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Review

Preventing the development and progression of diabetic kidney disease: Where do we stand?

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ABSTRACT

Diabetic kidney disease (DKD) is a major factor associated with increased cardiovascular (CV) and all-cause mortality and morbidity in patients with diabetes. Current standard therapy includes intensive management of hyperglycemia and blood pressure control with renin-angiotensin-aldosterone system (RAAS) blockers. Despite the implementation of this strategy, DKD remains the leading cause of end-stage renal disease (ESRD), mainly because of the increasing burden of diabetes mellitus. The aim of this review is to evaluate the available evidence, focusing on the benefit of current treatment in the development and progression of DKD.

Contents

Abbreviations: DKD, diabetic kidney disease; RAAS, renin-angiotensin-aldosterone system; ESRD, end-stage renal disease; T1DM, type I diabetes mellitus; T2DM, type II diabetes mellitus; CVD, cardiovascular disease; GFR, glomerular filtration rate; AER, albumin excretion rate; BP, blood pressure; NHANES, National Health and Nutrition Examination Survey; DCCT, diabetes control and complications trial; EDIC, epidemiology of diabetes interventions and complications; UKPDS, United Kingdom prospective diabetes study; VADT, veterans affairs diabetes Trial; CKD, chronic kidney disease; ADVANCE, action in diabetes and vascular disease: preterax and diamicron MR controlled evaluation; sCr, serum creatinine; ACCORD, action to control cardiovascular risk in diabetes; SGLT-2, sodium-glucose cotransporter 2; EMPA-REG OUTCOME, (Empagliflozin) cardiovascular outcome event trial in type 2 diabetes mellitus patients; RRT, renal replacement therapy; CANVAS, canagliflozin cardiovascular assessment study; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; SAVOR-TIMI 53, saxagliptin assessment of vascular outcomes recorded in patients with diabetes mellitus thrombolysis in myocardial infarction 53; ACR, albumin/creatinine ratio; LEADER, liraglutide effect and action in diabetes: evaluation of cardiovascular outcome results; SUSTAIN-6, trial to evaluate cardiovascular and other long-term outcomes with semaglutide in subjects with type 2 diabetes; JNC, joint national committee; ESH, European society of hypertension; ESC, European society of cardiology; KDIGO, kidney disease improving global outcomes; NKF KDOQI, National Kidney Foundation Kidney Disease Outcomes Quality Initiative; ACC, American College of Cardiology; AHA, American Heart Association; SPRINT, systolic blood pressure intervention trial; IDNT, irbesartan in diabetic nephropathy trial; ACEIs, angiotensin converting enzyme inhibitors; ARBs, angiotensin receptor blockers; BENEDICT, bergamo nephrologic diabetes complications trial; ROADMAP, randomized olmesartan and diabetes microalbuminuria prevention; RASS, renin–angiotensin system study; DIRECT, diabetic retinopathy candesartan trials; IRMA-2, irbesartan in patients with type 2 diabetes and microalbuminuria; RENAAL, reduction of endpoints in NIDDM with the angiotensin II antagonist losartan; ONTARGET, ongoing telmisartan alone and in combination wiht ramipril global Endpoint trial; VA NEPHRON-D, veterans affairs nephropathy in diabetes trial; ALTITUDE, aliskiren trial in type 2 diabetes using cardiorenal endpoints.

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1. Introduction

Diabetic kidney disease (DKD) occurs in approximately one third of patients with type I or type II diabetes mellitus (T1DM – T2DM) [1] and is a major factor associated with increased mortality and morbidity, mainly due to cardiovascular disease (CVD) [2]. Due to the increasing incidence of diabetes [3], DKD has become the leading cause of end-stage renal disease (ESRD) worldwide, accounting for 50% of the cases in the developed world [4]. Current treatment guidelines include intensive management of hyperglycemia and blood pressure control with RAAS blockers. Despite the implementation of this strategy, observational studies found that the prevalence of DKD among patients with diabetes has not changed significantly [5,6]. This is partly explained by the significant reduction in CVD mortality [7] as well as the emerging and increasingly recognized nonproteinuric phenotype of DKD [8].

The natural history of DKD has been described as a five-stage process. Stage I is characterized by hyperfiltration leading to increased glomerular filtration rate (GFR) and occasionally microalbuminuria (urinary albumin excretion rate – AER: 30–300 mg/d). In stage II ("silent" nephropathy), GFR falls to normal values accompanied with normoalbuminuria (AER < 30 mg/d). One third of the patients will enter stage III ("incipient" nephropathy), whose prominent feature is the presence of persistent microalbuminuria. AER gradually increases and blood pressure (BP) rises, leading to stage IV ("overt" nephropathy), characterized by macroalbuminuria (AER > 300 mg/d) or proteinuria (>0.5 g/d), declining GFR and elevated BP. If CVD death does not occur patients will reach ESRD, the final stage V of DKD [9]. This classic model has been recently challenged as evidence suggests that GFR loss may occur independently or may coexist with albuminuria [10]. Nonalbuminuric renal impairment is associated with increased CVD burden and predominance of macroangiopathy, rather than microangiopathy, as underlying renal pathology [11]. In a recent report from the cross-sectional NHANES cohorts, the overall prevalence of DKD was stable from 1988 to 2014 among patients with diabetes, whereas the prevalence of albuminuria declined and the prevalence of reduced estimated GFR (eGFR) increased [6].

