3. Jouet P, Meyrier A, Mal F, et al. Transjugular renal biopsy in the treatment of patients with cirrhosis and renal abnormalities. *Hepatology*. 1996;24:1143–1147.

4. Koppel MH, Coburn JW, Mimms MM, et al. Transplantation of cadaveric kidneys from patients with hepatorenal syndrome. *N Engl J Med*. 1969;280:1367–1371.

5. van Slambrouck CM, Salem F, Meehan SM, Chang A. Bile cast nephropathy is a common pathologic finding for kidney injury associated with severe liver dysfunction. *Kidney Int*. 2013;84:192–197.

6. Kanel GC, Peters RL. Glomerular tubular reflux—a morphologic renal lesion associated with the hepatorenal syndrome. *Hepatology*. 1984;4:242–246.

7. Takabatake T, Ohta H, Ishida Y, Hara H. Low serum creatinine levels in severe hepatic disease. *Arch Int Med*. 1988;148:1313–1315.

8. Proulx NL, Akbari A, Garg AX, et al. Measured creatinine clearance from timed urine collections substantially overestimates glomerular filtration rate in patients with liver cirrhosis: a systematic review and individual patient meta-analysis. *Nephrol Dial Transplant*. 2005;20:1617–1622.

9. Franch HA, Preisig PA. NH₄Cl-induced hypertrophy is mediated by weak base effects and is independent of cell cycle processes. *Am J Physiol Cell Physiol*. 1996;270:C932–C938.

**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 m² | 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). |

**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). 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)¹ and diffusion¹ magnetic resonance imaging (MRI) can provide information on renal oxygenation and fibrosis, respectively. The methods rely on endogenous contrast mechanisms that do not require exogenous contrast 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 1.73 m²) who participated in the COMBINE (CKD Optimal Management with Blinders 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.
nicotinamide and lanthanum carbonate would safely lower serum phosphate and FGF23 levels compared with placebo. Relaxation rate $R_2^*$ served as the BOLD MRI index; higher values represent decreased oxygenation.2 Apparent diffusion coefficient (ADC) was the diffusion MRI index; lower values may be due to increased fibrosis.4 Similar MRI data obtained in a small group ($n = 13$) of healthy volunteers were used for comparison. Detailed MRI methods are provided as Supplementary Methods and specific MRI parameters are listed in Supplementary Table S1.

### RESULTS AND DISCUSSION

Table 1 summarizes the baseline characteristics of the study population.

Figure 1 shows examples of MRI data in both a healthy volunteer and an individual with CKD. Table 2 summarizes the differences in MRI measurements between the trial participants with CKD and the healthy control group. Consistent with current literature on studies from single sites,5–7 cortical $R_2^*$ was modestly higher in the group with CKD versus the control group, suggesting decreased cortical oxygenation. $R_2^*_\text{Medulla}$ was lower in participants with CKD compared with healthy volunteers, suggesting increased medullary oxygenation. This seemingly contradictory observation has been reported before in preclinical studies8 using invasive measurements and in human studies using BOLD MRI.9,10 In a remnant kidney model, direct oxygen levels measured using microelectrodes at 6 to 8 weeks showed increased tissue oxygen levels.8

