Stacking the Deck for Drug Discovery in Diabetic Nephropathy: In Search of an Animal Model

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In the years after the introduction of life-saving insulin therapy for the treatment of diabetes, diabetic nephropathy emerged as a complication of chronic diabetes. Diabetic nephropathy has since metamorphosed from a clinical rarity to the single major cause of kidney failure in the industrialized world. Although tight glucose control and treatment of hypertension substantially delay the progression of diabetic nephropathy, the impact of these interventions will fail to stem the increased prevalence of renal failure projected over the next decade. Inhibition of angiotensin action with converting enzyme inhibition or receptor blockade confers added protection beyond treatment of hypertension and hyperglycemia, but only modestly slows the progression. Furthermore, after nearly 20 yr of use, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers remain the only clinically validated approach to treat specifically diabetic nephropathy. In part, this is because of the huge cost of clinical trials required to register new medicines for the treatment of chronic kidney disease (approximately $100,000,000 per trial). Because of the size and duration of these trials (typically 3 to 5 yr), not only have we few drugs to treat diabetic kidney disease, but also relatively few pivotal trials have been initiated for new drugs to treat kidney disease.

Taking the gamble on a new medicine to treat kidney disease relies now more than ever on its positive effect on a biomarker, typically albuminuria, obtained during multi-dose phase II safety trials, but the end point required for drug registration is doubling of serum creatinine, institution of dialysis, or death. In light of this, it is too much to ask for an animal model of diabetic kidney disease in which the impact of a molecule on renal insufficiency can be validated preclinically? Here exists a notorious disconnect, because most studies of mouse and rat models of diabetic nephropathy focus on albuminuria and histopathology, not renal insufficiency, as end points. Perhaps this is because rodent models of diabetic nephropathy that exhibit renal insufficiency have only recently been reported, and these models are validated only partially. Regardless of these reasons, effect of therapeutics on renal histopathologic changes is not one that can be used in a clinical trial. Conversely, whereas overt albuminuria may be predictive of a decline in renal function in human kidney disease, the same significance cannot be attributed to albuminuria in rodent models of kidney disease.

In this regard, Yuzawa et al., in this issue of JASN provide important evidence supporting the utility of a calmodulin transgenic FVB mouse model of diabetic nephropathy (called FVBOve26). As previously reported by Zheng et al., this model exhibits substantial and progressively increasing albuminuria as well as mesangial expansion, nodular glomerulosclerosis, and arteriolar hyalinosis. As in the previous report, the authors of this study also suggest this transgenic diabetic mouse exhibits a decline in renal function; however, analysis of the details of this assertion underscores the complexities of assessing renal function in diabetic mice. The authors unfortunately rely on an enzymatic measurement of serum creatinine to make their case. The measurement of serum creatinine in mice using either enzymatic methods or picric acid–based methods is complicated by the presence of substantial noncreatinine chromagens that contribute 50 to 500% of the measured serum creatinine compared with that determined using LC-MS/MS or HPLC methods. It is thus confusing to the authors of this study also suggest this transgenic diabetic mouse model exhibits substantial and progressively increasing albuminuria as well as mesangial expansion, nodular glomerulosclerosis, and arteriolar hyalinosis. As in the previous report, the authors of this study also suggest this transgenic diabetic mouse exhibits a decline in renal function; however, analysis of the details of this assertion underscores the complexities of assessing renal function in diabetic mice. The authors unfortunately rely on an enzymatic measurement of serum creatinine to make their case. The measurement of serum creatinine in mice using either enzymatic methods or picric acid–based methods is complicated by the presence of substantial noncreatinine chromagens that contribute 50 to 500% of the measured serum creatinine compared with that determined using LC-MS/MS or HPLC methods. It is thus confusing to the authors of this study also suggest this transgenic diabetic mouse model exhibits substantial and progressively increasing albuminuria as well as mesangial expansion, nodular glomerulosclerosis, and arteriolar hyalinosis. As in the previous report, the authors of this study also suggest this transgenic diabetic mouse exhibits a decline in renal function; however, analysis of the details of this assertion underscores the complexities of assessing renal function in diabetic mice. The authors unfortunately rely on an enzymatic measurement of serum creatinine to make their case. The measurement of serum creatinine in mice using either enzymatic methods or picric acid–based methods is complicated by the presence of substantial noncreatinine chromagens that contribute 50 to 500% of the measured serum creatinine compared with that determined using LC-MS/MS or HPLC methods. It is thus confusing
urine—approximately two times their body weight. This degree of polyuria is associated with the development of diabetic nephropathy in mice and, because of the profound dilution of the urine, significantly complicates the quantification of urine creatinine and albumin excretion.

Despite these and the aforementioned caveats, the FVBove26 transgenic mouse exhibits several features consistent with more advanced changes of diabetic nephropathy, including nodular glomerulosclerosis and profound albuminuria. Whether this model develops renal insufficiency and will allow testing of prospective therapies on progressive renal insufficiency remains to be seen. Certainly, effects of therapeutics allowing testing of prospective therapies on progressive renal injury. Whether this model develops renal insufficiency and will tent with more advanced changes of diabetic nephropathy, including nodular glomerulosclerosis and profound albuminuria. Whether this model develops renal insufficiency and will allow testing of prospective therapies on progressive renal insufficiency remains to be seen. Certainly, effects of therapeutics allowing testing of prospective therapies on progressive renal injury. Whether this model develops renal insufficiency and will tent with more advanced changes of diabetic nephropathy, including nodular glomerulosclerosis and profound albuminuria. Whether this model develops renal insufficiency and will allow testing of prospective therapies on progressive renal injury.

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DISCLOSURES

None.

REFERENCES


See related article, “Overexpression of Calmodulin in Pancreatic β Cells Induces Diabetic Nephropathy,” on pages 000–000.