Review Article

A narrative review of new treatment options for chronic kidney disease in type 2 diabetes

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Abstract: Diabetic kidney disease is a frequent and costly complication to type 2 diabetes. After many years with a lack of successful trials there are now significant developments that will change treatment, guidelines and future outcome. Since the last two decades blockade of the renin-angiotensin system (RAS) is standard treatment, but new antidiabetic treatments have shown potential for kidney protection. After cardiovascular outcome studies with glucagon-like peptide (GLP-1) receptor agonists it is evident that drugs like liraglutide, semaglutide and dulaglutide can reduce albuminuria levels and progression to macroalbuminuria. At present, a renal outcome trial with semaglutide is ongoing which will provide more evidence on the drug class in the future. The sodium glucose co-transporter 2 (SGLT2) inhibitor class has also demonstrated effects beyond glucose-lowering, as the drugs can reduce blood pressure, albuminuria and loss of renal function. In the first renal outcome study the SGLT2 inhibitor canagliflozin was found to reduce the risk of hard renal outcome with 30%. SGLT2 inhibition is now recommended in type 2 diabetes with chronic kidney disease. Renal outcome studies testing additional SGLT2 inhibitors and the GLP-1 receptor agonist semaglutide will report in the coming future potentially providing more and much needed options for treatment.

Keywords: Albuminuria; diabetic kidney disease; glomerular filtration rate; dialysis; type 2 diabetes

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Introduction

Much of the increased morbidity and mortality in type 2 diabetes (T2D) occurs in individuals who develop diabetic kidney disease. Mortality is mainly seen in people with microalbuminuria [urinary albumin creatinine ratio (UACR): 30–300 mg/g] or macroalbuminuria (>300 mg/g) and is not only due to renal failure but to a high degree of cardiovascular disease (1). The individual risk of developing chronic renal failure has decreased during recent decades due to improved T2D treatment with increased focus on lifestyle factors, and pharmacological glucose lowering, blood pressure control and lipid lowering therapy. However, the proportion of individuals with diabetic kidney disease as a cause of chronic kidney failure is more or less constant due to the increased prevalence of T2D and improvement in overall survival. Diabetic kidney disease accounts for approx. 25% of people in dialysis treatment in Denmark and approx. 40% in the US. This group of individuals have a particularly high cardiovascular morbidity and mortality. Thus, early detection with systematic measurement of albuminuria, as well as multifactorial prevention, remains important. Over the last few years, new treatment options have emerged. We present the following article in accordance with the Narrative Review reporting checklist (available at http://dx.doi.org/10.21037/atm-20-4841).

Table 1 Screening for diabetic kidney disease. Day-to-day variation in albuminuria can be up to 30%, so repeated urine testing is necessary

Category	Definitions based on urinary levels of albumin		
	Spot urine sample* (mg/g creatinine)	24 h collection (mg/24 h)	Timed collection i.e., overnight (μg/min)
Normal[1]	<30	<30	<20
Microalbuminuria[2]	30–300	30–299	20–199
Macroalbuminuria[3]	>300	>300	>200

*, first morning void recommended due to low day-to-day variability; [1], also termed normal to mildly increased (KDIGO); [2], also termed moderately increased (KDIGO); [3], also termed severely increased (KDIGO).

Diagnosis and clinical epidemiology

In clinical practice, the diagnosis of diabetic nephropathy is defined as:

- Persistent macroalbuminuria: Urinary albumin/creatinine ratio ≥300 mg/g in at least two out of three urine samples measured in a 1–12-month interval
- Exclusion of non-diabetic kidney disease

Other conditions support the diagnosis:

- Hypertension (seen in >90%)
- Diabetic retinopathy (seen in >60%; reflecting the presence of microvascular disease)

The precise diagnosis is established by kidney biopsy. However, in most cases, this invasive procedure is abstained from if disease course and clinical presentation concur (1). A broader and less specific term is diabetic kidney disease or chronic kidney disease (CKD) in diabetes which is defined by proteinuria and or reduced GFR in a person with diabetes but does not imply anything on the pathogenesis.

Global incidence of micro- and macroalbuminuria in T2D is approx. 50% (2). In 2017, 10.6% of the Danish T2D population had macroalbuminuria. In individuals with recently diagnosed T2D, about 3% already have signs of nephropathy. The risk of developing diabetic nephropathy in a normoalbuminuric person with a diabetes duration >30 years is low. Risk factors for progression to chronic kidney disease in type 2 diabetes include hypertension, smoking, male gender and elevated HbA_{1c}.

Pathology

The predominant cause of chronic diabetic complications is long-term exposure to hyperglycemia. The vascular endothelial cells are not able to down-regulate cell membrane glucose transport, leading to elevated intracellular glucose concentrations, causing oxidative stress and shifts in cellular glucose metabolism (3). Damage forms in the endothelial cells of the kidney's glomerular capillaries. In addition, the podocytes, which are important for the permeability of the glomerular basement membrane, are damaged resulting in the passage of albumin from blood to urine.

