Is Treatment of Nephropathy in Type 1 Diabetes Efficacious but Ineffective?

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Increased urinary protein excretion in patients with diabetes has long been known to predict increased mortality, and its absence is associated with near-normal life expectancy.1,2 Recent studies confirmed and extended these findings by illustrating the progressive increase in mortality by degree of albuminuria.3,4 The excess mortality is due primarily to ESRD5 and to cardiovascular disease,6 which share many risk factors. Differential expression of these risk factors within an individual may play an important role in determining which disease ultimately prevails.

Abundant observational data indicate that hyperglycemia and hypertension strongly predict the appearance and progression of albuminuria, and hyperlipidemia strongly predicts cardiovascular disease in those with elevated albuminuria, although its relationship with kidney disease is less clear. Together, these modifiable risk factors provided important therapeutic targets for a number of highly influential clinical trials that changed the management of diabetic kidney disease in recent years because of their demonstrated efficacy in slowing development or progression of kidney disease and in reducing the risk for cardiovascular disease in patients with diabetes and macroalbuminuria. Given the efficacy of these trials, their rapid incorporation into national guidelines, and generally widespread use by many healthcare providers, one might expect to see increased effectiveness of these therapeutic regimens in patients with type 1 diabetes and macroalbuminuria.

In this issue of JASN, two articles examine this expectation by evaluating adverse outcomes, namely pre-ESRD death and progression to ESRD in patients with type 1 diabetes and chronic kidney disease defined by macroalbuminuria. Forsblom et al.7 used an extension of the Cox proportional hazards analysis, a Fine and Gray analysis, to examine predictors for each of these outcomes in the FinnDiane study population while adjusting for the competing risk for the alternate outcome. By using this approach, they sought to avoid the confounding effect of the alternate outcome, which may be considerable when the incidence of the competing risk is high.

Progression to ESRD was by far the more common of the two outcomes, and the investigators found that of the modifiable risk factors, poor glycemic control increased the cumulative incidence of ESRD but was not associated with pre-ESRD mortality. Conversely, poor lipid control increased the cumulative incidence of both pre-ESRD death and progression to ESRD, suggesting that appropriate therapeutic targets for preventing or delaying each outcome may differ. Of note, despite aggressive treatment, 45% of the 592 patients who had type 1 diabetes and participated in this study progressed to ESRD or died before onset of ESRD during a median follow-up of just under 10 years. The authors expressed hope that the better treatment options and stricter therapeutic targets in recent years may have reduced the frequency of both outcomes during the study period, but they did not provide a secular trend analysis over the 10-year study period to confirm this hypothesis.

In a separate report in this issue of JASN, Rosolowsky et al.8 did find a secular trend in a similar cohort of patients with type 1 diabetes from the Joslin Clinic. They found a rate of ESRD that was virtually identical to that of the FinnDiane cohort and likewise observed that progression to ESRD was the predominant outcome among their patients with type 1 diabetes and macroalbuminuria. In their trend analysis, they found no significant decline in the rate of progression to ESRD over the past 20 years despite widespread adoption of renoprotective drugs during the same period accompanied by significant improvements in BP and total serum cholesterol concentration.

Although these results are disappointing, they are not universal. The Joslin Clinic investigators noted that investigators at the Steno Memorial Hospital in Denmark reported a diminishing risk for ESRD over time in a similar group of patients with type 1 diabetes.9,10 The factors responsible for this disparity are uncertain, although the pre-ESRD mortality in the Steno cohort was much higher than in the other two cohorts.

National data from the US Renal Data System, which include patients with either type 1 or type 2 diabetes regardless of the level of urinary albumin excretion, also suggested wide variations in secular trends of diabetic ESRD by age and ethnicity.11 In white patients aged 30 to 39 years, for

See related article, “Virological Synapses Allow HIV-1 Uptake and Gene Expression in Renal Tubular Epithelial Cells,” on pages 496–507.
example, the gender-adjusted incidence rate of ESRD declined by 7% between 2000 and 2008, whereas it increased by 2% in those aged 50 to 59 years. In black patients, by contrast, the incidence rate of ESRD, which is approximately fourfold higher than in white patients, increased by 65% in those aged 30 to 39 years and declined by 13% in those aged 50 to 59 years. Perhaps most troubling in the US Renal Data System report is the finding that incident ESRD as a result of diabetes has generally increased among younger minority patients, as illustrated by the remarkable increase among the younger black patients noted here, whereas it has been generally stable or declining in older populations and among white patients. A shift toward a younger age at onset of type 2 diabetes, particularly among some minority populations, may be partly responsible for this increase, as illustrated by the Pima Indians. Whereas the incidence of diabetic ESRD in Pima Indians aged ≥45 years declined after 1990, those who were younger than 45 years experienced no such decline. The lack of decline in the younger Pima Indians associates with a lower percentage use of renin-angiotensin system inhibitors than in older patients. Women of childbearing age were least likely to receive these inhibitors, presumably because of concerns about their use in pregnancy.

In epidemiologic parlance, *efficacy* refers to the effect of a given treatment in a controlled environment where the extraneous effects of other factors are eliminated from consideration through randomization, and *effectiveness* refers to the effect of the same treatment in a population in which no such conditions exist. The studies by Forsblom et al. and Rosolowsky et al. raise important questions about the effectiveness of efficacious treatments in patients with type 1 diabetes and macroalbuminuria. Which factors determine whether efficacious treatments will be clinically effective? Do improvements in general clinical management often found in the resource-intensive environment of a clinical trial enhance the efficacy of the study treatment beyond what can be reasonably expected in clinical practice? Do the high rates of progression to ESRD in these cohorts truly reflect a lack of effectiveness, or would the rates of ESRD have been even higher if newer treatments had not been used? What roles do age, ethnicity, type of diabetes, and stage of disease play in determining effectiveness of an intervention?

