REVIEW ARTICLE

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Native T1-Mapping as a Quantitative Biomarker of Renal Allograft Function and Its Relationship with Serum Cytokine Profiles after Paediatric Kidney Transplantation: A Comprehensive Narrative Review

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Abstract

Background: Pediatric kidney transplantation is the optimal therapy for end-stage kidney disease in children, yet long-term allograft survival remains inferior to adults due to heightened immunological reactivity, subclinical inflammation, and progressive fibrosis. Conventional monitoring with serum creatinine and protocol biopsies is limited by poor sensitivity and invasiveness.
Methods: This comprehensive narrative review synthesizes evidence on native T1-mapping MRI—a non-contrast technique quantifying renal parenchymal microstructure via elevated cortical T1 and reduced corticomedullary differentiation, reflecting inflammation, oedema, and interstitial fibrosis/tubular atrophy (IFTA)—and its mechanistic interplay with serum cytokine/chemokine profiles capturing alloimmune response phenotypes.
Results: Emerging data show strong pathophysiological/statistical correlations between pro-inflammatory cytokines (especially IL-6, TNF-α, CXCL10) and T1 prolongation, as cytokine-driven inflammation alters tissue relaxation properties detectable by MRI. Native T1-mapping demonstrates high diagnostic performance for IFTA (sensitivity 81-89%, specificity 78-85%), predicts graft dysfunction (HR 3.8 per 100 ms T1 increase), and tracks treatment response. Combined with cytokines, it identifies subclinical rejection with 94% specificity, outperforming eGFR/creatinine.
Conclusions: Native T1-mapping offers robust prognostic value in pediatric renal allografts. Integrated with targeted cytokine panels, it enables biopsy-sparing monitoring, early injury detection, and personalized strategies to improve outcomes. Multicenter trials with standardized protocols are needed.

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Introduction

Kidney transplantation in children restores growth, development, and quality of life far beyond that achievable with dialysis, yet graft half-life remains disappointingly short, particularly with deceased-donor organs (1). Acute rejection affects 20–40% of pediatric recipients in the first year, and chronic allograft dysfunction develops insidiously in many others despite

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apparently stable function by serum creatinine (2). Children exhibit unique immunological challenges: more robust T-cell responses, rapid de-novo donor-specific antibody formation after viral infection, frequent non-adherence in adolescence, and heightened susceptibility to calcineurin-inhibitor toxicity during growth spurts (3). These factors converge to produce subclinical inflammation and progressive interstitial fibrosis/tubular atrophy (IF/TA), the final common pathway to graft loss.

Serum creatinine and estimated glomerular filtration rate lack sensitivity for early microstructural injury, often remaining normal until more than 50% of nephrons are lost (4). Protocol biopsies, although valuable, are invasive, resource-intensive, and associated with rare but serious complications in small children (5). Consequently, there is intense interest in non-invasive, quantitative biomarkers capable of detecting inflammation and fibrosis before irreversible damage occurs.

Native T1-mapping, a magnetic resonance imaging technique that measures longitudinal relaxation time without gadolinium contrast, has emerged as one of the most promising candidates (6). Prolonged cortical T1 and loss of corticomedullary differentiation reflect increased tissue water from oedema or bound water in collagen-rich fibrotic matrix (7). At the same time, serum cytokine profiling provides a liquid biopsy of alloimmune activation, with distinct patterns characterizing T-cell-mediated rejection, antibody-mediated rejection, and viral infection (8). Recent studies reveal direct mechanistic links: pro-inflammatory cytokines induce endothelial permeability, tubular injury, and fibroblast activation, processes that manifest as altered T1 relaxation times (9,10). This review examines the evidence supporting native T1-mapping as a quantitative biomarker in pediatric renal transplantation and explores its relationship with circulating cytokine profiles.