Over time, distinct changes in the kidney structure occur. The classic glomerulosclerosis is characterized by increased width of the glomerular basement membrane, mesangial sclerosis, microaneurysms and hyaline arteriosclerosis. In addition, interstitial inflammation and fibrosis develops.

As not everyone with diabetes develops kidney disease, factors other than hyperglycemia are involved. Genetics, ethnicity and diabetes duration have an important impact, as do smoking, cholesterol and hypertension.

Microalbuminuria

Annual screening for microalbuminuria aims to identify individuals at increased risk of developing diabetic nephropathy who are at need for renoprotective therapy (4) (*Table 1*). It is recommended to measure urine-albumin-creatinine (UACR) ratio in spot urine samples for both screening and monitoring. Microalbuminuria is defined as UACR 30–300 mg albumin per g creatinine in at least 2 out of 3 urine samples. Day-to-day variation in albuminuria can be up to 30%, so repeated urine testing is necessary. Recent data from a large database including 2.6 million people with CKD from California in the US demonstrated that less than 5% of subjects with CKD were screened for albuminuria/proteinuria, and only 20.5% of subjects with CKD were treated with standard renoprotective therapy (RAS blocking treatment). More patients were treated with potentially kidney toxic agents like NSAIDs (5).

Diabetic nephropathy

Untreated, the course of diabetic nephropathy will involve a sustained, almost linear decrease in renal function (GFR) of

approximately 12 mL/min/1.73 m^2 per year with significant inter-individual variation (2–20 mL/min/year).

A number of factors play a role in the progression of diabetic kidney disease. There is a close correlation between blood pressure and the rate of decline in GFR. As the disease progresses, impaired or abrogated renal autoregulation of glomerulus (GFR) filtration and renal plasma flow is seen, exacerbating the deleterious effects of systemic hypertension in the capillaries. Here, the renin-angiotensin-aldosterone (RAAS) system plays an important role. It is particularly related to the deleterious effect of angiotensin II, which can lead to inflammation and fibrosis. In addition to regulating electrolyte and fluid balance, aldosterone also has a variety of effects both in the kidney and in other tissues including the vascular system, the central nervous system and the heart. Here, too, fibrosis is the suspected harmful effect (6).

Prevention and treatment

Glycemic control

Good glycemic control has a beneficial effect on progression from normoalbuminuria to micro- and macroalbuminuria. This was initially shown in a small Japanese study (7) and the finding was confirmed in the UKPDS (8). The ADVANCE study (9), in which 11,140 patients were followed for a median 5 years, showed that patients randomized to tight glycemic control (HbA_{1c} <48 mmol/mol or 6.5%) had a 21% (95% CI: 7–34) lower rate of nephropathy compared to patients randomized to standard glycemic control and even end stage kidney disease (ESKD) was reduced in the ADVANCE study (10).

Blood pressure

The blood pressure in the glomerular capillaries is an important factor in the pathogenesis of diabetic kidney disease. By treating with antihypertensive agents, the glomerular pressure is reduced. After six years of follow-up in the UKPDS study, there were 29% fewer individuals in the tight blood pressure control group who had developed microalbuminuria (11). A meta-analysis indicates that early intervention with RAAS blockade (in the case of normoalbuminuria), delays the development of microalbuminuria (12). Also, antihypertensive treatment has a renoprotective effect in hypertensive patients with microalbuminuria. The IRMA 2 study (13) investigated 590 hypertensive patients with T2D and microalbuminuria who were randomized to irbesartan either 150 or 300 mg daily or placebo for 2 years. The primary endpoint was the time of onset of diabetic nephropathy. The study showed that irbesartan is renoprotective, independent of the blood pressure lowering effect and that 300 mg daily had the best effect. Similarly, other studies have documented that the renoprotective effect is dose dependent; therefore focus in treatment should be aimed at reaching the maximum tolerated dose.

The basis for RAAS blockade being the standard for treatment of macroalbuminuria are two randomized, placebo-controlled studies with angiotensin II receptor antagonists (ARBs) in populations with hypertension and T2D with macroalbuminuria. The primary endpoint was a combination of a doubling of baseline creatinine concentration, end stage kidney disease (ESKD) or death, which was reduced by 16% and 20% in the two studies, respectively (14,15).

Combining ACE inhibitors with ARB or renin inhibitors is not recommended as such a 'double blockade' increases the incidence of hyperkalaemia, hypotension and acute renal failure without improved efficacy (16-18).

Lipid-lowering treatment

Observational studies suggest an association between cholesterol concentration and the development of nephropathy. A randomized study has shown that treatment with atorvastatin for one year in people with micro- and macroalbuminuria reduced albuminuria by 18% with no effect on eGFR (19). The SHARP study, which randomized both dialysis and predialysis patients to simvastatin in combination with ezetimibe versus placebo, demonstrated a beneficial effect on arteriosclerotic endpoints in individuals who started treatment prior to chronic dialysis (20).

