poor groups differed significantly between patients with and without liver cirrhosis (\( P = 0.048 \)).

Relationship between visual CMD and eGFR

In the patients with CKD with liver cirrhosis, the eGFR was 50.6 ± 6.2 mL/min/1.73 m\(^2\) (mean ± SD; range, 35.0 to 59.0 mL/min/1.73 m\(^2\)) for good CMD; 45.7 ± 9.6 mL/min/1.73 m\(^2\) (32.0 to 59.0 mL/min/1.73 m\(^2\)) for moderate CMD; and 18.8 ± 7.5 mL/min/1.73 m\(^2\) (9.0 to 27.0 mL/min/1.73 m\(^2\)) for poor CMD. In these patients, the eGFR differed significantly among the 3 CMD groups (\( P < 0.01 \)). The post hoc test showed significant differences in the eGFR between poor CMD and good or moderate CMD but not between good and moderate CMD in patients with liver cirrhosis (\( P < 0.01 \); Fig.1a).

In the patients with CKD without liver cirrhosis, the eGFR was 53.1 ± 5.1 mL/min/1.73 m\(^2\) (44.0 to 59.0 mL/min/1.73 m\(^2\)) for good CMD; 42.4 ± 9.6 mL/min/1.73 m\(^2\) (30.0 to 57.0 mL/min/1.73 m\(^2\)) for moderate CMD; and 28.0 ± 13.7 mL/min/1.73 m\(^2\) for poor CMD (6.0 to 44.0 mL/min/1.73 m\(^2\)). In these patients, the eGFR differed significantly among the 3 CMD groups (\( P < 0.01 \)). The post hoc test also showed significant differences between each group in patients without cirrhosis (\( P < 0.05 \) for all comparisons; Fig.1b).

Quantitative CMD in patients with and without liver cirrhosis

For both kidneys, we observed no significant differences in the mean distance between the kidney and posterior skin surface between patients with and without liver cirrhosis (right kidney, \( P = 0.42 \), 49.3 ± 13.5 mm, patients with cirrhosis, 47.3 ± 10.8 mm, patients without cirrhosis; left kidney, \( P = 0.45 \), 51.5 ± 13.6 mm, patients with liver cirrhosis, 49.8 ± 11.0 mm, patients without

Table. Visual corticomedullary differentiation (CMD) of the kidney in patients with and without liver cirrhosis

<table>
<thead>
<tr>
<th>Corticomedullary differentiation</th>
<th>Cirrhotic cases (n = 32)</th>
<th>Comparative cases (n = 32)</th>
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<tbody>
<tr>
<td>Good</td>
<td>22 (68.75)</td>
<td>12 (37.5)</td>
</tr>
<tr>
<td>Moderate</td>
<td>6 (18.75)</td>
<td>12 (37.5)</td>
</tr>
<tr>
<td>Poor</td>
<td>4 (12.5)</td>
<td>8 (25)</td>
</tr>
</tbody>
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good, CMD preserved and clearly visualized throughout the kidney; moderate, CMD less conspicuous or partly lost in the kidney; poor, CMD completely lost

The proportions of the groups with good, moderate, and poor CMD differed significantly between patients with and without liver cirrhosis (\( P = 0.048 \)).
liver cirrhosis).

In the patients with cirrhosis, the mean quantitative CMD was 1.4 (SD, 0.11; range, 1.2 to 1.6) for visually good CMD and 1.3 (SD, 0.2; range, 1.1 to 1.4) for visually moderate CMD. The quantitative CMD did not differ significantly between the 2 groups. In patients without liver cirrhosis, the mean quantitative CMD was 1.4 (SD, 0.1; range, 1.2 to 1.6) for visually good CMD and 1.1 (SD, 0.06; range, 1.0 to 1.2) for visually moderate CMD. The quantitative CMD differed significantly between the 2 groups ($P < 0.01$).

**Correlation between quantitative CMD and eGFR**

We observed no significant correlation between quantitative CMD and eGFR in the patients with cirrhosis ($P = 0.98$), but we did observe significant correlation between quantitative CMD and eGFR in the patients without liver cirrhosis ($P < 0.05$; $r = 0.62$; Fig. 2).

Figure 3 shows typical cases of CKD with and without liver cirrhosis.