### Table 2. Comparison of magnetic resonance imaging parameters between study groups

| Parameter | CKD/Control | n  | Mean  | SD   | P     | Mean difference (confidence interval) |
|-----------|-------------|----|-------|------|-------|--------------------------------------|
| Oxygenation |             |    |       |      |       |                                      |
| $R_2^*\text{Cortex}$ ($s^{-1}$) | Control | 13 | 18.74 | 2.37 | 0.022 | $-1.811 (-3.322 to -0.3)$ |
|                     | CKD | 123 | 20.55 | 3.10 |       |                                      |
| $R_2^*\text{Medulla}$ ($s^{-1}$) | Control | 13 | 29.03 | 3.87 | <0.01 | 5.278 (2.890 to 7.665) |
|                     | CKD | 121 | 23.75 | 3.22 |       |                                      |
| $R_2^*\text{Kidney}$ ($s^{-1}$) | Control | 13 | 22.15 | 2.25 | 0.38  | 0.611 (-0.810 to 2.032) |
|                     | CKD | 123 | 21.54 | 2.76 |       |                                      |
| $R_2^*\text{(Kid-Cor)}$ ($s^{-1}$) | Control | 13 | 3.41  | 1.89 | <0.01 | 2.453 (1.303 to 3.604) |
|                     | CKD | 123 | 0.96  | 0.89 |       |                                      |
| $R_2^*\text{MC ratio}$ | Control | 13 | 1.57  | 0.28 | <0.01 | 0.403 (0.230 to 0.577) |
|                     | CKD | 123 | 1.17  | 0.15 |       |                                      |
| Response to furosemide |     |    |       |      |       |                                      |
| $\Delta R_2^*\text{Cortex}$ ($s^{-1}$) | Control | 13 | 0.42  | 0.86 | 0.11  | $-0.461 (-1.035 to 0.112)$ |
|                     | CKD | 54  | 0.88  | 1.02 |       |                                      |
| $\Delta R_2^*\text{Medulla}$ ($s^{-1}$) | Control | 13 | 6.28  | 3.46 | 0.002 | 3.747 (1.578 to 5.915) |
|                     | CKD | 54  | 2.54  | 2.47 |       |                                      |
| $\Delta R_2^*\text{Kidney}$ ($s^{-1}$) | Control | 13 | 2.03  | 1.13 | 0.014 | 0.927 (0.217 to 1.638) |
|                     | CKD | 54  | 1.11  | 0.87 |       |                                      |
| Fibrosis |     |    |       |      |       |                                      |
| ADC | Control | 13 | 1.67  | 0.08 | <0.01 | 0.219 (0.165 to 0.273) |
|                     | CKD | 126 | 1.45  | 0.17 |       |                                      |

ADC, apparent diffusion coefficient; CKD, chronic kidney disease; $R_2^*\text{(Kid-Cor)} = R_2^*\text{Kidney} - R_2^*\text{Cortex}$; $R_2^*\text{MC ratio} = R_2^*\text{Medulla} / R_2^*\text{Cortex}$.

*By Student 2-tailed t test.

### Table 3. Comparison of magnetic resonance imaging measures by diabetes status

| Parameter | CKD/Control | n  | Mean  | SD   | P     | Mean difference (confidence interval) |
|-----------|-------------|----|-------|------|-------|--------------------------------------|
| Oxygenation |             |    |       |      |       |                                      |
| $R_2^*\text{Cortex}$ ($s^{-1}$) | Diabetes | 61 | 20.55 | 3.00 | 0.99  | 0.007 (-1.106 to 1.118) |
|                     | No diabetes | 62 | 20.54 | 3.23 |       |                                      |
| $R_2^*\text{Medulla}$ ($s^{-1}$) | Diabetes | 60 | 24.13 | 3.32 | 0.21  | 0.745 (-0.412 to 1.901) |
|                     | No diabetes | 61 | 23.38 | 3.10 |       |                                      |
| $R_2^*\text{Kidney}$ ($s^{-1}$) | Diabetes | 61 | 21.61 | 2.62 | 0.78  | 0.143 (-0.846 to 1.132) |
|                     | No diabetes | 62 | 21.46 | 2.92 |       |                                      |
| $R_2^*\text{MC ratio}$ | Diabetes | 60 | 1.19  | 0.17 | 0.11  | 0.043 (-0.010 to 0.097) |
|                     | No diabetes | 61 | 1.15  | 0.13 |       |                                      |
| Response to furosemide |     |    |       |      |       |                                      |
| $\Delta R_2^*\text{Cortex}$ ($s^{-1}$) | Diabetes | 17 | 0.78  | 1.178 | 0.634 | 0.156 (-0.510 to 0.822) |
|                     | No diabetes | 37 | 0.93  | 0.958 |       |                                      |
| $\Delta R_2^*\text{Medulla}$ ($s^{-1}$) | Diabetes | 17 | 1.76  | 1.47 | 0.054 | 1.137 (-0.022 to 2.296) |
|                     | No diabetes | 37 | 2.90  | 2.76 |       |                                      |
| $\Delta R_2^*\text{Kidney}$ ($s^{-1}$) | Diabetes | 17 | 0.96  | 0.93 | 0.439 | 0.208 (-0.335 to 0.751) |
|                     | No diabetes | 37 | 1.17  | 0.84 |       |                                      |
| Fibrosis |     |    |       |      |       |                                      |
| ADC | Diabetes | 83 | 1.40$^*$ | 0.15 | <0.02 | 0.097 (0.038 to 0.156) |
|                     | No diabetes | 83 | 1.50  | 0.19 |       |                                      |

ADC, apparent diffusion coefficient; CKD, chronic kidney disease.

