Magnetic resonance imaging $T_1$- and $T_2$-mapping to assess renal structure and function: a systematic review and statement paper

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ABSTRACT

This systematic review, initiated by the European Cooperation in Science and Technology Action Magnetic Resonance Imaging Biomarkers for Chronic Kidney Disease (PARENCHIMA), focuses on potential clinical applications of magnetic resonance imaging in renal non-tumour disease using magnetic resonance relaxometry (MRR), specifically, the measurement of the independent quantitative magnetic resonance relaxation times $T_1$ and $T_2$ at 1.5 and 3Tesla (T), respectively. Healthy subjects show a distinguishable cortico-medullary differentiation (CMD) in $T_1$ and a slight CMD in $T_2$. Increased cortical $T_1$ values, that is, reduced $T_1$ CMD, were reported in acute allograft rejection (AAR) and diminished $T_1$ CMD in chronic allograft rejection. However, ambiguous findings were reported and AAR could not be sufficiently differentiated from acute tubular necrosis and cyclosporine nephrotoxicity. Despite this, one recent quantitative study showed in renal transplants a direct correlation between fibrosis and $T_1$ CMD. Additionally, various renal diseases, including renal transplants, showed a moderate to strong correlation between $T_1$ CMD and renal function. Recent $T_2$ studies observed increased values in renal transplants compared with healthy subjects and in early-stage autosomal dominant polycystic kidney disease (ADPKD), which could improve diagnosis and progression assessment compared with total kidney volume alone in early-stage ADPKD. Renal MRR is suggested to be sensitive to renal perfusion, ischaemia/oxygenation, oedema, fibrosis, hydration and comorbidities, which reduce specificity. Due to the lack of standardization in patient preparation, acquisition protocols and adequate patient selection, no widely accepted reference values are currently available. Therefore this review encourages efforts to optimize and standardize (multi-parametric) protocols to increase specificity and to tap the full potential of renal MRR in future research.

Keywords: magnetic resonance imaging, kidney, mapping, relaxometry, chronic kidney disease

INTRODUCTION

Kidneys are morphologically complex organs. Renal pathologies induce (micro-) structural and functional changes that may be captured with magnetic resonance imaging (MRI) owing to its exceptional soft tissue contrast. Despite the frequent and successful use of magnetic resonance relaxometry (MRR) in other organs (e.g. cardiac MRI) to assess oedema, amyloid deposition and fibrosis, the application of renal MRR is still scarce.

Renal MRR holds the promise to non-invasively quantify tissue inflammation and alterations, such as interstitial or cellular oedema and/or fibrosis, as well as renal function. This review article evaluates and summarizes data on renal $T_1$ and $T_2$ mapping using clinical 1.5 and 3Tesla (T) systems and provides...
recommendations for upcoming research efforts to promote MRR in clinical practice.

MATERIALS AND METHODS

The European Cooperation in Science and Technology (COST) Action Magnetic Resonance Imaging Biomarkers for Chronic Kidney Disease (PARENCHIMA) (www.renalmri.org) initiated this systematic review by an extended PubMed search regarding renal mapping (see Supplementary data) on 25 October 2017 to identify human in vivo $T_1$ and $T_2$ measurements at 1.5 and 3T. Titles and abstracts of 357 publications were processed to identify matches aligning with the aim of this article. Furthermore, relevant references within the acquired papers and selected studies by the authors were added. Our analysis reaches back to the year 1983 and includes studies with field strengths below 1.5T. Some handpicked qualitative studies and preclinical studies were also included to present readers with relevant trends in the measurement of renal $T_1$ and $T_2$ values. Studies regarding renal neoplasms and/or dynamic contrast-enhanced MRI were excluded. For details on data collection, see Supplementary data.

BASIC PRINCIPLES OF MAGNETIC RELAXATION MECHANISMS

MRI is a non-invasive technique to map the human body using the interaction of three magnetic fields: (i) a strong static field ($B_0$ or main magnet) to magnetize the whole sample and to allow the signal to be measured; (ii) gradient coils producing three ($G_x, G_y, G_z$) linear, orthogonal gradients to allow the signal to be registered in space; and (iii) a radio frequency (RF) field ($B_1$ or excitation field) to change steady-state magnetization produced by $B_0$ and to enable the readout of the measured signal (using an appropriately frequency-tuned coil or antenna) [1].

