Diagnosis and treatment of early renal disease in patients with type 2 diabetes mellitus: what are the clinical needs?

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ABSTRACT

Renal disease is prevalent in patients with diabetes mellitus type 2. Aggressive metabolic control and lowering of systemic and/or intraglomerular blood pressure are effective interventions but not without side effects. Thus a better, early identification of patients at risk for incidence or progression to end-stage renal failure by the use of new, validated biomarkers is highly desirable. In the majority of patients, hypertension and hyperglycaemia are pathogenetically important pathways for the progression of renal disease. Nonetheless even aggressive therapy targeting these factors does not eliminate the risk of end-stage renal failure and experimental evidence suggests that many other pathways (e.g. tubulointerstitial hypoxia or inflammation etc.) also contribute. As their individual importance might vary from patient to patient, interventions which interfere are likely not to be therapeutically effective in all subjects. In this situation, an option to preserve the statistical power of clinical trials is to rely on biomarkers that reflect individual pathophysiology. In current clinical practice, albuminuria is the biomarker that has been best evaluated to guide stratified/personalized therapy but there is a clear need to expand our diagnostic abilities.

Keywords: diabetes mellitus type 2, innovative trial design, predictive biomarker, prognostic biomarker, renal disease

INTRODUCTION

Type 2 diabetes mellitus affects ~8% of adults worldwide and recent data for the USA estimate the lifetime risk to be diagnosed with diabetes to be close to 40% [1] (http://www.cdc.gov/Diabetes/data/statistics). It is expected that approximately one-third of all patients will develop chronic kidney disease (CKD) but unfortunately our current ability to identify those at highest risk before urinary albumin excretion increases and/or glomerular filtration rate declines is limited. As effective therapies for primary prevention of CKD in diabetic subjects are available (like ‘optimization’ of metabolic control) one could argue that consequently the clinical approach to be taken is simply to implement these more stringently on a general basis. During the Epidemiology of Diabetes Interventions and Complications (EDIC) observational trial, which followed the interventional Diabetes Control and Complications Trial (DCCT) study it became evident that in patients with type 1 diabetes mellitus and preserved glomerular filtration rate and mostly normoalbuminuria at baseline, intensified glucose-lowering therapy reduces late renal end points. However, the risk of severe hypoglycaemia was increased as well [2]. Very similar beneficial effects of intensified diabetes therapy on renal function have been obtained during the long-term observational period following the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) study [3] in a type 2 diabetes population. Interestingly, the intervention was most effective to prevent incident and progressive renal disease in individuals with normoalbuminuria and/or maintained eGFR values at baseline. Unfortunately, in type 2 diabetes mellitus intensive glucose-lowering therapy is also associated with side effects, especially in the presence of mild-to-moderate CKD. Papademetriou et al. studied 6506 participants of the Action to Control Cardiovascular
Risk in Diabetes (ACCORD) trial [4] without CKD and 3636 with CKD at baseline. The risk of all-cause and cardiovascular mortality was 87% higher in patients with CKD than in those without CKD. In patients with CKD, intensive glucose-lowering therapy increased all-cause and cardiovascular mortality by 31 and 41%, respectively, when compared with standard treatment. Thus, timely selection of the subgroup of patients at highest risk for incident or progressive CKD before an intervention is mandatory in order to improve the risk–benefit ratio.