*By Student 2-tailed t test.

Bold values indicate $P < 0.05$. 

**Table 3. Comparison of magnetic resonance imaging measures by diabetes status**

**Table 2. Comparison of magnetic resonance imaging parameters between study groups**

**Table 3. Comparison of magnetic resonance imaging measures by diabetes status**
same model, at an early phase (4–7 days), tissue hypoxia was observed.11 These observations suggest the possibility that with advanced kidney disease, the decrease in renal perfusion is surpassed by decreased oxygen consumption that results from reduced delivery of glomerular filtrate and reduced tubular sodium transport.12

Because cortico-medullary contrast is reduced in CKD,13 identification of medulla may be challenging, especially when using small regions of interest (ROIs). This difficulty may result in lower interreader agreement for medullary ROIs, as has been reported previously.14 We had a high interreader agreement in medullary ROIs (Supplementary Table S2), and we included whole-kidney ROI specifically to mitigate the limitation of small ROIs for evaluating medulla. The difference between kidney and cortex ROIs could be used as an indirect estimate of medullary R2* with a higher degree of objectivity. Consistent with R2*_Medulla, changes in R2*_Kid-Cor show a net positive mean difference value when compared with controls (Table 2), whereas R2*_Cortex had a negative mean difference. This supports that the observed increase in R2*_Medulla is not an artifact of using small ROIs. Prior studies have reported increased medullary oxygenation using both small ROIs10 and more objective concentric ROI method.9

The response to furosemide provides an index of active tubular sodium reabsorption in the medulla.15 Consistent with prior reports, we observed a blunted response to furosemide in participants with CKD compared with controls.6,16 Notably, for the analysis of response to furosemide, we excluded participants with CKD who were chronically treated with loop diuretics, given a prior study reporting lower response in such individuals.17

Lower ADC values are associated with the presence of fibrosis.3,4 The cortical ADC estimates from this study in the healthy volunteers are comparable with a recent report,1 and as also previously reported, we observed lower cortical ADC in participants with CKD compared with controls (Table 2). The cortical ADC values in our participants with CKD were lower

![Figure 2](image-url)
Table 4. Spearman correlations between magnetic resonance imaging parameters and renal function in the participants with CKD

| Variable                  | ADCdiffusion | eGFR   | Log(UACR)  |
|---------------------------|--------------|--------|------------|
| Oxygenation               |              |        |            |
| R2*_Cortex                | ρ 0.011      | −0.027 | −0.111     |
| R2*_Medulla               | P 0.903      | 0.769  | 0.225      |
| R2*_Kidney                | n 122        | 123    | 122        |
| R2*_MC ratio              | ρ 0.184a     | 0.195b | −0.311b    |
| R2*_Medulla               | P 0.044      | 0.032  | 0.001      |
| R2*_Kidney                | n 120        | 121    | 120        |
| R2*_MC ratio              | ρ 0.062      | 0.026  | −0.209     |
| R2*_Kidney                | P 0.500      | 0.775  | 0.021      |
| R2*_MC ratio              | n 122        | 123    | 122        |
| R2*_Medulla               | ρ 0.223a     | 0.150  | −0.226a    |
| R2*_Kidney                | P 0.014      | 0.100  | 0.013      |
| R2*_MC ratio              | n 120        | 121    | 120        |
| Response to furosemide    |              |        |            |
| ΔR2*_Cortex               | ρ −0.009     | 0.045  | −0.080     |
| ΔR2*_Medulla              | P 0.962      | 0.748  | 0.571      |
| ΔR2*_Kidney               | n 53         | 54     | 53         |
| ΔR2*_MC ratio             | ρ 0.257      | −0.018 | −0.139     |
| ΔR2*_Medulla              | P 0.063      | 0.899  | 0.321      |
| ΔR2*_Kidney               | n 53         | 54     | 53         |
| ΔR2*_MC ratio             | ρ 0.053      | 0.086  | −0.239     |
| ΔR2*_Medulla              | P 0.705      | 0.539  | 0.085      |
| ΔR2*_Kidney               | n 53         | 54     | 53         |
| Fibrosis                  |              |        |            |
| ADC                       | ρ 1.000      | −0.053 | −0.167     |
| eGFR                      | P 0.557      | 0.063  |            |
| n 126                     | 125          | 125     |
| Conventional parameters   |              |        |            |
| ρ −0.053                  | 1.000        | −0.105 |            |
| eGFR                      | P 0.557      | 0.244  |            |
| n 125                     | 126          | 125     |
| ΔLog(UACR)                | ρ −0.167     | −0.105 | 1.000      |
| Log(UACR)                 | P 0.063      | 0.244  |            |
| n 125                     | 126          | 126     |

