Do We Now Have a Prognostic Biomarker for Progressive Diabetic Nephropathy?

Frank C. Brosius*† and Rajiv Saran*‡
*Departments of Internal Medicine and †Molecular and Integrative Physiology and the ‡Kidney Epidemiology and Cost Center, University of Michigan, Ann Arbor, Michigan

J Am Soc Nephrol 23: 376–377, 2012.
doi: 10.1681/ASN.2012010090

While there have been significant inroads in the prevention and treatment of diabetic nephropathy over the last 20 years, it only takes one afternoon in a busy nephrology clinic to recognize that diabetic nephropathy remains the major clinical challenge in nephrology today. The 2011 US Renal Data System reported that the number of patients with ESRD resulting from diabetic nephropathy continues to rise and that diabetic kidney disease accounted for 44.5% of all incident ESRD patients in the United States in 2009.[1] Based on National Health and Nutrition Survey data gathered between 1999 and 2006, it appears that approximately 40% of prevalent patients with either type 1 or type 2 diabetes had CKD,[2] and approximately 31% of CKD patients (stages 1–5) had diabetes in the 2007–2008 NHANES data (R. Saran, *et al.*, unpublished analysis). Thus, diabetes continues to be the dominant cause of CKD in the United States, with no clear evidence of abatement.

Arguably, one of the major reasons for the unmitigated growth in ESRD from diabetic nephropathy is the difficulty in accurately identifying diabetic patients at high risk of developing progressive nephropathy that will likely lead to ESRD. At present, no prognostic biomarkers have been identified that can reliably identify such a population of diabetic patients. Another reason for the lack of better progress in preventing or treating diabetic kidney disease is there has been no substantial advance in treatments since angiotensin converting enzyme inhibitors were shown to delay progression of nephropathy almost 20 years ago.[3] The absence of good surrogate endpoints for progressive disease requires that new therapies be shown to significantly improve the so-called three Ds of doubling of serum creatinine, dialysis, and death, before the Food and Drug Administration will consider them for approval. These end points of very late disease plus the inability to identify patients at high risk of progression ensure that funded trials enroll patients who are quite late in the course of the disease, so that patients are more likely to reach one of the end points in a reasonable period of time. Thus, patients with earlier disease, that is potentially more amenable to intervention, are rarely included in major randomized controlled trials.

The onset and level of albuminuria has been considered as both a prognostic biomarker and a surrogate end point of progressive diabetic nephropathy. However, this marker fails on both accounts.[4] It lacks specificity as a prognostic biomarker for progressive diabetic nephropathy, at least when urinary albumin excretion is <300 mg/24 h (microalbuminuria). Its sensitivity as a prognostic biomarker is also limited because diabetic nephropathy can frequently progress without an increase in albuminuria and even in the presence of normalbuminuria.[5,6] Given these issues and others, it also does not serve well as a surrogate end point for progression of diabetic kidney disease.[7,8] Although creatinine and other indicators of GFR such as cystatin C are prognostic biomarkers of a sort, their insensitivity and unreliability as early indicators of progressive diabetic kidney disease, and CKD in general, have been bemoaned for decades. Unfortunately, despite great interest and effort, no sensitive and specific prognostic biomarkers or surrogate end points for progressive diabetic nephropathy have been validated.

In this issue of *JASN*, there are two articles from the Joslin Diabetes Center indicating that serum levels of members of the TNFα signaling pathway appear to serve as excellent biomarkers of progressive kidney disease in patients with either type 1[9] or type 2[10] diabetes. In both studies, TNF receptor (TNFR) levels were robust predictors of progressively declining GFR, and type 1 diabetic patients with TNFR2 levels in the highest quartile had a 60% cumulative incidence of reaching stage 3 CKD compared with less than a 20% incidence for patients with TNFR2 levels in the lower three quartiles.[9] In type 2 diabetic patients with extant proteinuria and with TNFR1 levels in the highest quartile, the risk of progressing to ESRD was nearly 80% in 12 years, but less than 20% in those with TNFR1 levels in the lowest three quartiles.[10] Similar results were seen in each study with both TNFR isoforms, but the TNFR1 levels were a bit more predictive in type 2 diabetic patients and TNFR2 levels in type 1 patients. Both free and total TNFα levels also tended to predict progressive nephropathy but less strongly than the receptor levels.

