KI REPORTS
KIReports.org

Urinary CD 80 in Nephrotic Syndrome: A Biomarker to Distinguish Minimal Change Disease From Other Glomerular Diseases

Om P. Mishra[1]

[1]Division of Pediatric Nephrology, Department of Pediatrics, Institute of Medical Sciences, Banaras Hindu University, Varanasi, India

Kidney Int Rep (2020) **5,** 1851–1852; https://doi.org/10.1016/j.ekir.2020.09.027

See Clinical Research on Page 2021

Nephrotic syndrome is the most common chronic kidney disorder with a remission and relapse course, and the response to corticosteroid treatment correlates with the prognosis of the disease. Minimal change disease and focal segmental glomerulosclerosis are the 2 common histopathologic lesions, besides other glomerular pathologies, found in a kidney biopsy of patients with idiopathic nephrotic syndrome.[1] The exact cause of minimal change disease is unknown; however, Reiser *et al.*[2] reported evidence of upregulation of B7-1 (also known as CD80) in podocytes induced by the injection of low-dose lipopolysaccharide in wild-type mice leading to proteinuria, whereas this effect was not found in mice lacking B7-1, which is indicative of a relationship between B7-1 expression and proteinuria. Subsequently, Ishimoto *et al.*[3] observed that lipopolysaccharide injection caused proteinuria with the expression of CD80 by the podocytes. Additionally, CD80 mRNA expressions were also observed in response to Toll-like receptor 3 ligand polyinosinic-polycytidylic acid and Toll-like receptor 4 ligand lipopolysaccharide in patients with minimal change disease.[4,5] Furthermore, it has been shown that sera of patients with minimal change disease in relapse were able to induce CD80 expression and its secretion by the podocytes.[3]

In the recent past, several studies have demonstrated significantly increased levels of urinary CD80 (uCD80) in patients with minimal change disease in relapse than in remission, focal segmental glomerulosclerosis, and other glomerular diseases with good sensitivity (86.6%–99%), specificity (71.4%–100%), and areas under the curve (0.82–0.99) at different cutoff levels.[5–8] In this issue of the journal, Gonzalez Guerrico *et al.*[9] reported the utility of a validated enzyme-linked immunosorbent assay of uCD80 in patients with nephrotic syndrome included from the Mayo Clinic and the Nephrotic Syndrome Study Network Consortium (NEPTUNE) study. The patients analyzed were as follows: minimal change disease, focal segmental glomerulosclerosis, lupus nephritis, IgA nephropathy, membranous nephropathy, polycystic kidney disease, diabetic nephropathy, pyuria, and controls. The value of uCD80/creatinine was highest in patients with minimal change disease compared with other glomerular diseases. The levels were significantly higher in patients with minimal change disease in relapse than remission, and uCD80 values were independent of proteinuria in nephrotic patients. The authors concluded that uCD80 differentiated minimal change disease from the other glomerular diseases presenting with proteinuria and also primary from secondary focal segmental glomerulosclerosis. The strength of the study is that it presents observations of uCD80 in a large cohort of patients of nephrotic syndrome reported to date using an enhanced enzyme-linked immunosorbent assay method, providing more reliable information related to uCD80 status in minimal change disease. However, the study had certain limitations because it was retrospective in nature, and some of the patients might have been on immunosuppressive drugs, which could have affected the uCD80 levels. The uCD80 levels in the follow-up after therapy were not performed, except paired samples of minimal change disease and focal segmental glomerulosclerosis in relapse versus remission; otherwise, it could have demonstrated the true status of uCD80 levels with reductions in proteinuria in patients with other etiologies. In

Correspondence: Om P. Mishra, Institute of Medical Sciences and In-Charge, Division of Pediatric Nephrology, Department of Pediatrics, Institute of Medical Sciences, Banaras Hindu University, Varanasi, India. E-mail: opmpedia@yahoo.co.uk

addition, it was not shown whether the origin of uCD80 was from the kidney or filtered by the glomeruli due to increased levels in serum as a systemic response.