When subjects are placed inside the MRI scanner, nuclear spins align with $B_0$ (Figure 1a and b). The application of an RF pulse ($B_1$; usually in the range of milliseconds and milliseconds) changes this macroscopic magnetization and proton spins are perturbed (i.e. tipped away from $B_0$). RF pulses are named after their effect on the net magnetization vector, i.e. an RF pulse tilts the magnetization into the $y$ direction ($B_0$) or excitation field) to change steady-state magnetization produced by $B_0$ and to enable the readout of the measured signal (using an appropriately frequency-tuned coil or antenna) [1].

The MOLLI sequence and its variants, based on the technique developed in 1970 by Look and Locker [6], sacrifice the requirement of pre-excitation equilibrium to save time and report a modified, shorter, apparent $T_1$ (often denoted $T_1^*$) derived from repeated efficient sampling of a single excitation pulse. This type of sequence is sufficiently fast, so it is well suited for cardiac imaging, but the comparability between $T_1$ and $T_1^*$ is limited [7, 8].

$T_1$ relaxation time

The gold standard for $T_1$ measurement, the inversion recovery (IR) technique, first inverts the magnetization in the $z$ direction using a 180° pulse, which is followed by a waiting time, TI (inversion time), and a successive 90° pulse to initiate data readout with further 180° pulses. This IR preparation module has to be repeated several times by incrementing TI to acquire three to eight data points using a long TR (repetition time; i.e. five to seven times $T_1$), to ensure full relaxation before each inversion pulse, which leads to long overall IR-T1 measurement times (Figure 1a and c).

The desire for faster $T_1$ measurement compatible with individual breath-holds has given rise to several efficient methods, the most common being variable flip-angle (VFA) and modified Look-Locker imaging (MOLLI).

In VFA, two or more spoiled gradient recalled-echo acquisitions with differing excitation pulse flip-angles give rise to signals modulated by $T_1$ [4]; while substantially faster than IR-T1, care must be taken before considering VFA to provide quantitative, rather than relative, $T_1$ measures [5]. VFA measurements are susceptible to $B_1$ inhomogeneity and thus require additional $B_1$ mapping. Also, the accuracy of the resulting $T_1$ depends on the relation of the chosen flip-angles with respect to the observed $T_1$ range.

The $T_2$ measurement is sensitive to imperfect slice selection pulse profiles, diffusion, flow and field inhomogeneities [9]. A $T_2$ preparation module decreases the influence of imperfect slice selection profiles, diffusion and flow. Carr–Purcell–Meiboom–Gill (CPMG) and similar preparations can help to compensate for field inhomogeneities. Therefore $T_2$ preparations are used in cardiac imaging to visualize oedema after myocardial infarction [10], and can be performed during free breathing, although image registration prior to $T_2$ calculation is required. Commonly at least three source images with
different echo times are recommended for accurate $T_2$ estimation using two- or three-parameter exponential fittings [10–13].

**RENA L $T_1$ MAPPING**

Reference values and physiological modulations

In the early 1980s, renal MRI detected relatively increased $T_1$ values in the medulla compared with the cortex in healthy subjects. This corticomedullary differentiation (CMD) is presumably caused by the higher free water content, i.e. higher mobility of water molecules, in the medullary tubules and collecting ducts [14, 15]. Additionally Hricak et al. [14] reported that hydration and the water balance management of the kidneys are important influencing factors, because $T_1$ CMD decreases during dehydration (relative cortical $T_1$ increase) and increases after rehydration, i.e. forced diuresis [14], but the impact in healthy subjects or patients was never reassessed at 1.5 T and 3T. Another inevitable variation is caused by the increase of $B_0$ from 1.5 and 3T, as $T_1$ generally increases. Further variation of renal $T_1$ values was reported due to different MRI acquisition schemes and breathing strategies [16, 17], even though high interexamination repeatability for single acquisition schemes was proven [18–20]. Therefore no widely accepted reference values are published and the given limitations have to be considered when comparing different studies (Table 1).