These data appear to corroborate the role of inflammation in general, and TNFα signaling in particular, in the progression of diabetic nephropathy, as has been underlined by a number of earlier studies.[11–13] However, whether higher serum TNFR levels reflect renal or systemic receptor activation remains to be determined, and the precise role, if any, that TNFα signaling plays in the progression of nephropathy will require additional investigation.

These results, of course, are not the first to identify TNFα signaling in the pathogenesis of diabetic nephropathy or CKD in general. Indeed, studies published >20 years ago first implicated this pathway in experimental diabetic kidney disease,[12] and more recently, a number of reports demonstrate correlations between either TNFα or TNFR levels and worsening diabetic nephropathy.[9] TNFα signaling can induce

Published online ahead of print. Publication date available at www.jasn.org.

Correspondence: Dr. Frank C. Brosius, III, University of Michigan, 5520 MSRB2, 1150 W. Medical Center Drive, Ann Arbor, MI 48109-0680. Email: fbrosius@umich.edu

cellular damage, trigger apoptosis, and augment inflammatory responses, as well as activate a number of other processes that may play a role in the progression of nephropathy. Which of these processes, if any, was reflected by the higher circulating TNFR levels found in patients with the quite diverse degree of CKD (none through stage 4) at entry into the study is uncertain. Indeed, given the diversity of the subjects in both studies, it is quite remarkable that a single serum level had such a high predictive value for ultimate renal outcome.

The implication of these findings is that TNFR levels are quite stable in any individual throughout the course of both types of diabetes and therefore could serve as robust prognostic biomarkers for progression to ESRD. In addition, the presence of high or low-normal TNFR levels were independent of and additive to albuminuria in predicting outcomes, at least in type 2 diabetic patients. If these results are corroborated in other larger and longitudinal analyses of different diabetic populations (*i.e.*, those patients living outside of Massachusetts and treated in different centers), the presence of a high TNFR level in these patients could serve as a signal to nephrologists and primary practitioners to aggressively target therapies that retard progression.

It should be emphasized that observational studies, however well conducted, only provide the basis for associations and not causality. Adjustment for confounders with relatively small sample sizes can at best attenuate but not eliminate the possibility of residual confounding. Hill's criteria[14] confirming a causal pathway remain fulfilled only in part for TNFα signaling in diabetic nephropathy. Biologic plausibility, consistency of associations in different studies, and a suggestion of a dose response appear to be satisfied; however, the criteria of specificity and temporal relationship are still not fully met.

Moreover, because progression of diabetic nephropathy is multifactorial, a single biomarker, while significant and exciting in its potential, at best reflects the synergistic effect of a variety of insults or biologic pathways. Although the authors deserve credit for their choice of biomarkers and careful conduct of long-term follow-up of cohorts among both type 1 and type 2 diabetic subjects, it is yet uncertain whether these biomarkers will be efficacious in clinical practice. Nevertheless, the two articles in this issue should serve to stimulate more vigorous research to identify causal mechanisms and therapeutic agents likely to abrogate TNFα signaling pathways that potentially lead to progressive nephropathy.

Pentoxyfylline, which reduces TNFα levels and has antiproliferative and anti-inflammatory effects, shows early promise in this regard. Its efficacy is currently being investigated in a single-center randomized controlled trial.[15] Moreover, identification of links between TNFα signaling pathways and the renin–angiotensin aldosterone system, glycemic control, sodium intake, and BP regulation could also exist and should be investigated to enhance the efficacy of existing therapies. Finally, high-risk diabetic patients with elevated TNFR levels both with and without persistent albuminuria would be candidates for focused randomized controlled trials that assess precisely tailored new approaches to forestall progression of this devastating complication.

DISCLOSURES

None.