ADC, apparent diffusion coefficient; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; UACR, urinary albumin to creatinine ratio.

Table 5. Linear regression of MRI indices with UACR and eGFR

| Dependent variable | Predictors | β   | SE  | P   | Adjusteda |
|--------------------|------------|-----|-----|-----|-----------|
| R2*_Medulla        | UACR       | −1.125 | 0.342 | 0.001 | −0.798 | 0.364 | 0.022 |
|                    | eGFR       | 0.081 | 0.040 | 0.048 | 0.080 | 0.039 | 0.044 |
| R2*_MC ratio       | UACR       | −0.039 | 0.016 | 0.017 | −0.035 | 0.017 | 0.048 |
|                    | eGFR       | 0.004 | 0.002 | 0.049 | 0.004 | 0.002 | 0.038 |
| R2*_Kidney         | UACR       | −0.569 | 0.300 | 0.061 | −0.533 | 0.316 | 0.267 |
|                    | eGFR       | 0.016 | 0.035 | 0.649 | 0.013 | 0.034 | 0.703 |

Table 6. Linear regression of ADC with R2* indices

| Dependent variable | Predictors | β   | SE  | P   | Adjusteda |
|--------------------|------------|-----|-----|-----|-----------|
| ADC                | R2*_Medulla| 0.010 | 0.005 | 0.036 | 0.011 | 0.006 | 0.043 |
|                    | R2*_MC ratio| 0.157 | 0.107 | 0.144 | 0.156 | 0.112 | 0.165 |

ADC, apparent diffusion coefficient.

Table 7. Linear regression for eGFR and UACR (Table 7). These relationships remained significant even after adjusting for eGFR and UACR (Table 6). ADC was also associated with diabetes status, and remained significant even after adjusting for eGFR and UACR (Table 7). Further studies are necessary to confirm these findings. Race and gender did not show differences in any of the MRI parameters (data not shown).

Limitations

Our study was performed in patients with a 20 < GFR < 45 ml/min, so conclusions based on these results cannot be generalized to patients with all stages of CKD. Sodium intake was not controlled, which has been shown to affect renal medullary oxygenation.19 Use of hand-drawn

than previously reported3 (1.45 ± 0.17 vs. 1.63 ± 0.14 × 10⁻³ mm²/s), probably due to the lower mean eGFR in our study in comparison with the mean eGFR in the prior study (33.4 vs. 71.2 ml/min per

1.73 m²). Interestingly, 50% of the group with CKD had diabetes, and participants with CKD with diabetes had significantly lower ADC compared with those without diabetes (Table 3).

To characterize MRI measurements across all clinical sites, we examined box-whisker plots for R2*_MC Ratio, ADC_Cortex, eGFR, and urine albumin to creatinine ratio (UACR) by individual sites (Figure 2). Analysis of variance showed no significant differences in any of these parameters between sites.