$T_1$ modulation by the inhalation of oxygen and carbogen. $T_1$ and $T_2^*$ relaxation times are modulated by oxygen level changes in the blood and/or tissue, although caused by different mechanisms [21]. $T_2^*$, i.e. blood oxygen level changes.
| Author          | Year        | Subject                                            | Sample size | Group                                      | In vivo repeatability | GFR  | Hydration  | Respiratory compensation | Sequence       | Cortex | Medulla | Other modalities |
|-----------------|-------------|----------------------------------------------------|-------------|--------------------------------------------|----------------------|------|------------|--------------------------|----------------|--------|---------|------------------|
| Blu¨ml et al.   | 1993        | Healthy                                            | 9           | —                                          | No                   | Not measured | None                  | BH                        | IR TurboFLASH | 966 ± 41 | 1320 ± 76 |                    |
| Jones et al.    | 2002        | Healthy                                            | 9           | Normoxia                                   | No                   | Not measured | None                  | BH                        | IR segmented half Fourier | 882 ± 59* | 1168 ± 118 |                    |
| de Bondt et al. | 2004        | Healthy                                            | 4           | —                                          | No                   | Not measured | None                  | BH                        | IR SS FSE, half Fourier | 966 ± 58 | 1412 ± 58 | T₂                |
| Blu¨ml et al.   | 1993        | Healthy                                            | 9           | —                                          | No                   | Not measured | None                  | BH                        | IR TurboFLASH | 966 ± 41 | 1320 ± 76 |                    |
| O'Connor et al. | 2007        | Healthy                                            | 5           | Normoxia                                   | No                   | Not measured | None                  | FB                        | VFA 3D T1w FFE | 961 ± 48 | 1228 ± 118 |                    |
| Breidthardt et al. | 2015      | Healthy                                            | 10          | Mean eGFR >101 ± 17                        | Yes                  | MDRD eGFR     | 4-h fasting           | TRIG                      | IR bFFE | 1080 ± 68 |                    |
| Chen et al.     | 2016        | Healthy                                            | 9           | —                                          | No                   | Not measured | None                  | BH                        | MOLLI          | 827 ± 50 | 1381 ± 95 |                    |
| Cox et al.      | 2017        | Healthy                                            | 8           | —                                          | No                   | eGFR          | 2-h fasting           | BH                        | IR SE EPI      | 1024 ± 71 | 1272 ± 140 |                    |
| Study | Year | Group | Number | Type | eGFR | BG or FB | Technique | TRIG | eGFR | Background | eGFR | p-Value |
|-------|------|-------|--------|------|------|--------|----------|------|------|------------|------|---------|
| Peperhove et al. [26] | 2018 | Healthy, LuTx and renal allograft mixed | 14 | Native kidneys | No Cockroft–Gault | BH | MOLLI | 987 ± 102* | 1428 ± 98* | – |
| | | Healthy, LuTx | 52 | Native kidneys | No Cockroft–Gault | BH | MOLLI | 1058 ± 96* | 1414 ± 101* | – |
| | | Renal allograft | 49 | Renal allograft | eGFR >90 | BH | MOLLI | 509 ± 105* | 1556 ± 76* | – |
| | | | | | eGFR 60–89 | BH | MOLLI | 1058 ± 108 | 1427 ± 89* | – |
| | | | | | eGFR 30–59 | BH | MOLLI | 1077 ± 132 | 1432 ± 123* | – |
| | | | | | eGFR 15–29 | BH | MOLLI | 1273 ± 97 | 1546 ± 51* | – |
| | | | | | eGFR <15 | BH | MOLLI | 1297 ± 113 | 1490 ± 97 | – |
| | | | | | | | | 1377 ± 109 | 1515 ± 45 | – |
| de Baudrejus et al. [11] | 2004 | Healthy | 6 | — | No | BH | IR SS FSE, half-Fourier | 1142 ± 154 | 1540 ± 142 | T1* |
| | | | | | Normoxia, conventional acquisition | BH | IR HASTE breath | 1187 ± 112 | 1523 ± 116 | – |
| | | | | | No | BH | IR SS FSE | 1387 ± 130 | 1587 ± 121 | T2* |
| | | | | | Pure O2, novel acquisition | BH | IR SS FSE | 1717 ± 212 | 1578 ± 123 | – |
| Gillis et al. [20] | 2014 | Healthy | 12 | MRI1, eGFR 98 ± 15 | Yes | CKD-eGFR 6-h fasting | BH | MOLLI | 1176 ± 104 | 1650 ± 86 | – |
| | | | | | MRI2, eGFR 98 ± 15 | | | | 1406 ± 96 | 1636 ± 80 | – |
| Li et al. [12] | 2015 | Healthy | 5 | — | No | BH | IR SS FSE | 1361 ± 86 | 1676 ± 94 | T1* |
| Chen et al. [17] | 2016 | Healthy | 26 | — | No | BH | IR SS FSE | 1544 ± 88 | 1640 ± 55 | – |
| Gillis et al. [28] | 2016 | Healthy | 24 | Mean eGFR 100 ± 14 | No | CKD-EPI-eGFR | BH | MOLLI | 1366 ± 112* | Not measured | – |
| | | | | | | | | 1500 ± 81* | Not measured | – |
| Fierec et al. [29] | 2016 | Renal allograft | 29 | Renal allograft | No | CKD-EPI-eGFR | BH | MOLLI | 1334 ± 57 | 1473 ± 48 | – |

