REVIEW

Chronic kidney disease in patients with diabetes mellitus

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Abstract

Chronic kidney disease is a common complication and concomitant condition of diabetes mellitus. The treatment of patients with diabetes and chronic kidney disease, including intensive control of blood sugar and blood pressure, has been very similar for type 1 and type 2 diabetes patients. New therapeutic targets have shown promising results and may lead to more specific treatment options for patients with type 1 and type 2 diabetes.

Key Words

- diabetes mellitus
- kidney disease
- diabetic nephropaty
- diabetic kidney disease

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Introduction

Diabetes mellitus is among the leading causes of chronic kidney disease and end-stage kidney disease in the western world. It was the most common diagnosis for the initiation of renal replacement therapy in the United States in 2018, accounting for 47% of the cases (1).

Type 1 and type 2 diabetes mellitus share many clinical characteristics and long-term complications, but they are in fact two different diseases with diverging pathophysiology (2). While type 1 diabetes results from autoimmune destruction of the insulin-producing beta-cells within the pancreatic islets of Langerhans, type 2 diabetes is most often characterized by insulin resistance together with insufficient insulin response, at least in White people.

Type 1 and type 2 diabetes mellitus can both cause long-term microvascular and macrovascular complications, contributing to the increased morbidity and mortality among these patients. Kidney disease in patients with diabetes can be a result of microvascular complications from diabetes, a concomitant kidney disease of other origin or a combination of the two. In type 1 diabetes patients, microvascular disease secondary to diabetes is the most common etiology to chronic kidney disease, while a spectrum of etiologies can cause kidney disease in type 2 diabetes patients.

The established treatment principals to prevent and halt progression of chronic kidney disease have been very similar in the two diabetic phenotypes. This review article intends to highlight the established and upcoming treatment for patients with type 1 and type 2 diabetes and chronic kidney disease. We have reviewed landmark papers published up till the fall of 2020 and publications dealing with new potential therapeutic targets. This review is based on literature search in Pubmed with the following combinations of keywords: 'diabetic nephropathy', 'diabetic kidney disease', 'diabetic nephropathy treatment' and 'diabetic kidney disease treatment' to complete our own bibliography. The search yielded a total of 79.367 search results and was closed on October 26, 2020. The relevance of the articles was initially assessed on the basis of title and abstract before relevant articles in English language were read in full text. Reference lists of all articles read were analyzed in order to identify reference articles for the review.

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Kidney disease in patients with type 1 diabetes mellitus

Type 1 diabetes usually affects young and middle-aged patients and among these patients, chronic kidney disease is most often caused by diabetes-related microvascular disease (3), a condition which has been referred to as diabetic nephropathy or 'diabetic kidney disease' in the literature.

Chronic kidney disease in type 1 diabetes patients typically can cause a progressive decline in renal function. Hyperglycaemia starts the pathophysiologic mechanisms with a subsequent interplay of altered haemodynamics, metabolic and inflammatory pathways (4). When glomerular foot processes merge and the integrity of the glomerular basement membrane is compromised by pathological processes, albumin and subsequently, larger proteins can leak into the urine. Urine albumin/creatinine ratio (UACR) spot analysis of first morning collection is preferred for proteinuria quantification, above assessment of albumin in 24 h urine collection. UACR are staged into moderate albuminuria, previously called microalbuminuria (30–300 mg/g) and overt albuminuria, previously called proteinuria (≥300 mg/g).

Chronic kidney disease in type 1 diabetes patients is initially characterized by hyperfiltration due to increased glomerular filtration pressure (5). Cherney *et al.* postulated hyperglycaemia-dependent hyperfiltration to be mediated through upregulated back-transportation of sodium and glucose from the renal tubular system (6). Sodium-glucose-co-transporter-2 (SGLT2) contributes to 90% of this transportation reducing distal tubular flux of glucose and sodium. Due to reduced sodium flux in the loop of Henle, macula densa signals dilatation of the afferent arteriolar tone through a tubuloglomerular feedback mechanism which increases tubular sodium flux at the expense of increase of intraglomerular pressure and hyperfiltration at the nephron level. Hyperfiltration is in the clinic seen as an increase in glomerular filtration rate (GFR) (5, 6). Albuminuria and hypertension subsequently occur as the kidney disease develops. After the initial hyperfiltration phase, nephrons are lost resulting in a steady GFR decline ranging 3–6 mL/min/year (4). Renal failure requiring replacement therapy may eventually occur within 20–25 years. During this process, the remaining nephrons compensate by hyperfiltration not only due to hyperglycemia but now also due to reduced total filtration surface. This represents a vicious circle with progressive loss of nephrons.

