Nephron Number as Predictor of Corticosteroid Response in Adult Minimal Change Disease

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Minimal change disease (MCD) is a clinicopathologic entity that includes nephrotic syndrome and diffuse foot process effacement in the absence of other histopathologic abnormalities. MCD is the predominant cause

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of nephrotic syndrome in children and is characterized by a rapid proteinuria response to corticosteroid treatment.[1] MCD is relatively less frequent in adults. Corticosteroid treatment ultimately leads to recovery of nephrotic syndrome in 90% of adult patients, and progressive loss of kidney function rarely occurs.

Despite typically favorable outcomes, MCD may cause life-threatening complications and treatment may prove difficult.[2] The onset of severe nephrotic syndrome is associated with risk for acute kidney injury and deep venous thrombosis. The time to treatment-induced proteinuria remission is variable and may require up to 6 months of high-dose corticosteroid treatment. The frequency of side effects and complications increases with prolonged corticosteroid exposure. Most patients will develop 1 or more relapses, necessitating repeat courses of corticosteroids and other immunosuppressive drugs, and repeat and prolonged treatment may increase the risk for severe infection and late malignancies.

Our current understanding of MCD pathogenesis and factors that determine corticosteroid response and relapse is limited. The "Shalhoub hypothesis" dating from 1974 states that MCD is caused by a T-lymphocyte–derived permeability factor.[3] This hypothesis was supported by experimental proteinuria in rats after injection of lymphocyte culture supernatants of patients with MCD.[4] Recent genetic association studies have confirmed susceptibility to immune dysregulation in children with MCD.[5] Nevertheless, responsible factors have not been identified, and disease-specific biomarkers that can guide treatment decisions are lacking.

In this issue of *Kidney Medicine*, Sasaki et al[6] from Jikei University report a significant association between low estimated nephron number and prolonged time to complete remission in 75 Japanese patients with MCD. The work was enabled by recent progress in methods to estimate nephron number in living individuals using kidney biopsy results in conjunction with imaging. Previously, autopsy studies were the main source of information regarding nephron number and morphology. Although nephron numbers may vary strongly between people of different ages and genetic backgrounds, low nephron number is considered a strong risk factor for progressive kidney disease.[7]

Kidneys with reduced nephron numbers have enlarged mean glomerular volume, indicating compensatory hyperfiltration.[8] Hyperfiltering nephrons may be unable to respond to increased hemodynamic load in settings such as acute nephrotic syndrome. Although MCD is considered a nonprogressive disease, increased mean glomerular volume in children with MCD was a strong risk factor for progression to treatment-resistant focal segmental glomerulosclerosis many years later.[9] Already in 2011, researchers from Jikei University reported a relationship between reduced glomerular density (number of glomeruli per cortex area) and delayed response to corticosteroid treatment in adults with MCD.[10] Increased mean glomerular volume in patients with reduced glomerular number suggested reduced nephron number. Still, glomerular density discriminated insufficiently between patients with early and late corticosteroid response for clinical use of the method.

Recent seminal work by Denic et al[11] proposed a method to estimate total nephron number by multiplying cortical volume (mm^3) measured using contrast-enhanced computed tomography (CT) and glomerular density (number per mm^3 of cortex) measured in a kidney biopsy (Fig 1). The method was applied on images from CT and biopsy material from a large cohort of living kidney donors in the United States. Estimated nephron numbers obtained using the novel method correlated well with nephron numbers obtained in autopsy studies. Sasaki et al initially evaluated the novel method in Japanese kidney donors.[12] Estimated nephron number was ~25% lower compared with American donors, which was in accordance with autopsy findings. Importantly, correlations between nephron density and estimated nephron numbers suggested that measurement of cortical volume had additional value. Requirement of nephrotoxic contrast material was an obstacle to the application of the method in patients with kidney disease. The authors subsequently demonstrated that cortical volume could be estimated with small error margins without the use of contrast, by measurement of kidney parenchymal volume on unenhanced CT.[13]

In the present study, Sasaki et al made use of biopsy material and unenhanced CT to investigate the relationship between estimated nephron number and treatment response in patients with nephrotic syndrome. Standardized pathologic evaluation of kidney tissue was performed, including parameters needed to assess nephron number and volume and semiquantitation of podocyte foot-process effacement on electron microscopy. Baseline clinical characteristics and laboratory results were recorded. Trends in clinical and histologic parameters were analyzed