In this article we will review the available evidence regarding the impact of current treatment strategy on the initiation and the progression of DKD. Outcomes will be evaluated in terms of both albuminuria and eGFR decline as markers of kidney disease and prognostic factors of progression to ESRD [12,13].

2. Glycemic control

The benefit of glycemic control on the prevention and progression of DKD has been postulated in several studies (Table 1). In the DCCT trial, 1441 patients with T1DM were randomly assigned to intensive vs conventional glycemic control (mean achieved HbA1c: 7.3 vs 9.1%) for 6.5 years and then entered the observational EDIC trial. After 18 years in EDIC trial, intensive control was associated with a reduction in the incidence of microalbuminuria by 49%, macroalbuminuria by 66% and a reduction in the development of sustained impairment of eGFR < 60 ml/min/1.73 m^2 by 44% [14,15]. The UKPDS trial included 3867 patients with newly diagnosed T2DM that were randomized to intensive or conventional glycemic control (HbA1c: 7.0% vs 7.9%) and followed for up to 15 years. A significant reduction in the development of microalbuminuria was consistent throughout the whole follow up period. Although the event rates of macroalbuminuria and doubling of serum creatinine were very low in both groups, there was still a significant reduction in the intensive control group after 9 and 12 years, but this difference was insignificant at 15 years of follow up [16]. The VADT trial demonstrated different results regarding the effect of intensive control on GFR decline. 1791 patients that were diagnosed with T2DM a mean of 11.5 years earlier, were randomized to intensive vs standard glycemic control (mean achieved HbA1c: 6.9% vs 8.4%) for a mean follow up period of 5.6 years. There was a significant difference, favoring intensive control group, in the progression to

Table 1
Major randomized trials of intensive vs conventional glycemic control.

		DCCT/EDIC [14,15]	UKPDS [16]	VADT [17]	ADVANCE [18]	ACCORD [20]
Baseline characteristics						
Number of patients		1441	3867	1791	11,140	10,251
Mean age (yr)		27	53	60	66	62
Mean duration of diabetes (yr)		6	0	11.5	7	10
Mean HbA1c (%)		9.1	7.08	9.4	7.5	8.1
Microalbuminuria (%)		11	12	N/A	27	26
Macroalbuminuria (%)		0	2	N/A	4	7
Mean sCr (mg/dL)		0.68	0.92	1.0	0.98	0.9
eGFR < 60 ml/min/1.73 m^2 (%)		0	0	0	19	0
Study design						
Target HbA1c (%)	Intensive control group	6.05	FPG < 6 mmol/L	1.5% difference between groups	<6.5	6.0
	Standard control group	N/A	FPG < 15 mmol/L		N/A	7.0–7.9
Median Achieved HbA1c (%)	Intensive control group	7.3	7.0	6.9	6.5	6.3
	Standard control group	9.1	7.9	8.4	7.3	7.6
Follow up (yr)		6.5 + 18[a]	10	5.6	5	3.5
Renal outcomes						
Microalbuminuria		0.51 (0.38–0.68)*	0.67 (0.55–0.81)**,b	0.68 (0.47–0.97)**	0.91 (0.85–0.98)*	0.79 (0.69–0.90)*
Macroalbuminuria		0.34 (0.22–0.50)*	0.66 (0.44–0.97)**,b		0.70 (0.57–0.85)*	0.69 (0.55–0.85)*
Doubling of sCr		N/A	0.26 (0.10–0.67)**,b	NS	NS	1.07 (1.01–1.13)*
eGFR < 60 ml/min/1.73 m^2		0.56 (0.36–0.88)*	N/A	N/A	N/A	N/A
ESRD		NS	N/A	NS	0.35 (0.15–0.83)*	NS

DCCT: Diabetes Control and Complications Trial, EDIC: Epidemiology of Diabetes Interventions and Complications study, UKPDS: United Kingdom Prospective Diabetes Study, VADT: Veterans Affairs Diabetes Trial, ADVANCE: Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation trial, ACCORD: Action to Control Cardiovascular Risk in Diabetes trial, sCr: serum creatinine, eGFR: estimated glomerular filtration rate, FPG: fasting plasma glucose, ESRD: end stage renal disease, RR: relative risk, HR: hazard ratio, NS: not significant, N/A: not available.

* Hazard Ratio (95% confidence interval).

** Relative Risk (95% confidence interval).

[a] DCCT: 6.5 ys, EDIC: 18 ys.

[b] 12 ys follow up.

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