Challenges of Conventional Monitoring in Pediatric Renal Allografts

Serum creatinine is particularly unreliable in growing children because of age-dependent muscle mass, variable tubular secretion under tacrolimus, and the confounding effect of corticosteroids on creatinine generation (11). Cystatin C offers modest improvement but is influenced by inflammation and thyroid function (12). Donor-derived cell-free DNA and urinary chemokine mRNA assays detect acute injury with high sensitivity yet struggle to quantify chronic fibrotic change or distinguish rejection from infection (13,14).

Surveillance biopsies remain the reference standard for detecting subclinical rejection and IF/TA. Subclinical tubulitis is found in up to 60% of protocol biopsies at three to six months in high-risk pediatric cohorts, and untreated inflammation predicts later graft dysfunction (15). However, repeated biopsies carry cumulative risk, and sampling error can miss focal lesions in small pediatric kidneys (16). The need for general anesthesia in younger children further limits acceptability.

Principles and Reproducibility of Native T1-Mapping

Native T1-mapping quantifies the time constant governing recovery of longitudinal magnetization after radiofrequency excitation. In healthy kidneys at 3 Tesla, cortical T1 ranges from approximately 1050 to 1200 ms and medullary T1 from 1400 to 1700 ms, producing a positive corticomedullary difference of 300–600 ms (17,18). Inflammation, oedema, and fibrosis increase free and bound water fractions, prolonging T1 and reducing corticomedullary differentiation (19).

Clinical sequences include modified Look-Locker inversion recovery (MOLLI), shortened MOLLI, and saturation-recovery single-shot acquisition (SASHA). In children, free-breathing radial acquisitions with motion correction achieve intra-individual coefficients of variation below 4% for cortex and 6% for medulla, even in patients younger than eight years under light sedation (20,21). Standardization initiatives by the PARENCHIMA consortium have established quality-control phantoms and recommended reporting guidelines, markedly improving inter-center comparability (22).

Diagnostic and Prognostic Performance in Adult Renal Transplant Recipients

Large adult cohorts have firmly established the clinical utility of native T1-mapping. Cortical T1 values exceeding 1300 ms at 3 T identify moderate-to-severe IF/TA (Banff ci+ct ≥2) with sensitivity 81% and specificity 78% (23). Loss of corticomedullary differentiation below 200 ms independently predicts progression to chronic kidney disease stage 4 within two years (hazard ratio 3.8) (24). In acute allograft dysfunction, T1 elevation precedes creatinine rise by several days and helps differentiate rejection from calcineurin-inhibitor toxicity or acute tubular necrosis (25,26). When combined with arterial spin labelling perfusion, T1-mapping distinguishes antibody-mediated rejection (high T1, low perfusion) from T-cell-mediated rejection (high T1, preserved or increased perfusion) (27). Longitudinal studies show that every 100 ms increase in cortical T1 confers a 25–35% higher risk of graft failure at five years, independent of baseline function (28).

Evidence in Pediatric Kidney Transplantation

Pediatric-specific data, though still limited, are highly encouraging. In a prospective series of 38 children

imaged at one, three, six-, and twelve-months post-transplant using a 3 T protocol, cortical T1 was significantly higher in the early post-operative period (1312 ± 118 ms) than in age-matched healthy controls (1086 ± 74 ms, p<0.001) and normalized only in grafts with stable long-term function (29). Persistent cortical T1 above 1250 ms at six months identified subsequent biopsy-confirmed IF/TA with 89% sensitivity and 85% specificity.

A multicenter cohort of 62 pediatric recipients demonstrated that reduced corticomedullary differentiation at three months was the strongest predictor of eGFR below 60 mL/min/1.73 m^2 at two years (odds ratio 5.6 per 100 ms decrease) (30). When intravoxel incoherent motion diffusion was added, the combined model correctly classified 93% of acute rejection episodes, including subclinical cases missed by creatinine (31). In adolescents with chronic allograft injury, cortical T1 correlated strongly with Banff chronicity scores (r=0.71, p<0.001) and outperformed eGFR for detecting moderate-to-severe fibrosis (32).

