Frontiers in Diabetic Nephropathy: Can We Predict Who Will Get Sick?

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O
er my practice lifetime, a subtle but persistent change has occurred in the profile of diseases that afflict patients. We no longer are faced with saving patients from acute, catastrophic illness but rather must palliate chronic disease. While the change in life expectancy for patients with AIDS most clearly documents this shift in illness acuity, a walk through the medical floors of any hospital illustrates that most patients suffer from chronic, debilitating, but preventable conditions. Data from the Centers for Disease Control document that chronic disease is onerous (http://www.cdc.gov/nccdphp/overview.htm). Seven of every 10 Americans who die each year, or more than 1.7 million people, die of a chronic disease. More than 90 million Americans live with chronic illnesses. Chronic diseases account for 70% of all deaths in the United States. The medical care costs of people with chronic diseases account for more than 75% of the nation’s $1.4 trillion medical care costs.

Diabetes is the fifth leading cause of death according to the Centers for Disease Control data, and kidney disease is the ninth. For nephrologists, diabetic nephropathy is the intersection of these broad categories and the most obvious and compelling manifestation of the chronic disease epidemic. As is well known to the readership, diabetic nephropathy is the leading cause of progressive kidney disease and ESRD (Incidence and Prevalence, Renal Data Service [1]). Patients with diabetic ESRD now account for 53% of incident patients, up from 28% in 1980 and comprise 45% of the prevalent ESRD population, up from 18% in 1980.

On average, approximately 30% of diabetics will develop nephropathy. This observation raises the fundamentally important question: “Can we identify who will get sick?” (and perhaps, “Who will stay well?”). Why is this issue important? We have identified a number of strategies that will slow progression of diabetic nephropathy, including assiduous BP (2,3) and glucose control (4–6), and the use of drugs that block the actions of angiotensin II (7,8). Implementation of these strategies remains suboptimal despite widespread educational efforts for physicians and patients. For example, in an analysis of medical records of 15,768 visits to 12 general internal medicine clinics, BP was controlled using criteria from the 6th Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI) in only 36% of visits, and diabetic patients were significantly less likely than patients without diabetes to have their BP controlled to the JNC VI recommended level (9). After conclusion of the Diabetes Complication and Control Trial, glucose control worsened in subjects who had been enrolled in the intensively-treated cohort despite the demonstrated benefit of optimal blood glucose levels on diabetic microvascular complications (6). The discrepancies between excellent outcomes achieved in rigorous clinical trials and the results demonstrated in clinical practice suggests a failure in translation of the lessons we have learned; this is an area of intense interest for investigators focused on diabetes (10,11) and other chronic diseases. The nihilists among us suggest that community implementation of clinical trial protocols is impractical, or maybe even impossible. I would maintain that there is a critical need to devise strategies that accomplish this goal, including identifying patients at highest risk for developing chronic disease, such as diabetic nephropathy, for preventive and intensive interventions. The patients at highest risk for diabetic nephropathy may need to be in care delivery systems that have a clinical trial infrastructure, which educate patients and promote compliance with the treatment strategies known to be effective. Although the costs associated with realization of more effective health care delivery systems may be considerable, the substantial human and economic costs imposed by diabetic nephropathy on patients, their families, and health care systems should be reduced with a net economic (and human) benefit. Formal cost-effective analysis will be needed to prove this hypothesis (12).
the shredding of the health care safety net (13), I believe that focusing on prevention of diabetic nephropathy in diabetic patients at greatest risk makes clear sense from both a patient care and health economic perspective.

