Limitations and Future Treatment Options in Type 2 Diabetes With Renal Impairment

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In the past two decades, nephropathy in type 2 diabetes has emerged as a major public health issue. The purpose of this presentation is to review the epidemiology of diabetic nephropathy, the controversy surrounding HbA_{1c} and blood pressure as targets for treatment, the efficacy of blocking the renin-angiotensin system (RAS) pathway, and finally the available add-on therapies in patients with "escape."

EPIDEMIOLOGY—Diabetic nephropathy in type 1 and type 2 diabetes emerged as a major issue in the 1970s, but knowledge of albuminuria in patients without primary kidney disease goes back to the work of Senator (1), who found albumin excretion in the urine of roughly 10% of the general population, including individuals with diabetes. In 1891, Schmitz (2) found albuminuria in 10–26% of diabetic patients and discussed its etiology and prognostic implications.

Renal failure in patients with diabetes became a major issue when continuously increasing numbers of diabetic patients were admitted for renal replacement therapy—a veritable "medical catastrophe of worldwide dimension" (3). According to the U.S. Renal Data System report, diabetes accounted for 54% of new patients in 2007. The incidence of end-stage renal disease (ESRD) in diabetic patients is currently 155 patients per million per year; it decreased by 3.3% between 2006 and 2007. In recent years, the prevalence was ~600 patients per million per year, illustrating the dimension of the problem.

In our own local experience in Heidelberg (4), 49%, or 98 patients per million per year, admitted for renal replacement therapy had diabetes; of these patients, 6% had type 1 diabetes, and 94% had type 2 diabetes.

Recently, however, the rate of admission of type 2 diabetic patients for renal replacement therapy reached its plateau (5) in Denmark and in Europe in general. Observations in the Pima Indian population show that there is a significant decrease in the incidence of end-stage disease in type 2 diabetes that cannot be explained by higher mortality before end-stage renal failure has been reached (6). This observation suggests at least some efficacy of current treatment strategies.

EPIDEMIOLOGY OF DIABETIC NEPHROPATHY—Not all patients with diabetes who develop terminal renal failure suffer from classic Kimmelstiel-Wilson syndrome. In our experience (4), classic Kimmelstiel-Wilson syndrome with enlarged kidneys and heavy proteinuria was seen in 70% of patients. Terminal renal failure without major proteinuria and with small kidneys (presumably ischemic nephropathy) was seen in 11% of the patients, and diabetes in the presence of known primary kidney disease was seen in 19% of the patients.

A new development is the frequent occurrence of irreversible acute kidney injury, mostly acute-on-chronic kidney disease (7). Even when (partial) restoration of kidney function occurs, subsequent progression to terminal renal failure is more frequent and faster in diabetic compared with nondiabetic individuals (8).

In our Heidelberg series (9), the diagnosis of diabetes was not known to the referring physician in 11% of patients. It is remarkable that several registries noted that in ~15% of patients admitted for renal replacement therapy, apparent "de novo" diabetes appeared 1–2 years after the start of dialysis. This presumably reflects the fact that because of anorexia and weight loss in the preterminal stage, hyperglycemia had disappeared so that, on admission, the diagnosis of diabetes was missed.

Another important finding is the observation that a considerable proportion of patients with type 2 diabetes develop impaired renal function without having significant albuminuria (10,11). In a 15-year follow-up of 5,032 patients with initially normal serum creatinine, 28% developed creatinine clearance <60 mL/min, and 51% of these patients did not develop albuminuria (11). Similar results were observed in the National Health and Nutrition Examination Survey (12). Reduction of renal function in the absence of albuminuria is presumably the result of a disease of small arteries, as also suggested by the recent Japanese observation (13) that cerebral micro infarcts detected by magnetic resonance imaging predicted the doubling of serum creatinine in nonalbuminuric type 2 diabetic patients.