Serum Cytokine Profiles after Pediatric Kidney Transplantation

Cytokine and chemokine levels mirror the type and intensity of immune activation. Interleukin-6, tumor necrosis factor-α, and interferon-γ rise dramatically within hours of T-cell-mediated rejection, often weeks before creatinine increases (33,34). Serum IL-6 above 30 pg/mL at the onset of graft dysfunction has a positive predictive value of 91% for acute rejection in children (35). CXCL9 and CXCL10 are elevated in both serum and urine during tubulitis and correlate with Banff inflammation scores (36). Antibody-mediated rejection is characterized by higher BAFF, IL-10, and IL-21 with relative suppression of Th1 cytokines (37). Longitudinal profiling in stable recipients shows progressive decline of pro-inflammatory mediators over the first year, whereas persistently elevated IL-6, IL-8, or MCP-1 heralds later chronic injury (38). Viral infections frequently confound interpretation, but combined cytokine and viral load assessment improves specificity (39).

Mechanistic and Clinical Interplay Between T1 Values and Cytokines

Pro-inflammatory cytokines directly alter renal microstructure in ways detectable by T1-mapping. Interferon-γ and tumor necrosis factor-α disrupt endothelial integrity and downregulate aquaporin-2, increasing tissue water within 24–48 hours (40). Interleukin-6 promotes TGF-β expression and myofibroblast activation, leading to collagen deposition and sustained T1 prolongation (41). In a pediatric cohort of 45 recipients who underwent simultaneous T1-mapping and 28-plex cytokine assay at three months post-transplant, cortical T1 correlated positively with IL-6 (r=0.68), TNF-α (r=0.59), and CXCL10 (r=0.62) and negatively with anti-inflammatory IL-10 (r=−0.51) (42). Multivariate analysis revealed that IL-6 and CXCL10 together explained 58% of T1 variance independent of eGFR.

In biopsy-controlled subgroups, the combination of IL-6 >25 pg/mL and cortical T1 >1280 ms identified moderate-to-severe inflammation (Banff ti ≥2) with 94% specificity (43). Serial measurements in 22 children treated for acute rejection showed parallel normalization of cytokines and T1 within four to six weeks when therapy succeeded, whereas persistent elevation of either marker predicted treatment failure and progression to IF/TA (44).

Clinical Advantages in the Pediatric Setting

Native T1-mapping avoids gadolinium exposure, a critical consideration in children with impaired allograft function. It provides operator-independent quantitative output, integrates easily into routine abdominal MRI protocols, and tracks treatment response longitudinally. Preliminary risk-stratification models suggest that normal T1 and cytokine values at three to six months could safely reduce protocol biopsy rates by 30–50% in low-risk patients (45).

Current Limitations and Ongoing Standardization Efforts

Access to 3 T scanners with cardiac packages remains limited in many pediatric centers. Motion artefact in young children can be mitigated by radial acquisitions and compressed sensing reconstruction, but general anesthesia is still required in a minority. Pediatric reference ranges are being established through multicenter initiatives including the European PARENCHIMA-II consortium and the North American Pediatric Renal Transplant Cooperative Study MRI working group (46,47).

Conclusion

Native T1-mapping has matured into a robust, non-invasive biomarker of renal allograft microstructure in pediatric transplantation. Its strong correlation with pro-inflammatory cytokine profiles reflects the fundamental pathophysiological link between immune activation and parenchymal injury. Combined use of T1-mapping and targeted cytokine panels offers the prospect of personalized, biopsy-sparing monitoring strategies that detect subclinical rejection and early fibrosis before irreversible damage occurs. Large, prospective, multicenter studies with standardized protocols and hard graft-survival endpoints are now

essential to translate these advances into routine clinical practice.

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Authors Contributions

The authors contributed to the data analysis. Drafting, revising and approving the article, responsible for all aspects of this work.

Conflict of Interest

None

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