In his first model of the disease, Mogensen suggested that the pathological processes in chronic kidney disease in type 1 diabetes patients were irreversible and that the disease gradually progressed (5). Later, this model has been challenged by reports describing that renal function may be reduced without concomitant proteinuria and that proteinuria may cease spontaneously in the course of the disease (7). These reports used estimated GFR based on cystatin c measurements, and they have, thus, been challenged since these estimates of GFR may differ substantially from measured GFR (8).

Kidney disease in patients with type 2 diabetes mellitus

While chronic kidney disease in type 1 diabetes most often is secondary to diabetes microvascular disease, there is a whole spectrum of chronic kidney disease etiologies in type 2 diabetes. Type 2 diabetes patients are often older at the time of diagnosis and kidney disease due to other causes than diabetes is likely to occur. Several studies have verified that kidney disease in type 2 diabetes may be a more compounded entity than what is seen in type 1 diabetes (9). One study from the United States which examined kidney biopsies in patients with type 2 diabetes and kidney disease found that typical diabetic microvascular disease were present in 37% of the cases, non-diabetic kidney disease in 36% of the cases, such as nephrosclerosis or immunological kidney disease, while mixed forms of diabetic and non-diabetic kidney disease were found in 27% of the cases (10). Interestingly, one study has found different insulin resistance phenotypes in diabetes to be associated with different risks for chronic kidney disease (11), but this needs to be studied further.

Regardless of kidney disease etiology, strict blood glucose control is on a group level the single-most important intervention to prevent kidney disease to develop in patients with type 1 and type 2 diabetes (12, 13, 14). Normalization of blood glucose might act renoprotective through different mechanisms: reduced hyperfiltration on the nephron level (15, 6), reduced generation of toxic intermediates such as reactive oxygen species (ROS) (16) and reduced activity in pathogenetic signalling pathways including the polyol, hexasamine, protein kinase C and advanced glycation end-product pathways (17).

Still as the chronic kidney disease progresses, GFR is reduced through nephron loss and hyperfiltration in remaining nephrons drives the process further.

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How to diagnose kidney disease in patients with diabetes?

Typically, patients with established diabetes are diagnosed with kidney disease when albuminuria is identified as elevated in two out of three spot urine analyzes, corresponding to urine albumin/creatinine ratio (UACR) at or above 30 mg/g **and/or** persistently impaired renal function, defined as estimated glomerular filtration rate (eGFR) below 60 mL/1.73 m^2.

Our clinical impression is that, in most cases, patients with diabetes are not referred for diagnostic kidney biopsy when kidney disease is verified, especially if the clinical characteristics do not differ from what can be expected from chronic kidney disease in diabetes (i.e. increased albuminuria, hypertension and slow decrease in estimated GFR). However, other diseases must be suspected when no other microvascular complications of diabetes are present and also in the presence of microscopic haematuria (9). The pathological classification system developed for chronic kidney disease in type 1 diabetes also includes type 2 diabetes (3). It has been argued that a common classification system is challenging due to the differences in renal lesions among the two diseases (18). While type 1 diabetes patients typically have glomerular lesions characterized by thickening of the glomerular basement membrane, mesangial expansion and glomerulosclerosis, only 30% of type 2 diabetes patients with microalbuminuria and 50% with proteinuria demonstrate such lesions (19).