REFERENCES

1. System URD: *USRDS 2011 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States,* 2011 ed., Bethesda, MD, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2011.
2. Plantinga LC, Crews DC, Coresh J, Miller ER 3rd, Saran R, Yee J, Hedgeman E, Pavkov M, Eberhardt MS, Williams DE, Powe NR; CDC CKD Surveillance Team: Prevalence of chronic kidney disease in US adults with undiagnosed diabetes or prediabetes. *Clin J Am Soc Nephrol* 5: 673–682, 2010
3. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD; The Collaborative Study Group: The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. *N Engl J Med* 329: 1456–1462, 1993
4. Levey AS, Cattran D, Friedman A, Miller WG, Sedor J, Tuttle K, Kasiske B, Hostetter T: Proteinuria as a surrogate outcome in CKD: Report of a scientific workshop sponsored by the National Kidney Foundation and the US Food and Drug Administration. *Am J Kidney Dis* 54: 205–226, 2009
5. Perkins BA, Ficociello LH, Ostrander BE, Silva KH, Weinberg J, Warram JH, Krolewski AS: Microalbuminuria and the risk for early progressive renal function decline in type 1 diabetes. *J Am Soc Nephrol* 18: 1353–1361, 2007
6. Perkins BA, Ficociello LH, Roshan B, Warram JH, Krolewski AS: In patients with type 1 diabetes and new-onset microalbuminuria the development of advanced chronic kidney disease may not require progression to proteinuria. *Kidney Int* 77: 57–64, 2010
7. Soni SS, Gowrishankar S, Kishan AG, Raman A: Non diabetic renal disease in type 2 diabetes mellitus. *Nephrology (Carlton)* 11: 533–537, 2006
8. Haider DG, Peric S, Friedl A, Fuhrmann V, Wolzt M, Hörl WH, Soleiman A: Kidney biopsy in patients with diabetes mellitus. *Clin Nephrol* 76: 180–185, 2011
9. Gohda T, Niewczas MA, Ficociello LH, Walker WH, Skupien J, Rosetti F, Cullere X, Johnson AC, Crabtree G, Smiles AM, Mayadas TN, Warram JH, Krolewski AS: Circulating TNF receptors 1 and 2 predict stage 3 CKD in type 1 diabetes. *J Soc Am Nephrol* 23: 516–524, 2012
10. Niewczas MA, Gohda T, Skupien J, Smiles AM, Walker WH, Rosetti F, Cullere X, Eckfeldt JH, Doria A, Mayadas TN, Warram JH, Krolewski AS: Circulating TNF receptors 1 and 2 predict ESRD in type 2 diabetes. *J Soc Am Nephrol* 23: 507–515, 2012
11. Navarro-González JF, Mora-Fernández C, Muros de Fuentes M, García-Pérez J: Inflammatory molecules and pathways in the pathogenesis of diabetic nephropathy. *Nat Rev Nephrol* 7: 327–340, 2011
12. Hasegawa G, Nakano K, Sawada M, Uno K, Shibayama Y, Ienaga K, Kondo M: Possible role of tumor necrosis factor and interleukin-1 in the development of diabetic nephropathy. *Kidney Int* 40: 1007–1012, 1991
13. Niewczas MA, Ficociello LH, Johnson AC, Walker W, Rosolowsky ET, Roshan B, Warram JH, Krolewski AS: Serum concentrations of markers of TNFalpha and Fas-mediated pathways and renal function in nonproteinuric patients with type 1 diabetes. *Clin J Am Soc Nephrol* 4: 62–70, 2009
14. Hill AB: The environment and disease: Association or causation? *Proc R Soc Med* 58: 295–300, 1965
15. Navarro-González JF, Muros M, Mora-Fernández C, Herrera H, Meneses B, García J: Pentoxifylline for renoprotection in diabetic nephropathy: the PREDIAN study. Rationale and basal results. *J Diabetes Complications* 25: 314–319, 2011

See related articles, "Circulating TNF Receptors 1 and 2 Predict ESRD in Type 2 Diabetes" and "Circulating TNF Receptors 1 and 2 Predict Stage 3 CKD in Type 1 Diabetes," on pages 507–515 and 516–524, respectively.