**PROGNOSTIC BIOMARKERS FOR INCIDENCE AND PROGRESSION OF CKD IN PATIENTS WITH DIABETES MELLITUS**

Many studies on biomarkers predicting onset or progression of nephropathy in patients with type 2 diabetes mellitus have been published recently. These markers cover various aspects of pathophysiology including oxidative stress, inflammation, fibrosis and tubular or glomerular injury as summarized in [5]. In a systematic review, Hellemons et al. [6] graded the methodological quality of these studies using Standard for Reporting of Diagnostic Accuracy criteria and also determined whether the biomarkers reported had a predictive value beyond conventional risk factors. Fifteen studies describing 27 biomarkers were identified but only 6 publications on 13 markers had sufficient methodological quality. Of these, serum interleukin 18, plasma asymmetric dimethylarginine, and urinary ceruloplasmin, immunoglobulin G and transferrin predicted onset, while plasma asymmetric dimethylarginine, vascular cell adhesion molecule 1, interleukin 6, von Willebrand factor and intercellular cell adhesion molecule 1 predicted progression of nephropathy. Plasma high-sensitivity C-reactive protein, E-selectin, tissue-type plasminogen activator, von Willebrand factor and triglycerides were considered valid markers for both onset and progression of diabetic nephropathy. However, the authors advocated that a more rigorous evaluation of all of these biomarkers and validation in larger studies is needed [6]. Fortunately, in the area of primary prevention, better tested biomarkers are becoming clinically available. Zürbig et al. [7] applied capillary electrophoresis-coupled mass spectrometry to profile the low-molecular weight proteome in urine in a longitudinal cohort of types 1 and 2 diabetic patients. In normoalbuminuric subjects, a biomarker classifier (CKD 273) predicted the progression to macroalbuminuria during the next 5 years with an area under the receiving operating characteristics curve (AUC) of 0.93, which was significantly better than baseline urinary albumin excretion (AUC = 0.67) [7]. These results were later confirmed by Roscioni et al. [8]. In the currently ongoing Proteomic prediction and Renin angiotensin aldosterone system Inhibition prevention Of early Diabetic Nephropathy in TYPe 2 diabetic patients with normoalbuminuria (PRIORITY) trial [9], the potential of this classifier to predict the progression of albuminuria is being prospectively validated in a representative cohort of more than 3200 type 2 diabetic patients with normal urinary albumin excretion at baseline. In addition, this study aims to demonstrate that early initiation of intensified preventive therapy with addition of spironolactone on top of conventional renin angiotensin system (RAS) inhibitor therapy directed by urinary proteomics reduces progression of albuminuria (see Figure 1). MicroRNAs (miRNAs), a class of small non-protein-coding RNAs, regulate gene expression via suppression of target mRNAs and are an additional class of biomarkers that could improve our prognostic capacities. miRNAs...

![Design of the PRIORITY trial.](http://ndt.oxfordjournals.org/)
are present in body fluids in a remarkably stable form as packaged in microvesicles of endocytic origin, named exosomes. Barurtta et al. [10] assessed miRNA expression in urinary exosomes from type 1 diabetic patients with and without incipient diabetic nephropathy. Results showed that miR-130a and miR-145 were enriched, while miR-155 and miR-424 were reduced in urinary exosomes from patients with microalbuminuria. Similarly, in an animal model of early experimental diabetic nephropathy, urinary exosomal miR-145 levels were increased and this was paralleled by miR-145 overexpression within the glomeruli [10].

Even though large numbers of potentially promising biomarkers have been described, they are generally not (yet) implemented in clinical practice. Mischak et al. [11] investigated additional reasons for this shortcoming, focusing on hurdles downstream of biomarker verification. They concluded that next to methodological issues, successful biomarker discovery and qualification alone does not suffice for clinical implementation. Additional challenges include insufficient funding, the often unmet need to validate new biomarker utility in interventional trials, and large communication gaps between the parties involved in implementation. To address these problems, the authors proposed an implementation roadmap, which involves a wide variety of stakeholders (clinicians, statisticians, health economists, and representatives of patient groups, health insurance, pharmaceutical companies, biobanks and regulatory agencies) and concluded that this approach may avoid unwarranted delays or failure to implement potentially useful biomarkers, and may expedite meaningful contributions of the biomarker community to healthcare ([11], see also Figure 2).