Established treatment of chronic kidney disease for type 1 and type 2 diabetes

Intensive blood sugar control

Long-term hyperglycaemia causes glomerular hyperfiltration together with glycation of cell proteins, especially intranuclar proteins and nucleic acids. Intensified blood sugar control reduces the risk for proteinuria to develop and also to progress (12, 13, 14). Prevention of overt proteinuria is beneficial for maintaining renal function over time (12, 13, 14). The effect is well-documented in patients with type 1 diabetes (12, 13) and has also been demonstrated at a group level for patients with type 2 diabetes (14). Most guidelines recommend glucose control corresponding to HbA1c around 53 mmol/mol (7%), provided good quality of life is maintained without causing repeated or even severe episodes of hypoglycaemia (20, 21).

The risk for severe hypoglycaemic episodes increases when GFR falls below 45 mL/min. Hypoglycaemic episodes may develop due to reduced gluconeogenesis and counter-regulation in the kidneys (22) and also the half-life of blood glucose-lowering drugs can be prolonged when renal function is impaired, which may necessitate dose-lowering or cessation of drugs such as insulin or sulfonylureas. The increased risk for metformin-related lactacidosis must also been taken into consideration when renal function is impaired (23).

Regulation of blood pressure and albuminuria is beneficial for chronic kidney disease in diabetes

Carl Erik Mogensen reported in 1976 on how blood pressure must be lowered in order to prevent decline in renal function in patients with type 1 diabetes (24). The treatment target for this patient group is blood pressure below 130/80 mmHg (25, 26). Blocking of the renin-angiotensin-aldosterone (RAAS) system is particularly effective in order to reduce proteinuria and preserve renal function, regardless of the blood pressure, first demonstrated for captopril in patients with type 1 diabetes and nephropathy (27) and later for losartan and irbesartan in type 2 diabetes (28, 29). Angiotensin-converting enzyme inhibitors (ACEi) and angiotensin II receptor blockers (ARBs) reduce intraglomerular filtration pressure by dilating the efferent glomerular arteriole, and the clinical effects of these two classes of drugs are considered as equivalent (30). If proteins are present in the urine, it is crucial to reduce the level of proteinuria in order to reduce the risk for kidney disease progression (31). To achieve a reduction of proteinuria, RAAS-blocking drugs are often needed in higher doses to reduce proteinuria than for reaching the blood pressure target alone (32). To be able to monitor and evaluate treatment effect, the amount of proteinuria should be quantified and followed with ACR in urine, which can be easily analyzed in spot samples of morning urine (33).

Other interventions beneficial for chronic kidney disease in diabetes

A comprehensive care is recommended for the management of diabetes patients in the recent KDIGO clinical practice guidelines (21), including statins to all patients with diabetes and kidney disease regardless of cholesterol levels to prevent cardiovascular disease. Moderate physical activity for at least 150 min per week is recommended in addition to smoking cessation, weight loss in the case of obesity, salt restriction and protein-reduced diet.

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Recent studies on glucose-lowering treatment with clinical impact for patients with type 2 diabetes

Patients with type 1 diabetes need treatment with exogenous insulin to obtain blood glucose control, while type 2 diabetes patients might reach treatment targets with life-style modifications, with or without addition of oral glucose lowering agents. The last decade has presented a large selection of blood-glucose lowering drugs for type 2 diabetes patients, and it has been demonstrated that especially two classes of drugs have particular beneficial effects in patients with kidney disease beyond the blood-glucose lowering effect: receptor agonists of the glucagon-like protein 1 receptor (GLP-1 RA) and inhibitors of sodium-glucose-co-transporter-2 (SGLT2i). In secondary analyses of the SAVOR-TIMI 53 and CARMELINA studies, the dipeptidyl peptidase-4 inhibitors (DPP4i) – saxagliptin and linagliptin were associated with less development of macroalbuminuria (34, 35) but with no effect on major cardiovascular endpoints (36, 35). However, the antiproteinuric effect is more pronounced with GLP-1 RAs. Renal outcomes were included in six out of the major GLP-1 RAs studies on cardiovascular outcome (CVOT): lixisenatide (ELIXA), liraglutide (LEADER), semaglutide (SUSTAIN-6), exenatide (EXSCEL), dulaglutide (REWIND and AWARD-7) (37, 38, 39, 40, 41, 42). Major adverse cardiovascular events and death were the primary outcomes of all these studies, while composite renal endpoints were among the secondary outcomes. The renal endpoints were not standardized, but all included proteinuria and change in estimated GFR. Lixisenatide, liraglutide, semaglutide, exenatide and dulaglutide all seemed to demonstrate a protective effect on composite renal outcomes. This effect was apparently driven by reduced development of macroalbuminuria and not by stabilization of GFR (37, 38, 40). However, dulaglutide seemed to preserve renal function better compared to insulin glargine after 1 year of treatment in patients with type 2 diabetes in AWARD-7 (42).