The given T1 relaxation times of the cortex and medulla are mean ± SD in ms. Patient studies are highlighted in grey.

3D, three-dimensional; 99mTc-DTPA, 99mTc-diethylene triamine pentaacetic acid; a, year; bFFE, balanced fast field echo; BOLD, blood oxygen level dependant; BH, breath hold; CKD, chronic kidney disease; CO2, carbon dioxide; DWI, diffusion-weighted imaging; EPI, echo-planar imaging; e/mGFR, estimated or measured glomerular filtration rate (in mL/min/1.73 m2); GE, gradient echo; FFE, fast field echo; FSE, fast spin echo; FLASH, fast low angle shot; FB, free breathing; HASTE, half Fourier acquisition single shot turbo spin echo; LuTx, lung transplantation; MDRD, modification of diet in renal disease; ME, multi-echo; MS, multishot; PC, phase contrast; SE, spin-echo; SS, single shot; T, Tesla; T1, spin–lattice relaxation time; T2, spin–spin relaxation time; T1w, T1 weighted; TRIG, triggered MRI acquisition with regards to breathing motion; trueFISP, true fast imaging with steady-state precession; TSE, turbo spin echo.

Other symbols refer to the statistical significance within the associated study:

- P < 0.0001
- P < 0.001
- P < 0.01
- P < 0.05
- P < 0.08
- P < 0.1
- P = 0.01
- P = 0.03
- P = 0.047
- P < 0.05
dependent (BOLD) MRI, associated changes are reviewed by Pruimj et al. [30].

To our knowledge, modulations of renal $T_1$ values during the inhalation of pure oxygen ($O_2$) and carbogen (5% carbon dioxide mixed with 95% $O_2$) were only observed in healthy volunteers. In 2002, Jones et al. [21] reported a significant decrease in cortical $T_1$ values during $O_2$ inhalation at 1.5T. These findings were confirmed in 2007 and 2009 with an even more pronounced reduction in cortical $T_1$ values following the inhalation of $O_2$ and carbogen [23, 24]. In these studies, the lack of a renal hydration protocol [except in O’Connor et al. [24]], the free breathing acquisition, the VFA method and dyspnœa during the carbogen inhalation (leading to increased breathing motion), as well as the temporal and spatial acquisition constraints, can be considered as important limitations [23, 24].

The first 3T study was carried out by Ding et al. [27] when healthy subjects were evaluated during exposure to normoxia and $O_2$. Thereafter a multiparametric renal MRI study evaluated five healthy volunteers who underwent a hyperoxia challenge (~80% $O_2$); again cortical $T_1$ values decreased, but unlike previous publications, no statistical significance was observed [18].

These studies show that cortical $T_1$ is sensitive to oxygenation level changes. However, the contribution of vasoconstriction and vasodilatation as well as perfusion changes during $O_2$ inhalation of $O_2$ and carbogen [23, 24]. In these studies, the lack of a renal hydration protocol [except in O’Connor et al. [24]], the free breathing acquisition, the VFA method and dyspnœa during the carbogen inhalation (leading to increased breathing motion), as well as the temporal and spatial acquisition constraints, can be considered as important limitations [23, 24].

Clinical studies

Renal transplants—early qualitative and semi-quantitative MRI studies. Imaging of renal transplants in the iliac fossae is less confounded by breathing motion, which enabled renal MRI evaluations in the 1980s [31]. Early qualitative and/or semi-quantitative renal MRI studies revealed a reduced $T_1$ CMD in acute allograft rejection (AAR), and even diminished $T_1$ CMD in chronic allograft rejection (CAR) [15, 31–34]. However, acute tubular necrosis (ATN) could not be sufficiently differentiated from AAR [32, 34–36], and even diminished $T_1$ CMD was reversible in some cases of ATN and AAR [36]. Thus scrutiny of the reduced $T_1$ CMD linked both oedema and fibrosis to prolonged $T_1$ values, which partially explains the low specificity of these renal transplant evaluations [37].