**NEW THERAPIES, REASONABLE TRIAL DESIGN AND STRATIFIED MEDICINE**

Blockade of the RAS reduces the incidence of renal events in patients with and without diabetes mellitus [12–14]. In a prospective randomized study, more than 1700 hypertensive patients with type 2 diabetes mellitus and nephropathy were treated with irbesartan, amlodipine or placebo [15]. Angiotensin receptor blockade reduced the incidence of doubling of baseline serum creatinine concentration, development of ESRD or death from any cause during a follow-up period of 2.6 years by 20% when compared with the placebo and 23% when compared with amiodipine therapy. Nevertheless, even under irbesartan therapy 50% of patients reached the primary end point after 54 months. In an effort to increase the efficacy of RAS antagonistic therapy, an angiotensin receptor blocker was combined with placebo or the ACE inhibitor lisinopril in a study by Fried et al. [16]. However, the combination therapy did not reduce the incidence of a combined renal end point (decline in estimated glomerular filtration rate or eGFR of >30 mL/min/1.73 m² in case the initial eGFR was >60 mL/min/1.73 m² or a decline of more than 50% in those with lower baseline eGFR values, end-stage renal disease or death). Quite the contrary, an increased risk of side effects such as hyperkalaemia and acute kidney injury was observed confirming other reports questioning the safety of ACE inhibitors and ARBs in combination or of the alternative approach to increased blockade of the RAS by combining direct renin inhibition with ACEi or ARB [17–19]. Thus, whereas blocking RAS has been the most successful treatment in established diabetic renal disease, more aggressive blockade of the system has not proved efficacious and even increased adverse events, and new strategies, targeting other pathways are urgently needed.

Irrespective of these issues regarding safety, these trials also show that even if we intervene with pathways supposed to be activated in almost every patient such as the diabetic milieu or systemic and/or intraglomerular hypertension, the response to pharmacological intervention is heterogeneous and far from complete. One possible explanation for this finding might be that the pathophysiology of CKD in patients with diabetes is complex, multifactorial and has interindividual variability in the sense that various mixtures of relevant pathways are activated in subgroups of patients.

Inflammation and oxidative stress are associated with the progression of tubulointerstitial fibrosis, which per se again is...
a multifactorial process predicting adverse outcomes in CKD independent of glomerular damage although a dynamic interaction between these two is likely [20]. Bardoxolone, a nuclear factor-erythroid-2-related factor 2 activator with anti-oxidative capacity is supposed to act on certain aspects of tubulointerstitial damage, and in a pilot study the drug increased eGFR in patients with advanced diabetic renal disease [21]. The subsequent large prospective controlled randomized trial with hard endpoints recruited patients based on the level of albuminuria and eGFR [22]. Both biomarkers are mostly indicators of glomerular function and thus they can be classified as prognostic only in the context of this study, not reflecting the relevance of tubulointerstitial pathology in the recruited population. Irrespective of the fact that the trial had to be stopped because of severe cardiovascular side effects it’s design pinpoints a crucial problem of extreme relevance for future clinical trials in nephrology. In a complex, multifactorial process like diabetic renal disease we have to improve our ability to correctly sub-classify our patient population based on (most likely a panel of) biomarkers that reflect pathophysiology rather than prognosis especially when we move from ‘universally acting’ treatment approaches to therapy that targets more specific pathways (see Table 1).

Before becoming part of clinical routine, interventions have to demonstrate their efficacy and safety in randomized controlled trials (RCTs). However, the interpretation of the results of an RCT assumes homogeneity of the population included. Especially trials (RCTs). However, the interpretation of the results of an RCT assumes homogeneity of the population included. Especially in CKD with a complex pathophysiology and comorbidity RCTs with broad inclusion criteria. Advanced glycation endproduct cross link breakers [28] Pyridoxamine [29] Growth hormone inhibition (Tarnow, personal communication) Benfothiamine [30] Pentoxifylline (MCPI inhibition?) [31, 32] Thioridinediones [33] Endothelin antagonist [34, 35] Connective tissue growth factor inhibition [36] Pirfenidone [37] Tested in experimental models Tissue transglutaminase inhibition [38] Monocyte chemoattractant CC chemokin ligand 2 (MCPI) [39] Uric acid lowering (allopurinol) [40] Nox 1/4 inhibition [41]

*Most of the studies are preliminary dealing with small numbers of patients and surrogate end points.