How GLP-1 RAs provide beneficial effects in the kidneys, outside lowering of blood glucose, is not fully understood. It has been suggested that GLP-1 agonism mediates reduced inflammation and oxidative stress. GLP-1 RA increases natriuresis, probably by inhibiting sodium/hydrogen isoform 3 (NHE3) in the renal tubules (43), but the renal haemodynamic effects seem neutral as the drug also causes glomerular vasodilatation (44). Weight loss, another known effect of GLP-1 RA leading to reduced hyperfiltration and improved proteinuria, might also have a role.

Promising results were found with the SGLT2-inhibitors early in the cardiovascular safety studies, for example, with empagliflozin (EMPA-REG), canagliflozin (CANVAS) and dapagliflozin (DECLARE- TIMI 58) (45, 46, 47, 48). Composite renal outcomes were studied as secondary endpoints also in these studies, and it was observed that SGLT2i not only seemed to reduce proteinuria but also to delay deterioration of renal function (eGFR).

How can we understand the SGLT2i effects in chronic kidney disease?

SGLT2-mediated retention of glucose in the kidneys is probably a calorie saving mechanism which enabled survival in times when access to exogenous energy resources were more restricted than today. In a normal diet, the kidneys reabsorb 180 g glucose (720 kilocalories) daily. During diabetes and hyperglycaemia, the reabsorption of glucose and sodium is increased even more and less sodium is presented to macular densa distal to loop of Henle. This in turn initiates a tubuloglomerular feedback mechanism which dilates the afferent arteriole leading to an increase in GFR. Thus, tubular sodium flux is reestablished at the expense of hyperfiltration which is detrimental for the glomerular tuft in the long run.

The excretion of sodium into the urine increases due to the co-inhibitory effect of SGLT2i, which again normalizes the afferent arteriole tone through its effect on macula densa (6). Increased afferent arteriole tone translates into a reduced filtration pressure in the glomeruli and, thus, reduced load on the glomerular tuft. Additional potential beneficial mechanisms of SGLT2i may be increased oxygenation of tubular cells, possible reduction of toxic effects on renal tubules secondary to reduced albuminuria, preservation of intravascular volume and reduced volume overload due to loop-diuretic sparing effect in addition to improved metabolic parameters (i.e. body weight and HbA1c) (49). One study found post-glomerular vasodilatation of the SGLT2 inhibitor dapagliflozin rather than pre-glomerular vasoconstriction in metformin-treated patients with type 2 diabetes (50).

The CREDENCE study was the first study that primarily included type 2 diabetes patients with kidney disease (51). This was a randomized placebo-controlled trial of more than 4000 type 2 diabetes patients with estimated glomerular filtration rate (eGFR) between 30 and 90 mL/min/1.73 m^2 and UACR ranging 300–5000 mg/g.

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The pre-specified efficacy criteria for the study were achieved earlier than expected and led to an early termination of the study (https://www.jnj.com/phase-3-credence-renal-outcomes-trial-of-invokana-canagliflozin-is-being-stopped-early-for-positive-efficacy-findings; accessed October 26, 2020). After a median follow-up of 2.6 years, the treatment group had a significant reduction in the combined renal-specific endpoint (development of terminal kidney failure, doubling of serum creatinine or death from renal-specific cause). These results were valid also for the patients with the most reduced renal function in the study. In fact, in a subset of patients with a GFR drop to less than 30 mL/min/1.73 m^2 just prior to randomization, safety and efficacy of the drug was in line with the whole study population (52). Renoprotective effects occur at GFR thresholds where glucose lowering is no longer observed. The ability for SGLT2i to lower blood glucose decreases sharply when estimated GFR falls below 60 mL/min/1.73 m^2 (53), while the CREDENCE study documented kidney protective effects in the patient group with estimated GFR ranging from 30 to 45 mL/min/1.73 m^2 and even lower.

