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## RESEARCH LETTER

**<sup>23</sup>NaMRI Assessed Cyst Sodium Concentration in Polycystic Kidney Disease to Identify Cyst Metabolic Activity: A Proof of Concept Study**

To the Editor:

Autosomal dominant polycystic kidney disease (ADPKD) is the most common form of inherited kidney cystic disease and appears as a heterogeneous disease with different progression rates, even within the same family. The assessment of ADPKD progression is critical to allow early initiation of kidney-protective measures and specific treatment. Therefore, surrogate prognostic biomarkers are required. Currently, kidney cystic phenotype evaluation is restricted to assessment of total kidney volume and growth, age-adjusted glomerular filtration rate, glomerular filtration rate decline, genetic testing, and family history.<sup>1</sup>

Proton-based magnetic resonance imaging (MRI) is of considerable value in terms of prognosis and provides information relating to morphological characteristics, but it is restricted to structural data alone.<sup>2</sup> Image texture analysis, diffusion tensor imaging, T2 mapping, and magnetization transfer ratio are promising new techniques to detect early structural changes in cystic kidneys.<sup>3</sup> There are also emerging urinary and serologic biomarkers that may potentially be used to assess inflammation, proliferation, tubular injury, and metabolic processes.<sup>4</sup>

In a previous study, we demonstrated the ability to discriminate the corticomedullary gradient within the kidney in healthy individuals and in patients with chronic kidney disease. In our exploratory analysis of the corticomedullary gradient, we were able to measure the sodium concentration in the patients' cysts. In the present study, we aimed to report the technical feasibility of measuring sodium content of cysts in patients with ADPKD.

We studied 4 patients with ADPKD recruited from the London Regional Renal Program (Ontario, Canada) with wide ranges of kidney function who fasted for 8 hours before the study visit. Urine samples were collected to measure fasting urinary osmolarity before the MRI scan. This was an entirely exploratory study, and thus, there was no estimate of an appropriate sample size.

MRI was performed using a GE MR750 3T (GE Healthcare) instrument. Proton anatomical images were acquired using the MRI built-in body coil. A custom-built 2-loop (18 cm in diameter) butterfly radiofrequency surface coil tuned for sodium frequency (33.786 MHz) was used to acquire kidney sodium images as reported previously (see [Item S1: Detailed methods](#)).<sup>5</sup>

The median (min-max) age of the patients was 58 (37-74) years, body mass index 28.2 (21.2-29.6) kg/m<sup>2</sup>, sodium 143 (139-145) mmol/L, urea 10 (2.6-28.1) mmol/L, estimated glomerular filtration rate (Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] equation)

31 (8-101) mL/min/1.73 m<sup>2</sup>, urine osmolarity 399 (239-441) mOsm/L, and sodium excretion fraction 1.28 (0.53-4.1)%. The characteristics of each patient are described in [Table 1](#). Within a representative <sup>23</sup>NaMRI image, a previously unappreciated but characteristically wide range of kidney cystic sodium content was evident, indicative of both tubular origin and metabolic activity. [Figure 1](#) shows proton anatomic and sodium MRI scans and the merge of both proton and sodium for the 4 ADPKD patients.

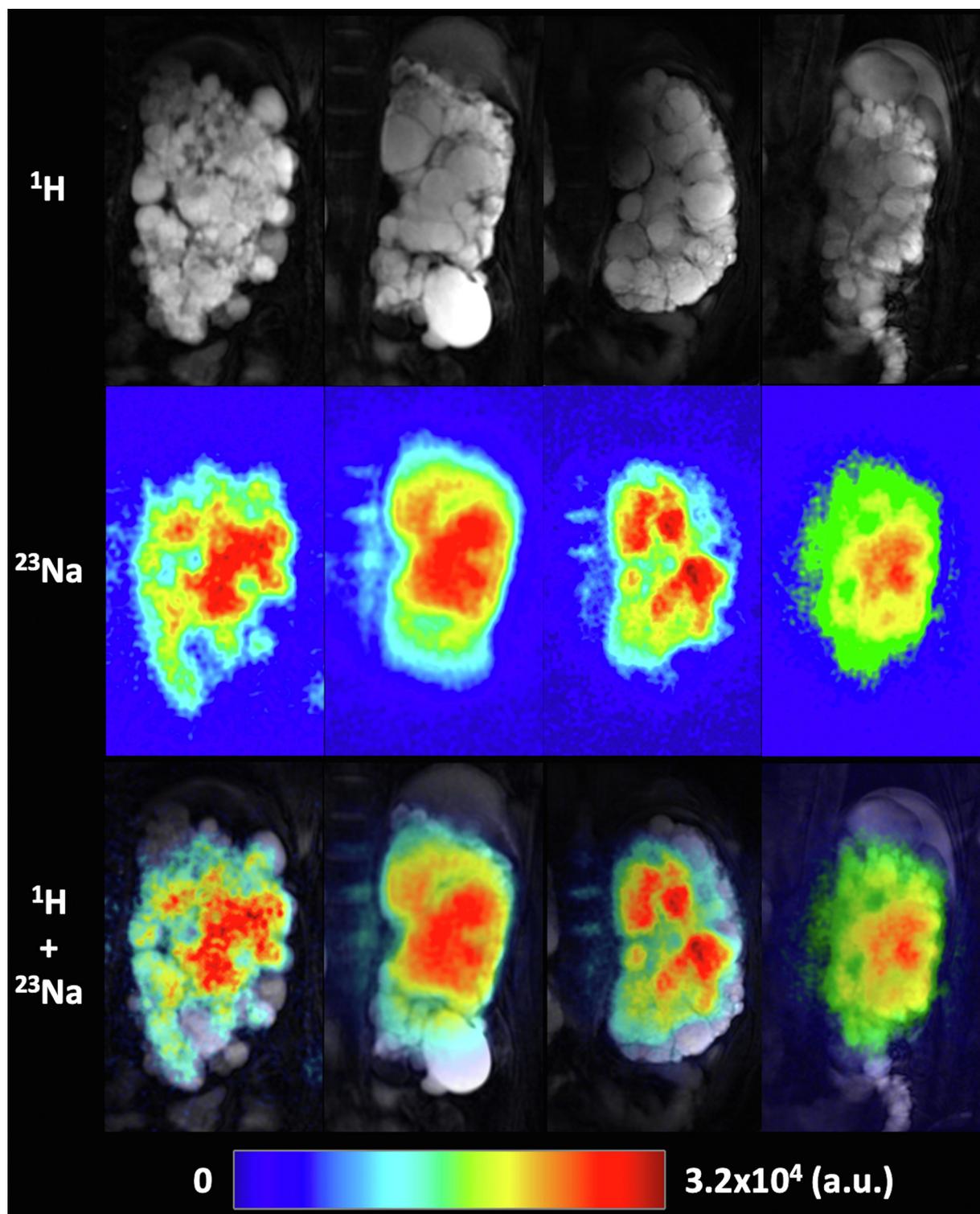
ADPKD is characterized by extremely active cysts, often exchanging their entire fluid contents multiple times in a single day.<sup>6</sup> In preclinical models, renal cyst sodium content is influenced by the cyst's location within the kidney and its daily fluid activity. Sodium content is heterogenous between cysts, and multiple aspirations would be required to acquire these data in humans, which is impossible to achieve. Functional imaging relating to the sodium content could provide clinicians and researchers the ability to probe metabolic activity of the cystic disease, both at rest and potentially when actively challenged with therapeutic agents. There are currently no clinical data available about sodium content in cysts in the intact human. To our knowledge, this is the first report that demonstrates the ability to acquire sodium images of ADPKD kidneys. This will allow improved prognostic prediction and potentially also the ability to assess suitability and/or response to disease-modifying therapeutic approaches early in the treatment course. A dedicated clinical trial exploring modification of salt content after tolvaptan in ADPKD will be of great interest.