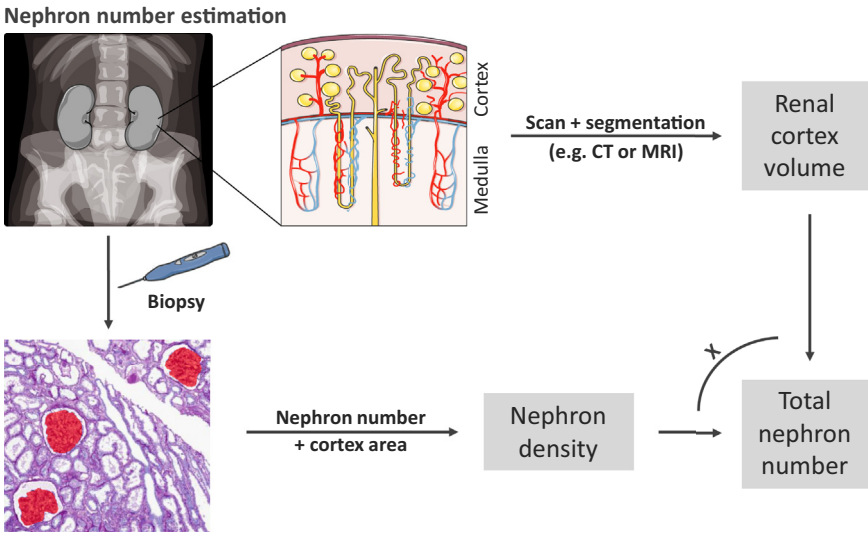

Figure 1. Graphical presentation of a method used to estimate nephron number in a kidney based on kidney biopsy tissue and enhanced computed tomography (CT). Abbreviation: MRI, magnetic resonance imaging.

according to tertiles of nephron number. The response to prednisolone treatment was evaluated frequently, and patients were followed up to identify proteinuria relapse at an early stage. Cox proportional hazard models were created to assess hazard ratios for complete remission and relapse.

Patients had typical features of MCD, including massive and highly selective proteinuria, low serum albumin levels, and moderately reduced estimated glomerular filtration rates (eGFR). The mean estimated number of almost 900,000 nephrons per kidney was comparable to previous data. There was a maximum 17-fold range in nephron number, a result that appears large. The lowest nephron number tertile was composed of patients with significantly older age, lower eGFR, and more hypertension. This group also had more severe nephrotic syndrome, based on lower serum albumin levels and high frequency of intravenous albumin administration.

As expected, low nephron numbers were associated with many morphologic variables, such as high mean glomerular volume, more sclerotic glomeruli, and smaller kidney parenchymal volume. Importantly, patients with lower nephron numbers had higher mean single-nephron proteinuria and single-nephron eGFR. More prominent podocyte foot-process effacement in patients with lower nephron numbers may indicate that increased proteinuria and GFR at the single-nephron level are accompanied by increased podocyte stress.

Complete proteinuria remissions occurred after initiation of corticosteroid therapy in all patients and were recorded after 3 and 7 weeks of treatment in the highest and lowest tertile of nephron numbers, repectively. More than 40% of patients had relapses, but there were no significant assocations between relapse and nephron number. In the multivariate model, the hazard ratio of complete remission was 1.1 per 100,000 nephrons per kidney.

The authors have successfully implemented an innovative method to estimate nephron number to study a clinically relevant research question. A predicted slow response to corticosteroid treatment based on low nephron number may lead to a decision to consider alternative initial treatment with proven efficacy such as tacrolimus or mycophenolate.[14,15] The effect size of nephron number may potentially be even larger in European and American patients with MCD, who may manifest delayed proteinuria response to corticosteroid treatment as compared with Asians.[2,16]

The study also raises questions regarding mechanisms explaining the relationship between nephron number and treatment response. Delayed proteinuria response time may reflect the process of structural recovery after of the underlying cause has disappeared. Such a mechanism of immunologic response before onset of a clinical response has been observed in membranous nephropathy, in which loss of detectable anti–phospholipase A_2 receptor preceded proteinuria remission by many months.[17] Additionally, potential direct stabilizing effects of corticosteroid treatment on podocytes may be less effective in the setting of increased podocyte stress resulting from reduced nephron numbers.[18] Delayed podocyte recovery of patients with reduced nephron numbers also suggests increased vulnerability in case of relapses, which may warrant preventive strategies such as rituximab treatment after complete remission is reached.[19]

Limitations of the method of nephron estimation should be addressed. A large variation coefficient for nephron number of 33% was reported, mainly due to variations in the biopsy sample.[11] This imprecision may explain the 17-fold variation in nephron number reported by Sasaki et al. Strong variations in glomerular morphology observed in progressive kidney disease with focal and segmental lesions will pose further challenges, which can

currently be addressed only by sophisticated methods involving optical tissue clearing.[20]

The podocyte is considered the main target of injury in patients with MCD, and a focus on assessment of podocyte morphologic changes associated with low nephron number may have prognostic value. Reproducible quantitative assessment of podocyte foot-process effacement with super-resolution microscopy is feasible and has been reported in patients with MCD.[21] In addition, the study of podocyte depletion in a biopsy section may provide relevant prognostic information.[22] It is expected that further advances in microscopy and imaging will provide methods that allow more precise information regarding nephron numbers and its consequences on the cellular level. The study by Sasaki et al confirms the clinical importance of such efforts for patients with kidney disease.

ARTICLE INFORMATION

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