Magnetic resonance T2 mapping and diffusion-weighted imaging for early detection of cystogenesis and response to therapy in a mouse model of polycystic kidney disease

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Polycystic kidney disease (PKD) is among the leading causes of end-stage renal disease. Increasing evidence exists that molecular therapeutic strategies targeted to cyst formation and growth might be more efficacious in early disease stages, highlighting the growing need for sensitive biomarkers. Here we apply quantitative magnetic resonance imaging techniques of T2 mapping and diffusion-weighted imaging in the *jck* mouse model for PKD using a clinical 3.0 T scanner. We tested whether kidney T2 values and the apparent diffusion coefficient (ADC) are superior to anatomical imaging parameters in the detection of early cystogenesis, as shown on macro- and histopathology. We also tested whether kidney T2 values and ADC have the potential to monitor early treatment effects of therapy with the V2 receptor antagonist Mozavaptane. Kidney T2 values and to a lesser degree ADC were found to be highly sensitive markers of early cystogenesis and superior to anatomical-based imaging parameters. Furthermore, kidney T2 values exhibited a nearly perfect correlation to the histological cystic index, allowing a clear separation of the two mouse genotypes. Additionally, kidney T2 values and ADC were able to monitor early treatment effects in the *jck* mouse model in a proof-of-principle experiment. Thus, given the superiority of kidney T2 values and ADC over anatomical-based imaging in mice, further studies are needed to evaluate the translational impact of these techniques in patients with PKD.

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Polycystic kidney disease (PKD) is the most common inherited kidney disease[1] and the fourth most common cause of kidney failure worldwide.[2] PKD leads to the development of numerous kidney cysts, kidney enlargement, and consecutive chronic kidney disease[3] and exhibits a highly variable disease severity.[2] Although cystogenesis leads to the continuous destruction of renal parenchyma, compensatory hyperfiltration in surviving glomeruli maintains renal function within the normal range for decades.[4]

Novel targeted therapies for PKD are being increasingly investigated in preclinical and clinical trials[5–9] and have been demonstrated to prevent cyst formation and cyst enlargement.[10] Because our understanding of the mechanisms that underlie cystogenesis continues to evolve, there is a great need for identifying sensitive biomarkers that can be used to monitor disease progression to assess patients who may benefit from new treatment protocols[2,11] and to quantify the effects of novel therapies.[12] In particular, biomarkers for PKD should be able to monitor disease progression in very early stages of the disease because there is increasing evidence that molecular therapies targeted at cyst formation and growth might be more efficacious when administered earlier.[10]

Total kidney volume (TKV), assessed using magnetic resonance imaging (MRI), has been proposed as the most suitable biomarker for monitoring disease progression[4,13] because kidney size has been shown to be associated with the severity of functional renal impairment.[14] However, PKD does not directly lead to renal failure in a substantial number of patients; however, it induces changes in the renal microstructure before anatomic distortions become obvious and measurable.[15,16]

Thus, we hypothesized that novel quantitative MRI techniques are able to noninvasively detect and monitor molecular changes in renal tissue characteristics even before macropathological changes occur, thereby enabling early phenotyping of affected individuals. T2 mapping and diffusion-weighted imaging (DWI) are currently routinely used in clinical practice to comprehensively assess different organs such as the heart and prostate.[17,18] T2 values displayed on parametric T2 maps[19] are strongly dependent on the amount of water present in tissues, whereas DWI and the derived parameter apparent diffusion coefficient (ADC) provide quantitative data regarding the movement of water in tissues.[18] Thus, both parameters might be interesting for cystic diseases such as PKD.

This study aimed to apply T2 mapping and DWI for the first time in a preclinical *juvenile cystic kidney* (*jck*) mouse model,[20] which develops massively enlarged polycystic kidneys that are reminiscent of PKD, and to compare the discriminatory value of kidney T2 values (kidney-T2) and ADC with regard to MRI-derived kidney length and volume, as well as macroscopic kidney length and the histologic cystic index at different stages of cystogenesis. Moreover, T2 mapping and DWI were investigated in a first proof-of-principle experiment with respect to their potential to monitor early response during treatment with the V2 receptor antagonist mozavaptan in *jck* mice. Finally, a first proof-of-principle experiment was performed, which translated the results from the preclinical model to a small group of PKD patients.

RESULTS

Sequential study cohort

Macroscopy and histology. In contrast to wild-type (WT) mice demonstrating kidney growth only until week 6, macroscopic kidney length and the histologic cystic index constantly increased with an increase in the age of *jck* mice, showing significant differences compared with those in WT mice from 2 weeks of age (Figure 1; Supplementary Table S1). No significant differences were observed for 1-week-old mice.