Another interesting finding on renal transplant observation was the clearly preserved $T_1$ CMD during an acute decline in renal function under cyclosporine therapy, which was linked to cyclosporine nephrotoxicity (CN) [32, 34]. However, three successive studies presented ambiguous outcomes [33, 37, 38]. Thereafter, no further research efforts were made, so no final conclusion can be made.

All these envisioned early MRI studies on renal transplants applied field strengths <1.5T, which today are not frequently in clinical use. However, in contrast to recent MRI evaluations, all of these studies applied histological validation. A low specificity was observed due to different acquisition settings (e.g. vendors and protocols), low reproducibility of the two-point method to calculate $T_1$ [31] and lack of a standardized patient preparation (e.g. hydration protocol) [14, 15]. In addition, loss of $T_1$ CMD was reversible after clinical improvement in some cases of ATN and AAR, which could have decreased the specificity further [36]. Therefore recommendations could not advocate qualitative and/or semi-quantitative MRI evaluations over ultrasound and scintigraphy [34].

Renal transplants—quantitative MRI studies. $T_1$ measurements on renal transplants at 1.5T were presented by Huang et al. [19] in 2011, when renal transplants and native kidneys with unknown underlying renal disease confirmed the trend of higher cortical and medullary $T_1$ values in renal transplants. They also achieved a high short-term in vivo repeatability (~±10%). In addition, strong correlations were observed between estimated glomerular filtration rate (eGFR) and cortical $T_1$ in both groups (native cortex: $r = -0.83, P = 0.0001$; transplant cortex: $r = -0.80, P = 0.0017$), but medullary $T_1$ values only significantly correlated with eGFR in the transplant group ($r = -0.94, P < 0.0001$) [19].

The second quantitative $T_1$ assessment of renal transplant was presented by Friedli et al. [29]. A total of 29 patients underwent a multiparametric MRI approach at 3T, including a validation against histological samples. With regard to $T_1$, only $T_1$ CMD showed a moderate correlation with renal interstitial fibrosis ($R^2 = 0.29, P < 0.001$) and eGFR ($R^2 = 0.22, P < 0.05$). No correlation was established between $T_1$ values and cellular inflammation [29].

In 2018, renal $T_1$ was evaluated in 49 renal transplant patients, 52 patients after lung transplantation (LuTx; native kidneys) and 14 healthy volunteers [26]. Their aim was to assess acute kidney injury (AKI) after LuTx (reported incidence ~60%), and after a 3- and 6-month follow-up. $T_1$ CMD was significantly decreased and mean cortical and medullary $T_1$ were significantly higher in renal transplants compared with healthy volunteers and the LuTx group ($P < 0.001$). However, $T_1$ CMD was also reduced in the LuTx group compared with volunteers ($P < 0.05$), which was linked to the incidence of AKI after LuTx. All patients and healthy volunteers were further grouped according to Kidney Disease Outcomes Quality Initiative (KDOQI) stages. Remarkable were the significantly lower cortical $T_1$ values in subjects with eGFR $\geq 60$ mL/min/1.73 m$^2$ as compared with $<60$ mL/min/1.73 m$^2$ and that cortical $T_1$ negatively correlated ($r = -0.642, P < 0.001$) and $T_1$ CMD positively correlated ($r = 0.542, P < 0.001$) with eGFR for all participants. In contrast, medullary $T_1$ showed only a weak correlation with eGFR ($r = -0.341, P < 0.001$). During the 3- and 6-month follow-up, cortical $T_1$ and $T_1$ CMD exhibited a significant correlation with eGFR ($P < 0.001$ and < 0.01, respectively) in the LuTx and renal transplantation groups [26].