**Discussion**

Our major findings were: a significant difference
in the proportions of the good, moderate, and poor groups between patients with and without liver cirrhosis in the visual assessment of CMD; a significant difference in the eGFR between the poor and moderate or good CMD groups but not between the good and moderate CMD groups in the patients with cirrhosis; correlation of neither visual CMD nor eGFR to quantitative CMD in the patients with cirrhosis; and more good CMD cases among the patients with cirrhosis despite the absence of significant difference in eGFR between patients with and without cirrhosis. These results indicate that CMD in patients with CKD with cirrhosis increased to a pseudonormal appearance and did not necessarily reflect the severity of renal insufficiency in patients with cirrhosis. A pseudonormal appearance of CMD of the kidney can result from increased SI of the cortex or decreased SI of the medulla. Lee and associates have assumed that increased CMD associated with liver cirrhosis may be attributed to decreased water content, decreased renal blood flow, or mineral deposition in the renal cortex. We speculate that the same mechanisms might occur in patients with cirrhosis, even with CKD. Patients with both liver cirrhosis and CKD may also have pleural or peritoneal fluid collection, extracellular fluid overload, or splanchnic blood pooling as a result of increased resistance to blood flow through the cirrhotic liver and vasodilation of the systemic and splanchnic circulation resulting from increased vasodilator production. The low effective circulating volume could lead to secretion of renin or vasopressin and the consequent vasoconstriction of the renal cortex and hypoperfusion. These mechanisms could lead to hepatorenal syndrome. One pathological study has shown that some types of glomerulonephritis are associated with hepatitis virus C infection. The complicated interaction between metabolism, neurohormonal status, blood flow, and inflammation could induce the shorter cortical $T_1$ relaxation times and pseudonormal CMD in patients with CKD with cirrhosis. The renal medulla has a much longer $T_1$ value than the renal cortex and other structures in the abdomen. Thus, the signal intensity of the renal medulla on $T_1$-weighted images may be decreased by severe necrosis and inflammation but not by other pathologies.

Our study has some limitations. First, as noted, the eGFR can change in response to hydration status or specific physiological conditions. Our clinical protocol called for patients to fast for 4 hours, but they did not always comply. On the other hand, the present study indicates that CMD may not change if the patients with or without cirrhosis use diuretics. Second, we excluded patients with apparent asym-
metry of the kidneys because SKGFR was not estimated using a nuclear medicine study or perfusion MR imaging.\textsuperscript{1,14} We cannot therefore extrapolate our present results to patients with CKD who have unilateral renal atrophy. Third, the observers were not completely blinded to whether the subjects belonged to the group with cirrhosis or the comparative group because liver cirrhosis was often obvious on the T\textsubscript{1}-weighted images. Nonetheless, this limitation would not affect quantitative CMD analysis. Fourth, the use of a multicoil and the array spatial sensitivity encoding technique could affect the quantitative assessment of the CMD.\textsuperscript{20} This may not allow us to compare the SI of the kidney with that of other structures such as the skeletal muscle. In this study, the observer placed the ROIs on the cortex and medulla as closely as possible to minimize their effects. Fifth, we did not measure the T\textsubscript{1} value or perfusion in the renal cortex and medulla and compare the measurements with the present results. However, such measurements may not be performed commonly in the clinical setting, such as during abdominal MR imaging for the observation of liver cirrhosis or pancreaticobiliary diseases. Sixth, the causes of CKD were not determined in three-fourths of the patients. Referring physicians did not investigate the causes in patients with moderate renal impairment (e.g., eGFR $\geq 30 \text{mL/min/1.73 m}^2$) because they focused on liver cirrhosis or pancreaticobiliary diseases. Finally, we did not observe whether renal function recovered after MR imaging in the patients with CKD with good or moderate CMD. Nevertheless, the present results allow us to pay greater attention to the interpretation of CMD in patients with CKD with liver cirrhosis.

Conclusion

Patients with CKD with cirrhosis demonstrated pseudonormal CMD of the kidney on T\textsubscript{1}-weighted MR imaging. In these patients, CMD did not correlate with the eGFR nor necessarily reflect the severity of renal insufficiency. Therefore, we should interpret CMD carefully in patients with CKD with cirrhosis.

References

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