Then randomizing the groups separately is another approach which, at least from a statistical point of view, is probably preferable to post hoc analysis [42]. An enrichment strategy is currently tested in the Study of Diabetic Nephropathy with Atrasentan (SONAR) study (http://clinicaltrials.gov/ct2/show/ NCT01858532). Patients with diabetes mellitus type 2 and CKD receive the endothelin receptor antagonist atrasentan, and those who experience a reduction in urinary protein excretion during a run-in phase are randomized to active therapy or placebo. Study design planning in this setting is complicated if the statistical distribution of drug response is unknown, or drug response on the intermediate surrogate is a continuous variable because cut-off levels need to be defined eventually without solid evidence. Additionally, as mentioned above, the value of proteinuria reduction as a major or sole predictive biomarker is questionable. In the study by Fried et al. [16], for example, no benefit was obtained by combined RAS-blocking treatment when compared with monotherapy as far as hard end points like a drop in GFR, incidence of ESRD or mortality is concerned despite a superior antiproteinuric efficacy.

In summary, next to the fact that we need better ‘pathophysiology-based’ and hence predictive biomarkers with respect to particular therapy we also have to recognize that in CKD multiple processes are activated (damaging as well as protective). An a priori stratification of patients based on an appropriately chosen biomarker panel that reflects the pathophysiology of a given patient (group) with subsequent tailored treatment may be a better approach than simply large RCTs with broad inclusion criteria.

Table 1. Potential new treatment modalities for diabetic nephropathy

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<tr>
<th>Tested in humans</th>
<th>Tested in experimental models</th>
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<tr>
<td>Vitamin D receptor stimulation [23, 24]</td>
<td>Tissue transglutaminase inhibition [38]</td>
</tr>
<tr>
<td>Tranilast and analogues [25, 26]</td>
<td>Monocyte chemoattractant CC chemokin ligand 2 (MCPI) [39]</td>
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<tr>
<td>Protein kinase C inhibition [27]</td>
<td>Uric acid lowering (allopurinol) [40]</td>
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<tr>
<td>Advanced glycation endproduct cross link breakers [28]</td>
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<td>Endothelin antagonist [34, 35]</td>
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FUNDING
This study was supported by a European Union grant within the SEVENTH FRAMEWORK PROGRAMME HEALTH-2009-2.4.5-2: Cellular and molecular mechanisms of the development of CKD. Project full title: Systems Biology towards Novel Chronic Kidney Disease. Grant agreement number: 241544

CONFLICT OF INTEREST STATEMENT
J.F.E. Mann has received fees for lectures or consultancy from Abbvie, Bayer, Novartis, Boehringer-Ingelheim, Fresenius, Roche, AMGEN and Novo Nordisk. P.R. has received fees for lectures or consultancy from Abbvie, Astellas, Astra Zeneca, BMA; Bayer, Novartis, Boehringer-Ingelheim, MSD, and Novo Nordisk, and received unrestricted research grants from Novo Nordisk and Abbott. All honoraria are paid to his institution. A.W. has received fees for lectures or consultancy from Astellas, AMGEN, Boehringer-Ingelheim and Fresenius. L.R. did not report any conflict of interest. P.M. has received fees for lectures from Merck Sharpe and Dohme and Fresenius. G.M. has received fees for lectures from AbbVie, Astra Zeneca, Merck Sharpe and Dohme, Amgen and TEVA. His institution received unrestricted grants from Roche, AMGEN, Fresenius, Novartis and TEVA.

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