In summary, we identified only three quantitative $T_1$ studies on renal allografts at 1.5 and 3T. In contrast to early qualitative and semi-quantitative MRI studies, only one quantitative study applied a histological validation, in which it was shown that...
Table 2. Quantitative T<sub>2</sub> studies at 1.5 and 3T

| Author                  | Year | Subject            | Sample size | Group | In vivo repeatability | GFR          | Hydration | Respiratory compensation | Sequence | Cortex | Medulla | Other modalities |
|-------------------------|------|--------------------|-------------|-------|-----------------------|--------------|-----------|--------------------------|----------|--------|---------|------------------|
| **1.5T**                |      |                    |             |       |                       |              |           |                          |          |        |         |                  |
| de Bazelaire et al. [11]| 2004 | Healthy            | 4           | —     | No                    | Not measured | None      | BH                       | SE T<sub>2</sub> prep | 87 ± 4 | 85 ± 11 | T<sub>1</sub>  |
| Zhang et al. [45]       | 2011 | Healthy            | 4 Day 1     | Yes   | Not measured          | None         | BH        | 2D ME TSE                | 112<sup>‡</sup> | 137<sup>‡</sup> | T<sub>2</sub>* |                  |
|                         |      |                    | 4 Day 2     |       |                       |              |           |                          |          |        |         |                  |
| Mathys et al. [46]      | 2011 | Healthy            | 6           | —     | No                    | TUC          | 2-h fasting | FB                       | ME SE    | 125 ± 7<sup>a</sup> | –    | T<sub>2</sub>* |                  |
|                         |      | Renal allograft    | 6 GFR >40   | No    | TUC                   | 2-h fasting | FB        | ME SE                    | 147 ± 13<sup>*</sup> | –    | T<sub>2</sub>* |                  |
|                         |      | Renal allograft    | 9 GFR <40   | No    | TUC                   | 2-h fasting | FB        | ME SE                    | 150 ± 20<sup>‡</sup> | –    |          |                  |
| **3T**                  |      |                    |             |       |                       |              |           |                          |          |        |         |                  |
| de Bazelaire et al. [11]| 2004 | Healthy            | 6           | —     | No                    | Not measured | None      | BH                       | SE T<sub>2</sub> prep | 76 ± 7 | 81 ± 8  | T<sub>1</sub>  |
| Li et al. [12]          | 2015 | Healthy            | 5           | —     | No                    | Not measured | None      | BH                       | CPMG T<sub>2</sub> prep | 121 ± 5 | 138 ± 7 | T<sub>1</sub>  |
| Franke et al. [47]      | 2017 | Healthy            | 3           | —     | No                    | Not measured | None      | ME GE SE                 | 132 ± 6<sup>v</sup> | –    |          |                  |
|                         |      | ADPKD              | TKV <300 mL | No    | Not measured          | None         | ME GE SE  | 417 ± 65<sup>*v</sup> | –        |       |          |                  |
|                         |      |                    | TKV 300–400 mL | No   | Not measured         | None         | ME GE SE  | 592 ± 231<sup>v</sup> | –        |       |          |                  |
|                         |      |                    | TKV >400 mL | No    | Not measured          | None         | ME GE SE  | 669 ± 170<sup>v</sup> | –        |       |          |                  |

The given T<sub>2</sub> relaxation times of the cortex and medulla are mean ± SD in ms. Patient studies are highlighted in grey.

2D, two dimensional; BH, breath-hold; FB, free breathing; GE, gradient echo; ME, multi-echo; prep, preparation; T<sub>T</sub>, Tesla; T<sub>1</sub>, spin–lattice relaxation time; T<sub>2</sub>, spin–spin relaxation time; T<sub>2</sub>*, apparent transverse relaxation time; T<sub>1</sub>W, T<sub>1</sub> weighted; TKV, total kidney volume; TUC, timed urine collection; TSE, turbo spin echo.

<sup>a</sup>Recalculated: reported values in mean ± SD: R<sub>D</sub> day 1: 8.9 ± 0.66<sup>s</sup> (cortex) and 7.3 ± 0.75<sup>s</sup> (medulla); day 2: 8.9 ± 0.66<sup>s</sup> (cortex) and 7.0 ± 0.75<sup>s</sup> (medulla).

Other symbols refer to the statistical significance within the associated study:

- H<sub>170</sub>10<sup>P</sup> < 0.001;
- H<sub>0.01</sub> < P < 0.05.

<sup>v</sup><sup>P</sup> < 0.001; <sup>v</sup><sup>H</sup> < 0.01; <sup>v</sup><sup>‡</sup> < 0.05.
state-of-the-art $T_1$ measurements, i.e. $T_1$ CMD, could be used to assess renal interstitial fibrosis in allografts [29]. Another important finding was that $T_1$ values were sensitive to presumable AKI alterations in the context of post-LuTx [26]. However, the specificity of renal MRR regarding AAR, CAR, ATN or drug-induced toxicity was not further assessed or improved. Furthermore, these studies show that $T_1$ mapping has the potential to estimate renal function.

