Editorial with respect to “Corticosteroids to prevent kidney scarring in children with a febrile urinary tract infection—a randomized trial”

Vasikar Murugapoopathy¹ · Indra R. Gupta^{1,2}

Received: 1 March 2021 / Accepted: 10 March 2021 / Published online: 7 May 2021
© IPNA 2021

In their study published in a recent issue of *Pediatric Nephrology*, Shaikh et al. hypothesize that inflammation may be the critical factor that drives kidney scar formation after a urinary tract infection (UTI) [1]. To test this hypothesis, they performed a randomized double-blind control trial to evaluate whether treatment with dexamethasone is effective in preventing kidney scar formation in children with UTI. This is an important topic because kidney scarring post-UTI with and without vesico-ureteric reflux remains a relatively common cause of kidney failure in both pediatric and adult databases.

Kidney scarring refers to the development of fibrosis in response to infection and/or inflammation. In children, kidney scarring is often seen in those who have UTIs that may occur with or without vesico-ureteric reflux. Although the majority of children are able to eliminate the bacteria during a UTI with antibiotic treatment and control the inflammatory response, approximately 10–25% will develop kidney scarring [2]. In the RIVUR trial, antibiotic treatment was shown to be effective in the prevention of recurrent UTIs; however, there was no difference in the rate of kidney scarring in children on antibiotic treatment compared to those in the placebo group. This suggests that there are other factors besides bacterial infection that predispose to kidney scarring. Additional risk factors were subsequently identified to be associated with kidney scarring in RIVUR participants. These included high-grade vesico-ureteric reflux, recurrent UTIs, older age (e.g., more than 2 years of age), and Hispanic ethnicity [3]. Taken together, there is a need to understand the mechanism by which kidney scars arise since this could reveal new therapeutic avenues to prevent scar formation.

Kidney scarring may arise from inflammation which is how the host's immune response responds to bacterial infection of the kidney. The inflammatory response in the kidney includes the recruitment of neutrophils and macrophages as well as the release of reactive oxygen species and lysosomal enzymes. Transforming growth factor β 1 is also stimulated as part of the initiation and the resolution of inflammation and provokes deposition of extracellular matrix proteins including collagen. If these effectors are not well regulated, there is a risk for an excessive response that damages the kidney and resolves with the deposition of collagen in a scar. To target the inflammation of the host immune response, different treatments have been administered in clinical trials of children with UTIs, with some success. Vitamin A, which is an antioxidant, has been shown to reduce kidney scarring in four trials (three from Iran and one from China) [4]. All of these trials were limited by a low number of participants, very few male subjects, and possible selection and performance bias. The efficacy of vitamin A to prevent kidney scar formation therefore requires further exploration. More recently, a group in Taiwan evaluated the effectiveness of oral methylprednisolone treatment (1.6 mg/kg once a day for 3 days) in patients with acute pyelonephritis and found a significant reduction in scarring in the treatment group [5]. This study was limited by small numbers, with 19 patients in the treatment group and 65 patients in the control group. Nonetheless, these promising findings set the stage for the current study by Shaikh et al., who performed a large-scale double-blind placebo-controlled randomized clinical trial to assess the use of dexamethasone to prevent kidney scarring in children with febrile UTIs [1].

Shaikh et al. used adjuvant oral dexamethasone (0.15 mg/kg/dose bid for 3 days) or placebo with antimicrobial therapy to treat children aged 2 months to 6 years who presented with their first UTI. Post-UTI, the children were assessed for kidney scarring using a DMSA scan which was performed anywhere from 5–24 months after the first UTI. Although rates of kidney scarring were 9.8% and 16.8% in the corticosteroid and placebo groups respectively, this was not a

✉ Indra R. Gupta
indra.gupta@muhc.mcgill.ca

¹ Department of Human Genetics, McGill University, Montreal, Canada

² Department of Pediatric, McGill University, Montreal, Canada

statistically significant difference ($p = 0.16$). The authors stated that their findings may have been limited by the fact that they did not reach the intended sample size for the trial [1].