Although we showed the feasibility of scanning sodium content in the ADPKD kidney, <sup>23</sup>NaMRI remains limited by

**Table 1.** Patients' Characteristics

	Patient 1	Patient 2	Patient 3	Patient 4
Age (y)	in his 60s	in his 30s	in his 50s	in his 50s
Gender (M/F)	M	M	M	F
Weight (kg)	91	75	81.6	84.5
Height (cm)	183	173	166	170
BMI (kg/m <sup>2</sup> )	27.1	25.1	29.6	29.2
Sodium (mmol/L)	139	140	143	145
Urea (mmol/L)	28.1	10.1	2.6	5.3
Creatinine (μmol/L)	644	258	78	107
eGFR (mL/min/1.73 m <sup>2</sup> )	8	27	101	54
CRP (mg/dL)	4.1	3.8	4.6	0.8
Urines osmolarity (mosm/L)	332	239	408	431
EFNa (%)	1.8	1.7	0.5	0.6
Tolvaptan (Y/N)	N	Y	Y	N
Diuretics (Y/N)	Y	N	N	Y
MAYO clinic status		1A	1A	
Kidney volume (mL/m)		773	1,200	

Abbreviations: CRP, C-reactive protein; EFNa, excretion fraction of sodium; eGFR, estimated glomerular filtration rate.



**Figure 1.** Representative coronal (A) proton anatomic and (B) sodium MRI scans along the renal long axis in a polycystic kidney disease participant and (C) the corresponding overlaid sodium and anatomic image.  $^{23}\text{Na}$ MRI has been pseudocolored to better visualize sodium content. Blue color corresponds with “no salt content” and dark red with “high sodium content.” Kidney sodium content of 4 different patients are shown. Patient 1 is in his 60s, eGFR 8 mL/min/1.73 m<sup>2</sup>; patient 2 is in his 30s, eGFR 27 mL/min/1.73 m<sup>2</sup>; patient 3 is in his 50s, eGFR 101 mL/min/1.73 m<sup>2</sup>; and Patient 4 is in his 50s, eGFR 54 mL/min/1.73m<sup>2</sup>. eGFR, estimated glomerular filtration rate; MRI, magnetic resonance imaging.

image resolution and signal-to-noise ratio due to sodium's low gyromagnetic ratio and its low biological concentration. Higher resolution and signal-to-noise ratio would require longer imaging time, which may not be practical in a clinical setting. Low image resolution could lead to gross partial volume effects. The acquisition parameters for this study were selected to achieve an acceptable resolution and signal-to-noise ratio within 31 minutes of scan time.

It would have been interesting to have genetic data and kidney volume. Unfortunately, we were unable to provide all kidney volume measurements or genetic testing results for these patients.

In conclusion, after establishing the feasibility of  $^{23}\text{NaMRI}$  to measure sodium cyst content, it seems suitable to use  $^{23}\text{NaMRI}$  to probe the biological differences in cyst populations and potentially to refine diagnosis, prognosis, and selection of patients for established and emerging ADPKD therapies.

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and Christopher W. McIntyre, MD, PhD

## SUPPLEMENTARY MATERIAL

### Supplementary File (PDF)

**Item S1:** Detailed methods.

## ARTICLE INFORMATION

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