The natural history of diabetic nephropathy is not clear. It is known that albuminuria may precede the onset of overt diabetes. Albuminuria may even be a predictor of subsequent diabetes, as found in individuals with microalbuminuria (14). This result raises the possibility that even in the prediabetic stage, minor functional and morphological (15) renal abnormalities may exist.

In type 1 diabetes as well as in the presence of normoalbuminuria, the width of the basal membrane was found to be increased, even when the measured

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glomerular filtration rate (GFR) was still within the normal range (16).

Interestingly, diffuse diabetic glomerulosclerosis was reported in some patients who had pathological glucose tolerance and later developed diabetes (17). There was even a report of nodular diabetic glomerulosclerosis that was found in a patient with metabolic syndrome and insulin resistance in the absence of overt diabetes (18). It is difficult, however, to exclude preceding transient episodes of overt diabetes, so doubt remains whether such glomerular abnormalities were truly prediabetic or were simply postdiabetic remnants.

It is certain, however, that the renal risk of diabetic patients increases progressively with increasing albuminuria, even within the range of normoalbuminuric values. This result has led to the recommendation to abandon the concept of microalbuminuria altogether (19). Because the risk of reduced GFR increases progressively with increasing urine albumin concentrations in the "normoalbuminuric" and "microalbuminuric" range, urine albumin concentration as a renal risk factor should be treated as a continuous variable similar to serum cholesterol.

There has been some discussion whether proteinuria is a legitimate target for intervention. However, the evidence for this is clear cut: in the Irbesartan in Diabetic Nephropathy Trial (IDNT) study, an increase in albuminuria increased the risk of reaching a renal end point, while a decrease of albuminuria decreased the risk (20).

DIABETIC NEPHROPATHY AND TARGET HbA_{1c}—The incidence of chronic kidney disease increases progressively with increasing levels of HbA_{1c}, showing that, as far as albuminuria is concerned, there is no threshold for the renal risk. Even HbA_{1c} variability is an independent predictor of nephropathy, as shown in the Diabetes Control and Complications Trial (DCCT) of type 1 diabetic patients (21). Intensified glycemic control reduces the cumulative incidence of microalbuminuria and macroalbuminuria, both in type 1 diabetes (DCCT) and type 2 diabetes (UK Prospective Diabetes Study [UKPDS]) (22).

The relation between HbA_{1c} and renal end points is confounded by "glycemic memory." In 1977, based on a prospective study in 4,400 patients observed between 1947 and 1973, Pirart (23) noted that glycemic control in the first 10 years of diabetes was a major determinant of late complications. The UKPDS (24) recently confirmed that this is also true with respect to renal end points: a relatively short period of intensified treatment reduced the long-term hazard ratio of microvascular disease (including renal end points) by ~20%. In the recent Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) study comprising 11,140 type 2 diabetic patients, 5,571 subjects were given intensified treatment with glicazide in addition to the routine antidiabetic medication that was administered to the control group. The achieved HbA_{1c} in the intensified treatment group was 6.5 vs. 7.3% in the control group: intensified treatment reduced renal end points by 21%, e.g., prevention of one renal event per 20 patients after 5 years of treatment (25). It is of note that the response of microvascular events to intensified blood glucose control was seen earlier than the response of macrovascular events (26).

There has recently been some controversy about the importance of lowering HbA_{1c} with respect to renal end points. The Veterans Affairs Diabetes Trial (VADT) (27) and Action to Control Cardiovascular Risk in Diabetes (ACCORD) studies failed to document a significant reduction of renal events by intensified glycemic control in type 2 diabetic patients, but a valid argument has been raised that these were patients with long-standing type 2 diabetes and considerable preexisting end-organ damage.

With respect to glycemic intervention, it is also of note that recent studies show that glitazones affect renal disease by not only lowering HbA_{1c}, but they also have direct effects on renal injury, independent of glycemia, e.g., attenuation of podocyte injury in nondiabetic proteinuric models of renal disease (28). Renal benefit is not only seen in experimental nondiabetic kidney disease, and the same may also be true in nondiabetic proteinuric human kidney disease (29,30).