Of the 1483 eligible participants, 783 participants (49.7%) declined participation and 199 were not recruited because study staff were not available to enroll them. If we assume a 50% rate of participation, those 199 children would have added 98 participants for the study (or 49 per group) which would have likely reached the intended sample size.

There was a lack of a baseline DMSA scan for each patient to determine the existence of kidney dysplasia/hypoplasia, which can phenocopy a severely scarred kidney on DMSA scan and can rule out the presence of preexisting kidney scars. The authors argued that from previous work, they anticipated a low rate of kidney scarring and that likely equal numbers would have been assigned to each treatment arm. Undoubtedly, the authors were also concerned whether a baseline DMSA scan would deter recruitment. The DMSA scan does result in radiation exposure with one study estimating the average exposure per scan to be ~ 2.84 mSv, which is equivalent to approximately 28 chest X-rays/year [6]. The radiation exposure of the DMSA scan may have resulted in some failures in recruitment and also failures in presenting for the follow-up DMSA scan post-infection. Interestingly, in one study that assessed patient and family satisfaction with a number of genitourinary imaging modalities, the voiding cystourethrogram and the DMSA scan were deemed equivalent in the pain inflicted on the child, the length of the procedure, and the anxiety that was induced in the child [7].

The DMSA scan continues to be the gold standard for the diagnosis of kidney scars in spite of the fact that it has never been validated as a gold standard in humans. It became accepted as the gold standard based on work using the pig as a model of pyelonephritis and kidney scarring [8]. In addition, since 2014, ^{99m}Tc -DMSA has been in short supply, prompting some centres to use ^{99m}Tc -glucoheptonate, which is inferior. ^{99m}Tc -DMSA exhibits 40–50% binding to the proximal tubules, while ^{99m}Tc -glucoheptonate exhibits 10–20% binding, which may limit its ability to identify kidney scars. For all of these reasons, some have suggested that we need new improved methods to diagnose kidney scars, such as the use of MRI which would avoid unnecessary radiation exposure [9].

The children recruited in the Shaikh et al. study did not undergo a voiding cystourethrogram to determine if vesico-ureteric reflux was present or not. Children with high-grade vesico-ureteric reflux are known to be at higher risk of kidney scars, and this could have been assessed as a secondary outcome. Here again, however, they would likely have been underpowered to complete the analysis of such patients. These patients, however, are the ones most likely to show benefit from the use of corticosteroids [5].

There was an underrepresentation of boys with UTIs who often have an abnormal DMSA scan, often due to congenital hypoplasia/dysplasia. Only 8% of the children studied were boys. Children of Hispanic descent were also underrepresented in the study, encompassing only 16% of the cohort. Children of Hispanic descent are also known to have a higher risk of kidney scarring [3]. Furthermore, the Hispanic children who were enrolled in the study were significantly less likely to return for the follow-up DMSA scan. Engaging the Hispanic community in medical research has been reported to be difficult for a number of reasons, including need to care for other family members, fears of additional costs to cover research medications, lack of trust, and time lost from work or family care [10]. This aspect of the study needs to be considered by all researchers so that children of Hispanic origin are not left out of important research that may have implications for their health. Funding agencies may need to consider this in their budget allotments. For example, if there is not a minimum quota of patients from a particular ethnic group, perhaps the grant duration should be extended and/or the investigators obliged to justify their failure to recruit from all ethnic groups. Somewhere within the biomedical research pipeline, there needs to be accountability, so no child is left behind.