Finally, we explored associations of MRI measurements with clinical parameters in participants with CKD (Table 4). R2*_Medulla and R2*_MC Ratio showed significant association with eGFR and UACR (Table 5). These relationships remained significant after adjusting for age, race, gender, and diabetes status. The association of medullary R2* with UACR may be interesting because higher UACR is considered to be a predictor of fast progression.18 R2*_Medulla was associated with ADC and remained significant even after adjusting for eGFR and UACR (Table 6). ADC was also associated with diabetes status, and remained significant even after adjusting for eGFR and UACR (Table 7). Further studies are necessary to confirm these findings. Race and gender did not show differences in any of the MRI parameters (data not shown).
ROIs for the medulla may not be objective. Ideally, future studies should use fully automated segmentation of the kidneys performed on high-contrast anatomic images that are coregistered to the BOLD MRIs. It is not clear whether stopping angiotensin-converting enzyme inhibitors/angiotensin receptor blockers for 1 day before MRI and oral loop diuretics only on the day of the MRI is sufficient in this group of participants with advanced CKD. Use of the same dose of furosemide in individuals with lower renal function may not be optimal. Participants in this study did not undergo kidney biopsy, so we cannot directly determine correlations of the MRI findings with biopsy-proven fibrosis measures. The 6 centers enrolled participants from varying clinic settings. The control group had a limited number (n = 13) and were all from a single center. All participating sites used MRI scanners from a single vendor.

In conclusion, our data support the feasibility of using renal BOLD and diffusion MRI in multicenter trials and the data are consistent with prior reports based on single-site studies. These data combined with other results from a recent report support planned international initiatives, such as BEAT-DKD, that involve longitudinal multicenter trials using multiparametric MRI. Overall, our observations in advanced CKD further confirm the reduced renal cortical oxygenation and presence of renal fibrosis consistent with the chronic hypoxia hypothesis. The medullary oxygenation was significantly increased compared with controls and is also consistent with prior reports. The significantly lower ADC in participants with diabetes is novel and may have clinical relevance. Future studies to monitor progressive changes in eGFR are needed to verify if and which of these MRI parameters are specific to progressive CKD. In participants with advanced CKD, evaluating response to furosemide may be limited by the low baseline medullary R2* and their potential chronic use of loop diuretics.

Pottumarthi V. Prasad¹, Wei Li¹, Dominic S. Raj², James Carr⁵, Maria Carr⁵, Jon Thacker¹, Leping Li¹, Chi Wang¹, Stuart M. Sprague¹, Joachim H. Ix⁴, Michel Chonchol⁶, Geoffrey Block⁸, Alfred K. Cheung⁷, Kalani Raphael⁷, Jennifer Gassman⁸, Myles Wolf⁹, Linda F. Fried¹⁰, Tamara Isakova³, and CKD Optimal Management with Binders (COMBINE) study group

¹NorthShore University HealthSystem, Evanston, Illinois, USA; ²George Washington University School of Medicine and Health Sciences, Washington, DC, USA; ³Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA; ⁴University of California San Diego School of Medicine, La Jolla, California, USA; ⁵University of Colorado Denver School of Medicine, Aurora, Colorado, USA; ⁶Denver Nephrology, Denver, Colorado, USA; ⁷University of Utah School of Medicine, Salt Lake City, Utah, USA; ⁸Cleveland Clinic, Cleveland, Ohio, USA; ⁹Duke University School of Medicine, Durham, North Carolina, USA; and ¹⁰University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA

Corresponding author: Potumarthi V. Prasad, Department of Radiology, NorthShore University HealthSystem, Walgreen Jr. Building, Suite G507, 2650 Ridge Avenue, Evanston, Illinois 60201, USA. E-mail: pprasad@northshore.org

DISCLOSURE

All the authors declared no competing interests.

ACKNOWLEDGMENTS

The COMBINE study is supported by grants U01DK099877, U01DK097093, U01DK099930, U01DK099933, U01DK099924, and R01DK102438 (TI) from the National Institute of Diabetes and Digestive and Kidney Diseases. The work also was supported in part by R01DK093793 (PVP) and F31HL123360 (JT).

SUPPLEMENTARY MATERIAL

Supplementary Methods.
Table S1. MRI acquisition parameters.
Table S2. Intra- and interreader agreement.
Supplementary material is linked to the online version of the paper at www.kireports.org.