Several types of investigations will be required to address the therapeutic challenges identified by these provocative studies. Forsblom et al. proposed that we may need to refine our therapeutic targets by defining more precisely the determinants of competing risks. This approach may ultimately enhance therapeutic effectiveness through better targeting of existing therapies. Rosolowsky et al. argued that new therapies targeted toward other causal pathways are needed. A careful examination of the process of health care delivery may also identify points in translation where corrective steps can be taken to enhance therapeutic effectiveness. Certainly, there was much room for further improvement of glycemia, lipid levels, and BP control in both of these study cohorts. Ultimately, the difference between efficacy and effectiveness is determined by clinical practice, which is fundamentally about individualizing treatments and depends on many factors that are outside the control of clinicians.

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DISCLOSURES

None.

REFERENCES

12. Pavkov ME, Bennett PH, Knowler WC, Krakoff J, Sievers ML, Nelson RG: Effect of youth-onset type 2 diabetes mellitus on incidence of


See related articles, “Competing-Risk Analysis of ESRD and Death among Patients with Type 1 Diabetes and Macroalbuminuria,” on pages 537–544 and “Risk for ESRD in Type 1 Diabetes Remains High Despite Renoprotection,” on pages 545–553.

Are Cubilin (CUBN) Variants at the Heart of Urinary Albumin Excretion?

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In this issue of JASN, Böger et al.1 report the results of a meta-analysis from approximately 63,000 individuals of European ancestry with genotype information identifying a susceptibility locus for the quantitative trait known as urinary albumin-to-creatinine ratio (UACR) and the clinical diagnosis microalbuminuria. A single variant within a protein-coding exon of CUBN, which encodes the proximal tubular epithelial cell apical protein, cubilin, reached genome-wide significance. The association of a cubilin variant with UACR and microalbuminuria resonates with existing knowledge about cubilin function from genetic, experimental animal, and in vitro studies.

CUBN mutations have been identified in patients with Imerslund-Gräsbeck syndrome (IGS).2 This rare autosomal recessive disease is characterized by megaloblastic anemia and a variable degree of proteinuria. Cubilin was first identified as the intrinsic factor-cobalamin (IF-Cbl) receptor in the ileal mucosa and kidney of the rat,3 and the IGS mutation identified as the intrinsic factor-cobalamin (IF-Cbl) receptor in the ileal mucosa and kidney of the rat,3 and the IGS mutation is roughly equivalent to 200 mg/d in humans.3 The quantity of albumin filtered through the normal glomerulus is a contentious issue9,10; however, under normal conditions, filtered albumin is efficiently reabsorbed in the proximal tubule.11

Filtered albumin binds to an amino terminal domain of cubilin. Megalin directly interacts with two noncontiguous sites of the cubilin protein,12 and the megalin-cubilin-albumin complex is endocytosed by the cell. Megalin and cubilin are recycled to the apical membrane, and albumin is delivered to the lysosomal compartment.13 These data demonstrate that CUBN mutations do result in impairments of proximal tubular albumin reabsorption but not nephrotic-range proteinuria and are consistent with the study by Böger et al.,1 in which the degree of albuminuria is very modest.

The variant identified in this report1 results in the conservative, nonsynonymous amino acid substitution I2984V. This residue falls within a protein domain previously reported to participate in the megalin—cubilin protein interaction.11 The identification of a coding variant within a functional protein domain suggests that the associated variant is causing increased albumin excretion. The cubilin protein, encoded by the variant gene, may be unable to bind megalin, a required event for normal endocytosis of albumin. However, the conservative nature of the substitution and the fact that bioinformatic algorithms predict the change to be benign with respect to function require this hypothesis to be experimentally proved. Further work will be needed to determine whether a variant cubilin with an I2984V substitution increases albuminuria.

The CUBN single-nucleotide polymorphism reported by Böger et al.1 accounts for only 0.15% of the variance in UACR, but because this variant is common, it would account for a large population-attributable risk for albuminuria. Regardless of whether the associated variant contributes to abnormal albumin excretion, its identification points to some interesting possibilities from a genetic perspective. First, if it is causal but has only a minor contribution to the variance in albuminuria, then CUBN should be scanned for rare variants not genotyped on current platforms that may have larger effects. Second, if it is not causal, then it must be viewed as a positional marker of a genomic region harboring the causal variant. The true causal variant may not have been identified because it was not genotyped in this study but lies in close proximity to the sentinel

CUBN mutations have identified mutations in AMN5 that encodes a protein, amnionless, which is required for the localization of cubilin to the apical surface of epithelial cells.6 Taken together, these studies identify a molecular pathway to explain the IGS phenotype. Megaloblastic anemia in patients with IGS results from defects in the intestinal absorption of IF-Cbl. The variable degree of proteinuria, averaging 750 mg/d, in these patients is related to cubilin’s role in the proximal tubular reabsorption of albumin.7 Megalin models of Cubn deletion demonstrate a sixfold increase in urinary albumin excretion, a degree of albuminuria that is roughly equivalent to 200 mg/d in humans.8 The quantity of albumin filtered through the normal glomerulus is a contentious issue9,10; however, under normal conditions, filtered albumin is efficiently reabsorbed in the proximal tubule.11

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