There is a significant heterogeneity in the host immune response to UTI and pyelonephritis. Children with an “over-active” immune response may experience excessive inflammation in their kidneys following pyelonephritis resulting in kidney scar formation. Conversely, too weak of an immune response may result in an inability to clear bacteria, sepsis, and/or prolonged infection and inflammation, which may also damage the kidney. The variations in the host immune response may be genetic (mutations in genes that regulate the immune response), environmental (e.g., ingestion of dietary antioxidants), or both. There are very few studies looking at biomarkers of children at high risk of kidney scarring from UTIs. It would have been extremely valuable to include some assessment of urine and blood biomarkers in this study to better understand the pathogenesis of inflammation and scar formation. One study from Japan of 49 infants examined a number of potential urinary biomarkers and identified angiotensin to be highly correlated with kidney scarring [11]. Future studies need to incorporate urinary biomarkers to understand the groups that are at high risk of kidney scarring. This could then be used to identify specific groups of children who would be most likely to benefit from treatments to prevent scarring.

References

1. Shaikh N, Shope TR, Hoberman A, Muniz GB, Bhatnagar S, Nowalk A, Hickey RW, Michaels MG, Kearney D, Rockette HE, Charron M, Lim R, Majd M, Shalaby-Rana E, Kurs-Lasky M,

- Cohen DM, Wald ER, Lockhart G, Pohl HG, Martin JM (2020) Corticosteroids to prevent kidney scarring in children with a febrile urinary tract infection: a randomized trial. *Pediatr Nephrol* 35: 2113–2120. <https://doi.org/10.1007/s00467-020-04622-3>
2. Hoberman A, Greenfield SP, Mattoo TK, Keren R, Mathews R, Pohl HG, Kropp BP, Skoog SJ, Nelson CP, Moxey-Mims M, Chesney RW, Carpenter MA; RIVUR Trial Investigators (2014) Antimicrobial prophylaxis for children with vesicoureteral reflux. *N Engl J Med* 370:2367–2376
3. Mattoo TK, Chesney RW, Greenfield SP, Hoberman A, Keren R, Mathews R, Gravens-Mueller L, Ivanova A, Carpenter MA, Moxey-Mims M, Majd M, Ziessman HA; RIVUR Trial Investigators (2016) Renal scarring in the randomized intervention for children with vesicoureteral reflux (RIVUR) trial. *Clin J Am Soc Nephrol* 11:54–61
4. Zhang GQ, Chen JL, Zhao Y (2016) The effect of vitamin A on renal damage following acute pyelonephritis in children: a meta-analysis of randomized controlled trials. *Pediatr Nephrol* 31:373–379
5. Huang YY, Chen MJ, Chiu NT, Chou HH, Lin KY, Chiou YY (2011) Adjunctive oral methylprednisolone in pediatric acute pyelonephritis alleviates renal scarring. *Pediatrics* 128:e496–e504
6. Michaud JE, Gupta N, Baumgartner TS, Kim B, Bosemani T, Wang MH (2016) Cost and radiation exposure in the workup of febrile pediatric urinary tract infections. *J Surg Res* 203:313–318
7. Nelson CP, Chow JS, Rosoklija I, Ziniel S, Routh JC, Cilento BG Jr (2012) Patient and family impact of pediatric genitourinary diagnostic imaging tests. *J Urol* 188(4 Suppl):1601–1607
8. Risdon RA, Godley ML, Gordon I, Ransley PG (1994) Renal pathology and the 99mTc-DMSA image before and after treatment of the evolving pyelonephritic scar: an experimental study. *J Urol* 152: 1260–1266
9. Freeman CW, Altes TA, Rehm PK, de Lange EE, Lancaster L, Mugler JP 3rd, Patrie JT, Corbett S, Leiva-Salinas C, Flors L (2018) Unenhanced MRI as an alternative to (99m)Tc-labeled dimercaptosuccinic acid scintigraphy in the detection of pediatric renal scarring. *AJR Am J Roentgenol* 210:869–875
10. Ulrich A, Thompson B, Livaudais JC, Espinoza N, Cordova A, Coronado GD (2013) Issues in biomedical research: what do Hispanics think? *Am J Health Behav* 37:80–85
11. Kitao T, Kimata T, Yamanouchi S, Kato S, Tsuji S, Kaneko K (2015) Urinary biomarkers for screening for renal scarring in children with febrile urinary tract infection: pilot study. *J Urol* 194: 766–771

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.