Renal reabsorption of filtered glucose will become an important target for treatment of diabetes in the future. The sodium glucose type transporter 2 (SGLT2) in the S1 segment of the proximal tubule can be blocked by selective inhibitors (31) derived from phlorizin. These inhibitors induce natriuresis and, as a result of sodium loss, cause a moderate decrease in blood pressure with an upregulation of RAS (presumably increasing the effectiveness of RAS blockade). An added benefit of glucosuria is weight loss.

There is no unanimity concerning glycemic control in kidney disease. In type 2 diabetic patients of the ADVANCE study (26), strict glycemic control (mean HbA_{1c} 6.5%) compared with standard control reduced renal events. In the PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive) study, type 2 diabetic patients with early stages of chronic kidney disease (CKD) treated with pioglitazone also had significantly less cardiovascular end points than control subjects (32). The importance of near-normal glycemia in renal patients with minor renal dysfunction is also illustrated by diabetic patients with kidney grafts: patients receiving simultaneously a pancreas graft with the resulting normoglycemia had significantly better long-term survival (33).

Glycemic control becomes problematic in advanced CKD because of the risk of hypoglycemia secondary to reduced renal gluconeogenesis and cumulation of insulin as well as of some antiglycemic agents and/or their metabolites; in addition, the reliability of HbA_{1c} is limited because of the reduced erythrocyte half-life and by erythropoietin therapy. As a result, in more advanced stages, the risk of hypoglycemia may override the benefit of glycemic control, and a more cautious approach is advisable.

A particular bone of contention is the glycemic control in dialyzed diabetic patients. In hemodialyzed Japanese patients with diabetes, mortality was significantly lower at HbA_{1c} <7.5 or <7.3% (34,35). In a 7-year observational study, mortality was markedly higher in diabetic dialysis patients with HbA_{1c} >8% (36). These observational data from Asia are not completely in line with U.S. data indicating no correlation between HbA_{1c} and 12-month survival (37). In the German 4D study, the frequency of sudden death was twofold higher in patients with HbA_{1c} >8% compared with 6%, and there was also a trend for lower rates of death from stroke and heart failure (38).

In view of such conflicting data, we recently proposed that, in diabetic patients, an HbA_{1c} of 6.5–7% should be the target in early stages of CKD, whereas in advanced stages of diabetic kidney disease, higher HbA_{1c} values of ~7.5% are acceptable (39).

TARGET BLOOD PRESSURE—In the Kaiser Permanente cohort, blood pressure predicted subsequent uremia in individuals without renal disease at baseline. This was also found for blood pressure

values between 120 and 140 mmHg both in nondiabetic and even more so in diabetic individuals (40). In diabetic patients, it is of note that, conversely, hyperglycemia is also a risk factor for onset of hypertension as shown in type 1 diabetes in the DCCT–Epidemiology of Diabetes Interventions and Complications (EDIC) study (41), presumably by triggering renal mechanisms.

The use of office blood pressure measurements as an indicator of renal damage is problematic. Both in nondiabetic and diabetic patients, office blood pressure measurements were the least predictive indicator of nephropathy, retinopathy, coronary heart disease, etc. (42). Self-measured morning blood pressure (and even better, 24-h ambulatory blood pressure) was much more predictive.

A recent meta-analysis (43) concluded that, in type 2 diabetic patients, treatment of hypertension to the target of 135/80 mmHg caused definite improvement with less evolution of diabetic sequelae, including renal sequelae. The authors concluded that lowering blood pressure aggressively is presumably the most important factor in the prevention of pathological events in type 2 diabetic patients.