The DAPA-CKD study studied whether the SGLT2 inhibitor dapagliflozin could have beneficial renal effects also in non-diabetic patients with chronic kidney disease (CKD). Due to superior effects on the renal endpoints, the study was halted before scheduled time (54). The study involved 4.304 patients with CKD out of which only 68% had type 2 diabetes, and the primary end-point was: decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes. Patients with eGFR down to 25 mL/min/1.73 m^2 were included. The study found significant reduction in the primary endpoint and the effect was found independently of presence of diabetes. The number of patients needed to be treated to prevent one incident was as low as 19 during follow-up (median 2.4 years). The EMPEROR-Reduce study, published simultaneously, studied the effect of empagliflozin in heart failure patients already on RAAS blockage and found that empagliflozin was superior to placebo in preventing cardiovascular death or hospitalization for heart failure (55). Rate of eGFR decline was a secondary outcome of the study. The annual decline in eGFR was slower in the empagliflozin group compared to the placebo group (0.55 mL/min/1.73 m^2 vs 2.28 mL/min/1.73 m^2). The DAPA-HF trial studied the effect of dapagliflozin in heart failure patients and found a lower risk of heart failure worsening or death from cardiovascular causes in the treatment group compared to placebo, regardless of the presence of absence of diabetes (56). The incidence of the prespecified renal composite outcome did not differ between the treatment groups. The number of patients with kidney disease in the DAPA-HF trial was low which may have reduced the power to detect statistically significant differences.

The VERTIS study could not demonstrate a significant effect of ertugliflozin on the primary major adverse cardiovascular events endpoint, but the results showed numerically beneficial outcome for preservation of GFR compared to placebo (57). Table 1 summarizes the recent SGLT2i studies with demonstrated effects on renal endpoint.

The ongoing EMPA-KIDNEY study also addresses the renal outcome of using the SGLT2 inhibitor empagliflozin in persons with CKD. In this study also patients with type 1 diabetes are included, in addition to patients with type 2 diabetes or no diabetes (ClinicalTrials.gov. NCT03594110). The study plans to recruit in total 5000 patients including type 1 diabetes, type 2 diabetes and non-diabetic patients with impaired renal function (eGFR $\geq$ 20 to <45 mL/min/1.73 m^2 or eGFR $\geq$ 45 to <90 mL/min/1.73 m^2 and UACR $\geq$ 200 mg/g) and the results are estimated to be published by summer 2022.

In the 2020 KDIGO guidelines for diabetes management in chronic kidney disease, the combination of metformin and SGLT2i is now recommended as first line treatment for all type 2 diabetes patients with chronic kidney disease if eGFR is above 30 mL/min per 1.73 m^2 regardless of glucose control, even in patients with HbA1c within the target range. If the patient does not achieve the individualized glycaemic target, the addition of a GLP-1 RA is recommended (21). Previous and upcoming studies on SGLT2-inhibitors studies are all performed in patients already treated with RAAS blockage or inhibition. Thus, one might expect that current treatment with ACEi or ARBs will still be a basic therapy in the future.

Other therapeutic targets recently tested

Atrasentan, an endothelin A-receptor antagonist, was investigated in the SONAR study (58). Atrasentan is thought to have beneficial effects in several pathophysiological processes involved in chronic kidney disease in patients with diabetes, altered haemodynamics, inflammation and fibrosis. The study included type 2 diabetes patients with eGFR 25–75 mL/min/1.73 m^2 and UACR 300–5000 mg/g and demonstrated a lower reduction in eGFR and reduced proteinuria when compared to placebo. Another and smaller clinical study on pirfenidion,

Table 1 Summary of recent SGLT2i studies with effects on primary and secondary renal endpoints.