Non-invasive assessment of renal function. The first quantitative $T_1$ measurements on patients at 1.5T were published in 2007 [22]. A small and unbalanced group was primarily enrolled for the evaluation of a renal artery stenosis: one patient with CKD and hypertension and nine patients with hypertension alone. A loose hydration protocol was applied before the MRI acquisition, and afterwards all patients underwent a $^{99m}$Tc-diethylene triamine pentaacetic acid renography to measure the single-kidney GFR (SKGFR). A significant correlation was depicted only between cortical $T_1$ values and the SKGFR ($r = -0.5$, $P = 0.03$) [22].

In 2015 the association between cortical $T_1$, renal perfusion (from arterial spin labeling (ASL); see also Odudu et al. [39]) and eGFR in patients with chronic heart failure (HF) and control subjects with different levels of renal impairment was evaluated [25]. Renal perfusion was similar in chronic HF patients with and without renal impairment, but cortical $T_1$ showed a significant correlation with eGFR ($r = -0.41$, $P = 0.013$), which reflects the potential to assess CKD. Chronic HF patients had significantly higher cortical $T_1$ compared with all control subjects, and chronic HF patients with renal impairment had significantly higher cortical $T_1$ compared with chronic HF patients without renal impairment [25].

After the ASL reproducibility study of Gillis et al. in 2014 [20], a follow-up study evaluated renal perfusion and cortical $T_1$ in healthy volunteers and CKD patients with different aetologies at 3T. Significantly higher cortical $T_1$ values were found in CKD patients and a correlation between cortical $T_1$ and eGFR was observed ($r = -0.58$, $P < 0.001$) [28].

One year later a multiparametric renal MRI study assessed $T_1$ in healthy subjects and CKD patients with various renal diseases after a short fasting period ($>2$ h) at 3T [18]. Compared with volunteers, CKD showed significantly higher cortical $T_1$, and $T_1$ CMD was reduced ($P < 0.01$). They achieved an interscan coefficient of variation of $<2.9\%$ and high intraclass correlation for the cortex and medulla (0.848 and 0.997, respectively, using spin-echo echo-planar imaging) [18].

As previously envisioned also, three renal transplant studies assessed the correlation of $T_1$ values and the renal function at 1.5 and 3T (see above) [19, 26, 29].

In summary, the envisioned studies show that the degree of renal impairment correlates moderately to strongly with cortical $T_1$ and $T_1$ CMD in CKD with various renal diseases [18, 22, 28], renal transplants [19, 26, 29], and chronic HF patients [25]. These findings are also in line with some qualitative assessments in the 1990s [40, 41], but not with all [42], due to the fact that renal $T_1$ values are modulated by many confounders, such as the degree of fibrosis [29], comorbidities (e.g. liver cirrhosis) [43, 44], the acquisition protocol (e.g. breathing motion) and fastening and hydration level [14], which all together seem to be responsible for the accomplished correlations in the envisioned quantitative studies at 1.5 and 3T. To our knowledge, only one study correlated renal $T_1$ values with measured GFR [22]. It should be noted that adequate patient preparation (e.g. hydration protocol, medication intake), patient selection in the context of comorbidities and acquisition protocols (e.g. triggered breath-hold) together with reference measurement of the renal function can improve $T_1$ renal function correlations, which advocates for further research in this field.

RENAL T2 MAPPING

Reference values and physiological modulations

In healthy subjects, medullary $T_2$ is consistently longer than cortical $T_2$. As previously envisioned, Hricak et al. [14] evaluated the effect of fasting and hydration and showed that $T_2$ CMD decreased during hydration (i.e. forced diuresis), but these findings were never re-evaluated. Additional variation can also be found due to the increase in $B_0$ from 1.5 and 3T, which is accompanied by a general decrease in $T_2$, and by the fact that different MRI acquisitions and breathing strategies report unequal values. But for healthy subjects a high day-to-day repeatability was shown by a multi-echo spin-echo method with a mean variability of $<4\%$ for both cortex and medulla at 1.5T [45].

Closely linked to $T_2$ is $T_2^*$, which is thought to reflect tissue oxygenation [45, 46]. For measurement of $T_2^*$, both $T_2$ and $T_2^*$ are required. $T_2^*$, i.e. renal BOLD MRI, is discussed by Pruijm et al. in this issue [30].