In principle, this conclusion is supported by the analysis of Mancia et al. (44) in controlled trials, in which patients (including diabetic patients) were randomized to more aggressive or less aggressive blood pressure–lowering interventions; benefits from lower blood pressure were seen in all but one (underpowered) trial. The analysis of de Galan et al. (45) showed that reduction of blood pressure reduced renal events in type 2 diabetic patients even when the blood pressure at baseline was in the normotensive range, but this apparently applies only to patients in early stages without major target organ damage.

In the IDNT trial, however, Berl et al. (46) found that higher pulse pressure increased all-cause mortality, and lower diastolic pressure was specifically associated with a higher risk of myocardial infarction. This finding is in line with the observation that pulse pressure and by implication, low diastolic pressure (below 70 mmHg), may reduce coronary perfusion in patients with preexisting cardiovascular disease and thus increase the risk of myocardial infarction (but not the risk of stroke) (47).

It has recently become increasingly clear that a single target blood pressure is not appropriate for all diabetic patients and that lowering blood pressure should be less aggressively pursued in patients with preexisting cardiovascular problems. Obviously, a single target blood pressure does not fit all diabetic patients.

BLOCKING THE RAS PATHWAY—In the past, there was much discussion about the specific renal benefit provided by ACE inhibition. The meta-analysis of Jafar et al. (48) showed clearly that ACE inhibitors are only superior to alternative antihypertensive treatments in patients that have proteinuria >1 g/day. In nonproteinuric patients, a specific benefit from blocking the RAS pathway is not well documented. Furthermore, the analysis of Pohl et al. (49) in the IDNT study showed that lowering blood pressure has a much greater impact on renal end points than the blocking of RAS with irbesartan.

A major problem with blocking the RAS pathway is the phenomenon of escape, i.e., the return of protein excretion to baseline values after months or years. This phenomenon is well known in nondiabetic kidney disease (Effect of Strict Blood Pressure Control and ACE Inhibition on the Progression of CRF in Pediatric Patients [ESCAPE] study [50]) and is also common in proteinuric diabetic kidney disease (51).

ADD-ON THERAPY—In the treatment of patients with escape, reduction in salt intake, increased diuretic treatment, and an increased dose of ACE inhibitors or angiotensin receptor blockers (ARBs) above the recommended doses for antihypertensive treatment is a logical first step. The study of Mehdi et al. (52) showed that in proteinuric patients who were treated with 80 mg/day lisonopril and in whom escape had occurred, the addition of 25 mg/day spironolactone was more effective than 100 mg/day losartan. The results of the ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET) study indicate that the combination of ACE inhibitors and ARBs does not provide additional benefit. In diabetic patients with escape, spironolactone or eplerenone has been shown to cause secondary reduction of proteinuria (53,54).

An additional intervention is the renin blocker aliskiren, which when given in addition to ARBs caused in the Aliskiren in the Evaluation of Proteinuria in Diabetes (AVOID) study significant further reduction of albuminuria in type 2 diabetic patients (55). Studies on hard renal end points are forthcoming.

Wenzel et al. (56) reported that in early stages of type 2 diabetes with nephropathy, the endothelin (ET_A) receptor blocker avosentan reduced albuminuria, but in more advanced kidney disease, avosentan caused an unacceptable rate of heart failure and pulmonary edema (57). Therefore, avosentan is clearly contraindicated in advanced diabetic nephropathy (58).

Preliminary data show that the vitamin D receptor activator paricalcitol at a dose of 1 μg and 2 μg/day reduces albuminuria further by ~20% in type 2 diabetic patients with CKD (59).

NEW TARGETS OF INTERVENTION—The established interventions target primarily the glomerulus, i.e., proteinuria and glomerulosclerosis. It has become increasingly clear that in advanced stages, tubulointerstitial fibrosis is an important treatment target. Fibrosis is driven via transforming growth factor β, chemokine receptors, receptor for advanced glycation end products, and nuclear factor-κB, i.e., by inflammation as well as by hypoxia and many other processes. These pathologies have become the target of experimental and preliminary clinical studies.

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