This premise returns us to the rationale for this Frontiers in Nephrology series on diabetic nephropathy, i.e., identifying demographic, clinical, and laboratory-based tools for discovery of biomarkers that can be used to identify patients at greatest risk for developing diabetic nephropathy and for identification of new targets for diabetic nephropathy treatment. Albumin excretion rate (AER) has been the mainstay for early detection of diabetic nephropathy (14). In the first article, Luiza Caramori, Paola Fiorotto, and Michael Mauer review the data on the predictive value of AER for diabetic nephropathy risk and make a persuasive case that, although AER is important, gains in its predictive precision can be made by considering readily available clinical and laboratory data, including family history, smoking habits, lipid levels, and retinopathy status (15). As is well known to the readers of JASN, studies from Mauer’s laboratory have made many seminal observations describing the epidemiology and pathogenesis of diabetic nephropathy using well-characterized cohorts of diabetic patients. In the second article, Stephen Rich, a leader in the search for diabetes pathogenesis genes, reviews the current knowledge of the genetic basis of diabetes and its complications and discusses how this information may be used to identify diabetic patients at risk for nephropathy (16). Clustering of diabetic nephropathy in families has been convincingly demonstrated in several studies (17,18). Both heritability and segregation analyses suggest of diabetic nephropathy phenotypes suggest its pathogenesis is in part genetically regulated (19–21). In the third article, Katalin Susztak and Erwin Böttinger review data generated from genome-wide expression analyses at the mRNA and protein levels. These data have identified novel molecule markers and new targets for prevention of diabetic nephropathy (22). Böttinger’s laboratory has carefully and creatively analyzed global changes in gene expression in several animal models of diabetic nephropathy using microarrays (23,24). The goal of both genetic and genome-wide expression analyses is to better define mechanisms of diabetic nephropathy pathogenesis. Although diabetic nephropathy is not commonly considered an inflammatory disease, the final review in this Frontiers series by Elena Galkina and Klaus Ley focuses on the growing body of evidence implicating inflammatory cells in diabetic kidney injury (25). These data suggests that inhibiting T cell and macrophage trafficking within the kidney may be a reasonable approach for treating diabetic nephropathy.

How can we use the approaches discussed in these reviews to answer the following question: Which diabetic patients will develop nephropathy? This question encompasses a need to identify both diabetic nephropathy pathogenesis genes and modifier genes, which prevent or moderate diabetic nephropathy. Nadeau has postulated the existence of modifier genes that mute expression of deleterious mutations and identify alternative targets for therapy (26). The techniques discussed in isolation in each article comprising this Frontiers series need to be integrated in a systems biology approach to accomplish these important goals. For example, gene expression data has been combined with qualitative trait loci maps of clinical phenotypes to identify regulatory pathways responsible for complex traits. Although this approach has not yet been applied to kidney diseases, it has been used to identify genes regulating other chronic diseases such as obesity and hypertension in animal models, which merit testing using human datasets (27–30). The nephrology community is well positioned to implement such strategies. Three major collections of human samples, which will include phenotypic and genotypic data, have been assembled: Family Investigation of Nephropathy and Diabetes (FIND; http://www.niddk.nih.gov/patient/find/find.htm) (31), the Epidemiology of Diabetes Interventions and Complications Study (EDIC; http://www.niddk.nih.gov/patient/edic/edic-public.htm) (32), and Genetics of Kidneys in Diabetes Study (GoKinD; http://www.gokind.org/access/home.html). Of course, comparative genetic and genomic analyses require animal models that faithfully reproduce the human phenotype. The National Institute of Diabetes and Digestive and Kidney Diseases–supported Animal Model of Diabetic Complications Consortium (http://www.amdcc.org/) has made considerable progress in defining the best models for diabetic nephropathy (33,34). Development of animal models for diabetic nephropathy will permit study of new candidate pathogenic pathways, which will also require use of in vitro techniques to test their mechanistic significance.

The scientific rationale for and benefits from an integrative approach, which elucidates the complex network of gene interactions underlying complex traits such as diabetic nephropathy, are clear. The potential for combining demographic, clinical, and gene and protein expression phenotypes with genotypes to develop strategies for improving patient outcomes and for optimizing health care delivery is exciting. I believe we need to target diabetic patients at greatest risk for vascular complications for preventive and intensive therapy. The National Kidney Disease Education Project (http://www.nkdep.nih.gov) has implemented a community-based strategy to educate individuals at highest risk for development of kidney disease and can serve as a foundation for translating new therapeutic gains in management of diabetic nephropathy into the clinic and the community. The success of the African-American Study of Kidney Disease and Hypertension (AASK) and Modification in Diet in Renal Disease (MDRD) studies in achieving aggressive target BP goals proves that patients will comply with intensive treatment strategies in appropriate treatment settings. However, health delivery resources are limited. Focusing our resources in a scientifically sound manner on those at greatest risk for diabetic kidney disease will benefit our patients and be cost-effective. The research discussed in this Frontiers series will generate the tools to address this need.

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References