In contrast, Minamikawa *et al.*[S1] reported that urinary CD80 is an unreliable diagnostic marker to differentiate among minimal change disease in relapse, focal segmental glomerulosclerosis, and other acquired and inherited kidney diseases, with the major limitation of small sample sizes in the study groups. In addition, Ling *et al.*[S2] showed that the raised uCD80 level as a prognostic biomarker with patients having >328.98 ng/g creatinine had a better response to immunosuppression (100% vs. 34.5%) and a lesser proportion of patient progression to chronic kidney disease (2.9% vs. 41.4%) than below the cutoff level. The raised uCD80 excretion was found to have a decreased risk (relative risk 6.171, $P = 0.013$) of progression to chronic kidney disease in children with minimal change disease. The uCD80 also correlated significantly with proteinuria.[5,S1]

CD80 is a transmembrane protein that is expressed on antigen-presenting cells or natural killer cells. It functions as a ligand and has important roles in T-cell activation or inactivation by binding with CD28 on T cells or cytotoxic T-lymphocyte–associated 4 on T-regulatory cells.[S3] The podocytes can act as antigen-presenting cells, and a higher expression of CD80 can lead to reorganization of actin molecules in podocytes causing the disruption of structures, which, in turn, can cause elevation of the podocytes' permeability, resulting in proteinuria.[4] CD80 expression in glomeruli and its excretion in urine have been predicted for their response to abatacept therapy.[S4,S5] Furthermore, it was also reported that uCD80 excretion in minimal change disease with positive CD80 staining in the glomeruli decreased after abatacept treatment with a temporary improvement in proteinuria.[S4] Therefore, it appears that the origin of uCD80 may be from the podocytes.[3,7] It has been emphasized that patients of idiopathic nephrotic syndrome expressing CD80 in their podocytes and showing increased urinary levels are steroid responsive and have long-term preservation of renal function.[S6]

The high uCD80 in nephrotic syndrome may be a potential urinary biomarker indicating minimal change disease, especially in children who mostly respond to steroid treatment, thus avoiding the need of a kidney biopsy.

DISCLOSURE

The author declared no competing interests.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary References.

REFERENCES

1. Trautmann A, Schnaidt S, Lipska-Ziętkiewicz BS, et al. Long -term outcome of steroid-resistant nephrotic syndrome in children. *J Am Soc Nephrol*. 2017;28:3055–3065.
2. Reiser J, von Gersdorff G, Loos M, Oh J, et al. Induction of B7–1 in podocytes is associated with nephrotic syndrome. *J Clin Invest*. 2004;113:1390–1397.
3. Ishimoto T, Cara-Fuentes G, Wang H, et al. Serum from minimal change patients in relapse increases CD80 expression in cultured podocytes. *Pediatr Nephrol*. 2013;28:1803–1812.
4. Shimada M, Ishimoto T, Lee PY, et al. Toll-like receptor 3 ligands induce CD80 expression in human podocytes via an NF-kappa B-dependent pathway. *Nephrol Dial Transplant*. 2012;27:81–89.
5. Mishra OP, Kumar R, Narayan G, et al. Toll like receptor-3 (TLR-3), TLR-4 and CD 80 expressions in peripheral blood mononuclear cells and urinary CD 80 levels in children with idiopathic nephrotic syndrome. *Pediatr Nephrol*. 2017;32:1355–1361.
6. Garin EH, Diaz LN, Mu W, et al. Urinary CD80 excretion increases in idiopathic minimal-change disease. *J Am Soc Nephrol*. 2009;20:260–266.
7. Garin EH, Mu W, Arthur JM, et al. Urinary CD80 is elevated in minimal change disease but not in focal segmental glomerulosclerosis. *Kidney Int*. 2010;78:296–302.
8. Cara-Fuentes G, Wei C, Segarra A, et al. CD80 and suPAR in patients with minimal change disease and focal segmental glomerulosclerosis: diagnostic and pathogenic significance. *Pediatr Nephrol*. 2013;29:1363–1371.
9. Gonzalez Guerrico AM, Lieske J, Klee G, et al. Urinary CD80 discriminates among glomerular disease types and reflects disease activity. *Kidney Int Rep*. 2020;5:2021–2031.