REFERENCES

1. Fine LG, Orphanides C, Norman JT. Progressive renal disease: the chronic hypoxia hypothesis. Kidney Int Suppl. 1998;65:S74–S78.
2. Prasad PV, Edelman RR, Epstein FH. Noninvasive evaluation of intrarenal oxygenation with BOLD MRI. Circulation. 1996;94:3271–3275.
3. Mao W, Zhou J, Zeng M, et al. Intravoxel incoherent motion diffusion-weighted imaging for the assessment of renal fibrosis of chronic kidney disease: a preliminary study. Magn Reson Imaging. 2018;47:118–124.
4. Togao O, Doi S, Kuro-o M, et al. Assessment of renal fibrosis with diffusion-weighted MR imaging: study with murine model of unilateral ureteral obstruction. Radiology. 2010;256:772–780.
5. Inoue T, Kozawa E, Okada H, et al. Noninvasive evaluation of kidney hypoxia and fibrosis using magnetic resonance imaging. J Am Soc Nephrol. 2011;22:1429–1434.
6. Prasad PV, Thacker J, Li LP, et al. Multi-parametric evaluation of chronic kidney disease by MRI: a preliminary cross-sectional study. PLoS One. 2015;10:e0139961.
7. Pruim M, Milani B, Pivin E, et al. Reduced cortical oxygenation predicts a progressive decline of renal function in patients with chronic kidney disease. Kidney Int. 2018;93:932–940.
8. Priyadarshi A, Periyasamy S, Burke TJ, et al. Effects of reduction of renal mass on renal oxygen tension and erythropoietin production in the rat. Kidney Int. 2002;61:542–546.
9. Milani B, Ansaloni A, Sousa-Guimaraes S, et al. Reduction of cortical oxygenation in chronic kidney disease: evidence
obtained with a new analysis method of blood oxygenation level-dependent magnetic resonance imaging. Nephrol Dial Transplant. 2017;32:2097–2105.

10. Wang ZJ, Kumar R, Banerjee S, et al. Blood oxygen level-dependent (BOLD) MRI of diabetic nephropathy: preliminary experience. J Magn Reson Imaging. 2011;33:655–660.

11. Manotham K, Tanaka T, Matsumoto M, et al. Evidence of tubular hypoxia in the early phase in the remnant kidney model. J Am Soc Nephrol. 2004;15:1277–1288.

12. Neugarten J. Renal BOLD-MRI and assessment for renal hypoxia. Kidney Int. 2012;81:613–614.

13. Lee VS, Kaur M, Bokacheva L, et al. What causes diminished corticomedullary differentiation in renal insufficiency? J Magn Reson Imaging. 2007;25:790–795.

14. Thacker JM, Li LP, Li W, et al. Renal blood oxygenation level-dependent magnetic resonance imaging: a sensitive and objective analysis. Invest Radiol. 2015;50:821–827.

15. Gomez SI, Warner L, Haas JA, et al. Increased hypoxia and reduced renal tubular response to furosemide detected by BOLD magnetic resonance imaging in swine renovascular hypertension. Am J Physiol Renal Physiol. 2009;297:F981–F986.

16. Pruim M, Hofmann L, Piskunowicz M, et al. Determinants of renal tissue oxygenation as measured with BOLD-MRI in chronic kidney disease and hypertension in humans. PLoS One. 2014;9, e95895.

17. Hall ME, Rocco MV, Morgan TM, et al. Chronic diuretic therapy attenuates renal BOLD magnetic resonance response to an acute furosemide stimulus. J Cardiovasc Magn Reson. 2014;16:17.

18. Lorenzo V, Saracho R, Zamora J, et al. Similar renal decline in diabetic and non-diabetic patients with comparable levels of albuminuria. Nephrol Dial Transplant. 2010;25:835–841.

19. Pruim M, Hofmann L, Maillard M, et al. Effect of sodium loading/depletion on renal oxygenation in young normotensive and hypertensive men. Hypertension. 2010;55:1116–1122.

20. Cox EF, Buchanan CE, Bradley CR, et al. Multiparametric renal magnetic resonance imaging: validation, interventions, and alterations in chronic kidney disease. Front Physiol. 2017;8:696.

21. Li LP, Thacker J, Li W, et al. Consistency of multiple renal functional MRI measurements over 18 months. J Magn Reson Imaging. 2018;48:514–521.

22. Biomarker Enterprise to Attack Diabetic Kidney Disease (BEAt-DKD). Available at: www.beat-dkd.eu. Accessed on August 6, 2018.