Imaging of kidney length and TKV. MRI measurements of kidney length and TKV revealed significant size differences

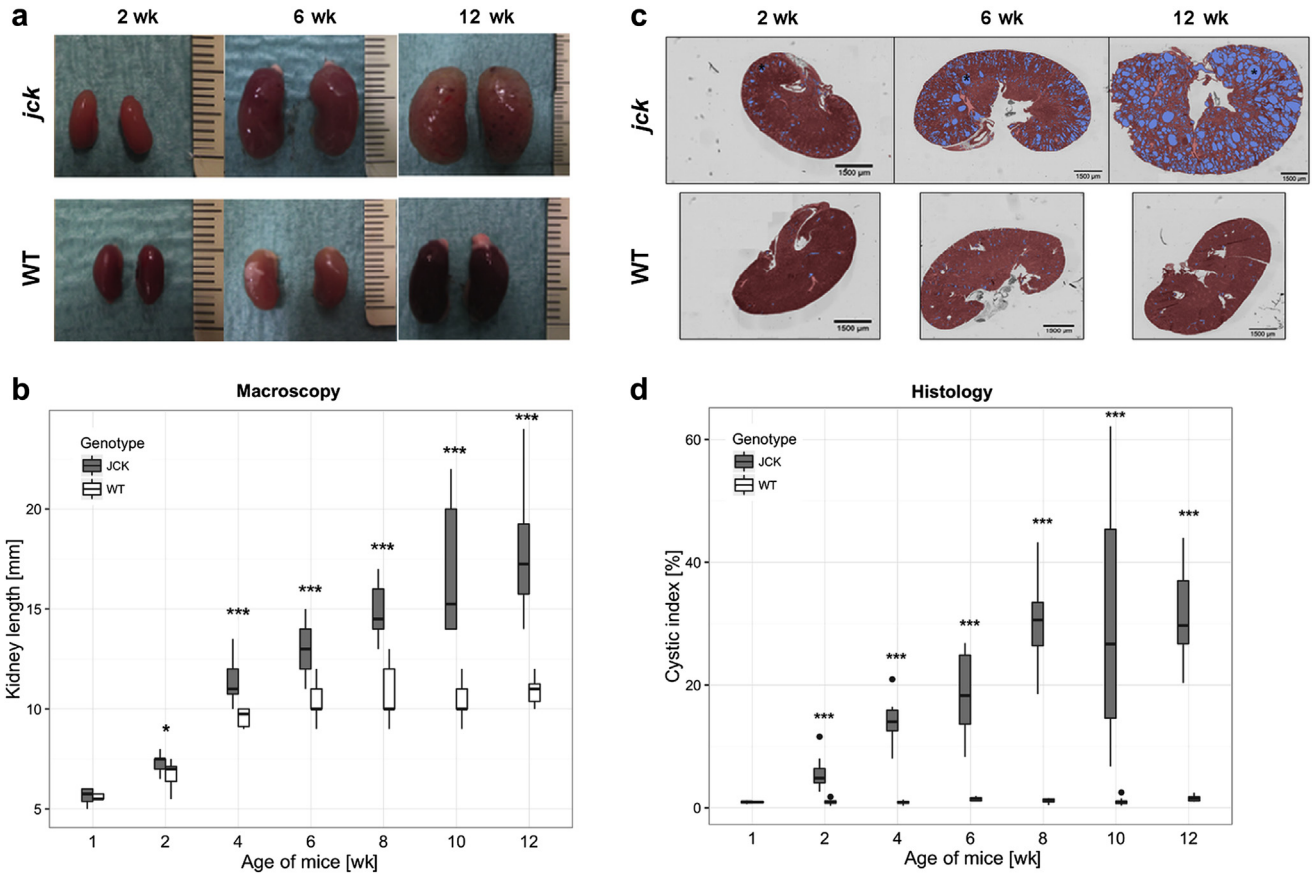

Figure 1 | Macroscopic kidney length (a,b) and histologic cystic index (c,d) in *juvenile cystic kidney* (*jck*) mice and wild-type (WT) mice at 2, 6, and 12 weeks of age (a). Notice, in the histologic cystic index (**c**), renal tissue is colored in red and cysts are colored in blue. Macroscopic kidney length and the histologic cystic index constantly increase with age progression in *jck* mice, showing significant differences compared with WT mice from 2 weeks of age. In the box-whisker plots, the centerline in each box represents the median, whereas the lower and upper limits of each box represent the 25th and 75th percentiles, respectively. Whiskers extend to the most extreme observations within the 25th and 75th percentiles $\pm$ 1.5 $\times$ interquartile range. Observations outside these whiskers are shown as dots (*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$). To optimize viewing of this image, please see the online version of this article at www.kidney-international.org.