These variations have to be considered when comparing different studies (Table 2).

Clinical studies

In the 1980s renal transplants were evaluated regarding $T_2$, and MRI was shown to be useful to identify fluid collections in necrotic transplant, perinephric lymphocele and haematoma [31].

To our knowledge, the first quantitative clinical, i.e. renal transplant, study on $T_2$ values at 1.5 Tesla (T) was reported in 2011. One of two $T_2$ acquisition protocols identified a significant increase in cortical $T_2$ in 15 renal transplants compared with 6 healthy subjects. However, no significant difference was observed with regards to the allograft function [46].

In 2017, whole kidney $T_2$ values in animals with juvenile cystic kidneys and nine autosomal dominant polycystic kidney disease (ADPKD) patients were reported. A strong significant increase in $T_2$ values was seen in early-stage ADPKD patients compared with healthy volunteers. Based solely on $T_2$ values, early-stage ADPKD patients with a kidney volume $<300$ mL could be distinguished from healthy volunteers, which was not possible based on total kidney volume (TKV) [47].

In summary, human in vivo measurements of renal $T_2$ are relatively scarce. Therefore no final conclusion can be made regarding renal function estimation or renal transplant assessments. Nevertheless, interesting findings were obtained, which clearly advocate for future research. Early-stage ADPKD
patients could benefit from the $T_2$ evaluations and the potentially improved assessment of early-disease progression compared with TKV [47]. This might be of special interest in the evaluation of novel therapeutic agents such as tolvaptan. The assessment of AKI in the context of ischaemia reperfusion injury, e.g. induced kidney damage during renal allograft surgery, also seems to be a potential application for $T_2$, as in vivo measurements were shown to be feasible [46]. Animal studies have shown that $T_2$ is sensitive to ischaemia–reperfusion injury [48, 49]. During initial ischaemia, $T_2$ decreases, probably due to deoxygénation, followed by an increase during reperfusion [50]. In the longer term, an elevation of $T_2$ that is more pronounced in the medulla compared with the cortex has been found [51, 52], which was attributed to consecutive inflammation and oedema ($T_2$ increase) [50–52]. Human studies are necessary to determine whether the $T_2$ changes following AKI can predict the recovery of renal function.

**DISCUSSION**

In recent decades, quantitative renal $T_1$ and $T_2$ mapping have been shown not only to be feasible, but also to provide non-invasive valuable information regarding renal structure and function in healthy, AKI, CKD, renal transplant and ADPKD patients at 1.5 and 3T (Tables 1 and 2).

Renal $T_1$ has been shown to be modulated by hydration and, in particular, cortical $T_1$ is sensitive to oxygenation. $T_1$ CMD is a potential candidate biomarker to assess AAR, CAR, ATN, CN, fibrosis and renal function. Renal $T_2$ was measured in only a few studies but showed the potential to evaluate renal transplants and to improve the diagnosis and progression of early-stage ADPKD.

However, the variation in $T_1$ and $T_2$ values is large, mainly due to the great diversity of the MRR methods applied, but also due to physiological (e.g. water balance management during fasting and forced diuresis) and pathological alterations (e.g. fibrosis) of the renal parenchyma. In virtually all renal diseases, renal function and microstructure are altered together, and this review on $T_1$ and $T_2$ unveiled the high sensitivity towards each of these processes as well as the complicated interpretation of the acquired data due to the low specificity.

In conclusion, currently available data suggest that the full potential of renal $T_1$ and $T_2$ mapping has not yet been tapped and adequate patient selection, with regard to comorbidities, alongside technical and physiological standardization, will significantly increase the specificity of renal MRR. On route towards renal $T_1$ or $T_2$ mapping as a biomarker it will be necessary to validate renal MRR against widely accepted reference measurements (e.g. nuclear medicine evaluations) as well as against histological findings, when possible. Last but not least, the integration of different quantitative renal MRI data into a multiparametric approach will likely enable us to gain the best insight into renal pathophysiology. The COST Action PARENCHIMA (www.renalmri.org) is working on standardization of multiparametric renal MRI techniques to tackle these challenges.

**SUPPLEMENTARY DATA**

Supplementary data are available at ndt online.

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**CONFLICT OF INTEREST STATEMENT**

None declared.

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