Trial	Drug	Kidney-related outcome	Effective kidney outcome
		Primary endpoint	
DAPA-CKD (2020)	Dapagliflozin	Composite of decline in the eGFR of at least 50%, ESKD ,or death from renal or CV causes	HR: 0.61; 95% CI: 0.51–0.72
CREDENCE (2019)	Canagliflozin	Composite of ESKD outcomes, doubling SCr, or death from renal or CV causes	HR: 0.70; 95% CI: 0.59–0.82
		Secondary endpoint	
VERTIS CV (2020)	Ertugliflozin	Composite of death from renal causes, KRT, or doubling of SCr	HR: 0.81; 95.8% CI, 0.63–1.04
EMPEROR-Reduced (2020)	Empagliflozin	Composite of KRT, sustained reduction eGFR ≥ 40%, sustained eGFR < 15mL/min per 1.73 m^2 if baseline eGFR ≥ 30 mL/min per 1.73 m^2, sustained eGFR < 10 mL/min per 1.73 m^2 if baseline eGFR < 30 mL/min per 1.73 m^2	HR: 0.50; 95% CI: 0.32–0.77
DECLARE-TIMI 58 (2019)	Dapagliflozin	Composite of ≥ 40% decrease in eGFR to < 60 mL/min per 1.73 m^2, ESKD, death from CV or renal causes	HR: 0.76; 95% CI: 0.67–0.87
DAPA HF (2019)	Dapagliflozin	Composite of sustained decline in the eGFR ≥ 50%, ESKD or death from renal causes	HR: 0.71; 95% CI, 0.44–1.26
EMPA-REG OUTCOME (2016)	Empagliflozin	Incident or worsening nephropathy (progression to severely increased albuminuria, doubling of SCr, initiation of KRT, or renal death) and incident albuminuria	HR: 0.61; 95% CI: 0.53–0.70
CANVAS (2017)	Canagliflozin	Sustained 40% reduction in eGFR, initiation of KRT, or death from renal causes	HR: 0.60; 95% CI: 0.47–0.77

an inhibitor of TGF-β (transforming grown factor beta), included patients with both type 1 and type 2 diabetes with kidney failure and proteinuria and reported improvement in eGFR after 1 year treatment compared to placebo (59). Sulodexide, a glycosaminoglycan described as being able to prevent structural changes in the glomerular basement membrane, has shown positive effects on proteinuria in two small studies (60, 61). Bardoxolone mathyl is demonstrated to improve inulin GFR in a Japanese phase 2 study, the phase 3 study results are expected early in 2022 (62). Lowering of the serum urate level with allopurinol was ,however, not shown to slow the decrease in the glomerular filtration rate (GFR) in persons with type 1 diabetes and early-to-moderate diabetic nephropathy (63). FIDELIO-DKD found promising results with finerenone, a selective mineralocorticoid, on diabetic nephropathy and cardiovascular endpoints (64).

Studies in progress

In addition to the EMPA-KIDNEY study which examines SGLT2i in type 1 diabetes patients, other studies are of potential interest. The FLOW trial (Semaglutide on the progression of renal impairment in subjects with type 2 diabetes and chronic kidney disease) is designed to show whether the GLP-1 RA semaglutide can slow the decline in eGFR among type 1 diabetes patients with chronic kidney disease. The trial is still recruiting patients and will evaluate when a sufficient amount of end-points has been obtained, alternatively after 5 years. The primary endpoint is persistent eGFR decline of >50%, reaching end-stage renal disease, death from kidney disease or death from cardiovascular disease (ClinicalTrials.gov identifier: NCT03819153).

FIGARO-DKD will give us more answers to the role of finerenone in the treatment of chronic kidney disease in type 1 diabetes patients and cardiovascular endpoints (ClinicalTrials.gov: NCT02545049). Another interesting study investigates whether reduced oxidative stress by inhibiting NADPH oxidase can reduce proteinuria and preserve renal function in patients with type 1diabetes and moderate renal failure (65).

Conclusion

The established treatment of diabetes patients with chronic kidney disease has up till now been very similar for type 1 or type 2 diabetes patients. Recent studies have, however, demonstrated that type 2 diabetes patients with impaired renal function have beneficial renal effects beyond the glucose- lowering effects of especially SGLT2i but also GLP-1 RA. Future studies will clarify if new drugs will arrive in the treatment of type 1 diabetes patients with chronic kidney disease.

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