Still a big black hole

Diabetic renal disease is still an extremely important and common complication in both type 1 and type 2 diabetic patients. Every clinician and nephrologist knows that diabetic patients constitute a large proportion of clientele in the dialysis unit, perhaps ~50% or more, particularly in the U.S. and Japan. The figure is increasing for type 2 diabetes, whereas, encouragingly, a declining number is seen in type 1 diabetes, at least in Scandinavia. The cumulative incidence of proteinuria was previously estimated to be ~40%, but it is less now, at least in type 1 diabetes, but figures vary from one country to another.

Increased basement membrane thickness and mesangial expansion are hallmarks of glomerulopathy, but on the molecular level the exact renal locus or loci as well as detailed mechanisms for development of diabetic renal disease remain unclear, whereas it is well established that the major risk factors for development of nephropathy are poor glycemic control and elevated blood pressure. In particular, the two in combination, the so-called “double jeopardy,” is critical (1), but the concept of a dual jeopardy may have led to some confusion.

Some patients who have poor glycemic control escape nephropathy, but such patients seem to have low blood pressure in long-term follow-up studies, also supporting the concept of dual jeopardy (2). A single risk factor like hyperglycemia may thus not always be sufficient to provoke clinical nephropathy. The cumulative absence of nephropathy in 60–80% of patients (probably more now than 10–20 years ago) who were poorly controlled is an enigmatic phenomenon. As a consequence, some investigators believe that nephropathy predominantly is genetically determined (3,4), and considerable effort is and has been invested in clarifying potential genetic markers, both for those with nephropathy and those who escape the complication using both candidate gene and whole genome approach.

Protective genetic mechanisms may indeed also operate, but still a single “destructive” factor may not be sufficient to provoke severe organ damage. This may be a general “protective” biological phenomenon for survival. Importantly, a multitude of antihypertensive and antihyperglycemic intervention studies have confirmed the concept of dual jeopardy. Rapid progressors of “fast-track” diabetic nephropathy show all of the typical phenotype risk factors (3).

Some positive results were obtained using the distribution of the insertion deletion (I/D) polymorphisms of the ACE gene, but unfortunately initial promising results (4) were not confirmed (5,6). The genetic component may be investigated in prevalence and incidence studies; however, in prevalence studies in particular there are biases. Very long-term incidence studies are still not available. In experimental biopsy-based morphometric studies, a huge overlap between I/D groups is seen (7), making any borderline statistical significance of uncertain value, especially from the clinical viewpoint.

Another important methodological approach is to investigate the rate of progression according to genotype. This concept has been used in diabetic as well as nondiabetic renal disease and initially some interesting positive results were obtained (8), but again, these were not confirmed in subsequent and rather similar follow-up studies (9).

Thus, Andersen and coworkers (9,10) from the Steno Diabetes Center undertook an important study with type 1 diabetic patients who were treated with an angiotensin receptor blocker. Interestingly, the rate of decline in glomerular filtration rate (GFR) was very similar regardless of ACE genotypes in carefully matched patients. The decrease in rate for GFR was ~3 ml·min⁻¹·year⁻¹, which is much less than my original findings of a rate of decline in GFR of 10 ml·min⁻¹·year⁻¹ in typical proteinuric patients. Obviously, albuminuria and blood pressure level were reduced by the treatment but with no difference between the groups. If a 40 year-old patient starts out with a GFR of 150 ml/min (typical hyperfiltration), it may last >40 years before end-stage renal disease evolves.

Thus, again we have a situation that is not unusual—initial interesting and positive results that cannot be confirmed in subsequent larger and perhaps more carefully planned and performed studies. The initial “effect” studies of genes are followed by “lack-of-effect” studies (11,12) or vice versa from two major genetic centers.

The conclusion today from a clinical point of view is pretty clear; all patients with poor metabolic control and high blood pressure are at risk of progressing to diabetic renal disease, in particular if both risk factors are present. Any genetic risk or protection (and obviously also any value of screening) is uncertain. Therefore, major efforts should be exercised to minimize modifiable risk factors, tasks that are indeed clinically feasible; blood pressure in particular can be reduced very efficiently (1,9).

We are dealing with a long and possibly never-ending story. Years ago, it was widely believed, especially in parts of the U.S., that diabetic renal disease and complications in general were mainly genetically determined and therefore there was no imperative reason to carefully control risk factors because patients would develop renal disease anyway. Siperstein et al. (13) was a proponent for the genetic standpoint, a concept that was later disputed (14) and in my view finally to a large extent refuted. In fact, because of the genetic view, it was opposition against conducting the Diabetes Control and Complications Trial (DCCT) study despite the fact that early studies (1952) from the Joslin Clinic by a visiting Danish researcher and his Joslin colleagues supported the metabolic hypotheses (15). Pi-rart (16) in Europe clearly confirmed the association to poor metabolic control.

However, more work needs to be done in the genetic area, especially regarding the combination of genotypes...
and gene interaction that could be an important factor in provoking renal disease. Single gene contribution is clearly limited (17). A literature search on “genetics and diabetic nephropathy” over the last 5 years unveils >100 studies per year and reveals that a multitude of genes has been proposed. Even larger studies are now being undertaken, but they will probably not shake the concept of the important role of glycemia and blood pressure elevation, including borderline blood pressure elevation. However, as the authors conclude (9), “suggestions of selective renoprotective therapy for different genotypes require further prospective studies, ideally a randomized prospective comparison of ACE inhibition and AT1 receptor blockade in II and DD patients.” But who will or can do such studies?

Interestingly, it seems possible to perform incidence-based genetic studies based on the U.K. Prospective Diabetes Study (UKPDS) study (type 2 diabetes) as well as the large DCCT study (type 1 diabetes), but so far no data seem to be available. At least, a literature search provides no such publications. However, by dual intervention strategy, the UKPDS clearly confirmed the double jeopardy concept (1) and the DCCT the metabolic concept. The same idea was suggested among The Pima Indians in Arizona versus northwestern Mexico (18). The Pima Indians seem to have an extraordinary (genetic?) susceptibility to renal disease and diabetics not seen in Mexico, but the majority of the U.S. Pima population is extremely overweight, in contrast to the Mexican population. Further genetic studies are also awaited here.

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References