The Steno 2 study showed that multifactorial intervention (pharmacological treatment of hyperglycemia, hypertension, dyslipidemia and microalbuminuria, as well as lifestyle intervention) significantly prevents progression to nephropathy, retinopathy and autonomic neuropathy, and reduces cardiovascular disease and mortality (21). Thirteen years after the end of the study, the development of ESKD was reduced to approx. one third in the group with intensive intervention (22).

New treatment options

Several new anti-diabetic, glucose-lowering drugs have

shown renoprotective potential. The effect is primarily demonstrated as reduction of albuminuria, while three studies so far has investigated the hard renal outcome as the primary endpoint. The interesting thing is that the effect seems to be related to mechanisms independent of the glucose-lowering effect.

In cardiovascular endpoint studies, some GLP-1 receptor agonists (liraglutide, semaglutide, dulaglutide) (23-28) have shown renoprotective effects in people with T2D. In addition to reducing albuminuria, the treatment may delay the development of macroalbuminuria (29). In some studies, as a secondary endpoint, there have also been minor effects on loss of renal function. No studies have yet been conducted with the development of renal disease as the primary endpoint, but for semaglutide such a study is ongoing. The mechanism GLP-1 RA mediated renoprotection is unknown so far.

SGLT2 inhibitors are another treatment which, in addition to its glucose-lowering effect, have been shown to have a positive effect on cardiovascular death and renal and cardiac failure. Since 2015, when cardiovascular death was reduced in the first study with empagliflozin (30), reduction of albuminuria and decrease in renal function decline have been observed in post-hoc analyses, even at eGFR down to 30 mL/min/1.73 m^2. This is despite the fact that with reduced renal function (eGFR <60 mL/min/1.73 m^2) there is less glucosuria and thus less reduction in HbA_{1c} (31-33). The mechanism is probably a hemodynamic/vascular effect, in which reduced co-reabsorption of sodium with glucose in the tubules leads to decreased glomerular pressure. There were high expectations for the first randomized trial (CREDENCE) in a risk population with macroalbuminuria (>300 mg/g creatinine) and eGFR between 30–90 mL/min/1.73 m^2, where canagliflozin 100 mg daily was compared with standard treatment with a primary renal endpoint. Canagliflozin reduced the incidence of ESKD, doubling of creatinine and cardiovascular and kidney-related mortality by 30% (34), with an NNT of 22 over 2.6 years. The side effects for participants with renal impairment were similar to those of normal renal function; increased genital infections and rare but increased incidence of ketoacidosis (2.2 *vs.* 0.2 per 1,000 patient-years).

Against this background, SGLT2 inhibitors are recommended as renal protection therapy in kidney disease in T2D (especially macroalbuminuria and eGFR 30–90 mL/min/1.73m^2) (35). Recently, the DAPA-CKD trial (36), investigating the effect of dapagliflozin on renal outcomes, was stopped prematurely based on input from the data monitoring committee, due to overwhelming efficacy in analyses for the data safety management committee. The publication showed a remarkable 39% reduction in the primary outcome, a composite of a sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes (37). The number needed to treat to prevent one primary outcome event was 19and the effect was also present in patients with non-diabetic kidney disease, as about a third of the included patients did not have diabetes at baseline. A study investigating the effect of empagliflozin on renal parameters is ongoing (38).

Small studies using low doses of the aldosterone antagonist spironolactone in addition to ACE or ARB have been shown to reduce albuminuria, but hyperkalemia has been a limiting factor and more importantly endpoint studies are lacking. Finerenone is a new non-steroidal mineralocorticoid receptor antagonist, which in clinical phase 2 studies has shown the potential to reduce albuminuria without increased risk of hyperkalaemia. A specific kidney outcome study in type 2 diabetes (39) showed a 18% risk reduction for the composite of kidney failure, a sustained decrease of at least 40% in the eGFR from baseline, or death from renal causes (40).

Treatment with atrasentan, an endothelin receptor antagonist, also showed effect on renal endpoints; with a 35% lower incidence of the combined endpoint compared to placebo (41). The manufacturer has decided not to market atrasentan, but similar substances are under development.

Conclusions

Diabetic kidney disease is a frequent and serious complication of type 2 diabetes as it is closely associated with increased morbidity and mortality. Early detection by detection of microalbuminuria and control of risk factors may prevent or slow down development. As evident from recent outcome trials, canagliflozin, dapagliflozin and finerenone have shown results with renal endpoints, leading to more treatments to choose from. Thus, continued focus on the implementation of the established treatment with RAAS blockade and the recently documented treatment with SGLT2 inhibitors remains essential, as outlined in the recent KDIGO guidelines for diabetes management in CKD (42). As the renal outcome trial with semaglutide is awaited, future research will also focus on improved understanding of underlying mechanisms of the new drugs, improved precision in diagnosis and improved

individualized treatment.

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Footnote

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Ethical statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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