

Targeted Literature Review of the Burden of Illness in Patients With Chronic Kidney Disease and Type 2 Diabetes

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Introduction

The Kidney Disease Improving Global Outcomes 2011 report defines chronic kidney disease (CKD) as an estimated glomerular filtration rate (eGFR) below 60 mL/min/1.73m² or a urinary albumin to creatinine ratio (UACR) of greater than 30mg/g.¹ As the disease progresses, persistent albuminuria, hypertension, and deterioration of renal function are observed. CKD can be classified based on level of kidney function, or eGFR, and the amount of protein in the urine. The lower the eGFR level (G1-G5) and the higher the albuminuria (A1-A3), the more severe the disease. Therefore, CKD is characterized by a gradual loss of kidney function and the frequent cooccurrence of other complications, including cardiovascular (CV) events, kidney failure requiring renal replacement therapy, mortality, and poor quality of life for survivors.^{2,3}

Kidney damage from diabetes is also called diabetic kidney disease (DKD) or diabetic nephropathy.⁴ CKD is among the most severe complications of type 2 diabetes (T2D), making up the most significant contribution to the global CKD burden, with a heavy weight on the Western world.⁵ CKD occurs in 20% to 40% of patients with diabetes, and it can progress to end-stage renal disease (ESRD) that requires dialysis or kidney transplantation.⁶ Approximately 85% to 95% of all cases of diabetes are T2D, and diabetic nephropathy is the most frequent cause of ESRD in most countries.⁴ Moreover, among patients with diabetes, the presence of CKD markedly increases CV disease (CVD) risk.

Currently, treatment strategies focus on treating the underlying cause of kidney disease, controlling blood pressure, preventing CVD, slowing the progression of renal disease, and preventing death, creating an accumulation of patients with mid- to late-stage disease.⁷ Antihypertensive treatments that target the renin-angiotensin-aldosterone system (RAAS), such as angiotensin-converting-enzyme inhibitors (ACEIs) and angiotensin-receptor blockers (ARBs), have been shown to reduce proteinuria and delay disease progression.⁸⁻¹⁰

The current standard of care in the treatment of patients with CKD and T2D includes RAAS blockers; namely, ACEIs and ARBs in patients with hypertension and albuminuria,^{3,6} as well as sodium-glucose

ABSTRACT

Objectives: Chronic kidney disease (CKD) is increasingly prevalent among patients with type 2 diabetes (T2D). CKD is associated with increased mortality rates, clinical and humanistic burden, and substantial health care costs in the T2D population. The objective of this review was to summarize the burden of illness among patients with CKD and T2D, including the profile of patients, incidence, prevalence, mortality, progression, diagnosis and screening rates, and cardiovascular (CV) events.

Methods: A targeted literature review of published studies was conducted using Embase; Medline; Medline In-Process Citations, Daily Update, and Epub Ahead of Print; Igaku Chuo Zasshi databases; and 7 websites. Methods recommended by the Cochrane collaboration handbook, the Centre for Reviews and Dissemination, and the Joanna Briggs Institute critical appraisal checklist were employed.

Results: A total of 1290 full-text articles were reviewed for eligibility and 73 were included in this analysis. Patient profiles indicated older age was associated with more severe disease and number of comorbidities. The definition of kidney disease varied between studies reporting incidence and prevalence, with reported values up to 37.0% and 43.5% for incidence and prevalence, respectively. CKD among patients with T2D contributed to higher mortality rates. Higher disease progression rates were associated with higher albuminuria and lower estimated glomerular filtration rate levels. The available literature suggested annual screening rates for CKD declined over time. CV events were reported to have a substantial effect on morbidity and resource use.

Conclusions: This review highlights the burden of CKD among patients with T2D and underscores a need for new treatment alternatives to reduce the burden of disease.

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For author information and disclosures, see end of text.

cotransporter-2 inhibitors, which are emerging treatment options based on results from recent clinical trials.^{11,12}

Medical costs associated with CKD in T2D increase substantially as the disease progresses to a more severe stage.¹³ In 2017, total CKD in T2D-related expenditures in the US Medicare population were approximately \$21.5 billion.¹⁴ Analysis of data collected in 2012 to 2017 revealed that patients with T2D and CKD at stage 4 or 5 had substantially higher medical costs compared with those with earlier stages of CKD. Each 1 mL/min/1.73m² lower eGFR (starting from 30 mL/min/1.73m²) was associated with an increase of \$1870 in all-cause total medical costs and \$1805 of all-cause nondrug medical costs per patient.¹³ Data from 2016 and 2017 showed that annual mean medical costs per patient grew exponentially with increasing stages of CKD across all subgroups of patients with different comorbidities.¹⁵

In addition to the substantial economic burden, patients with CKD and T2D have a high burden of disease and remain at a high risk of associated complications. The objective of this review is to summarize the evidence available from studies that report the burden of illness among patients with CKD and T2D. This literature review aimed to present the evidence on the profile of patients, incidence, prevalence, mortality, progression, diagnosis and screening rates, and CV events among the specified populations.

Methods

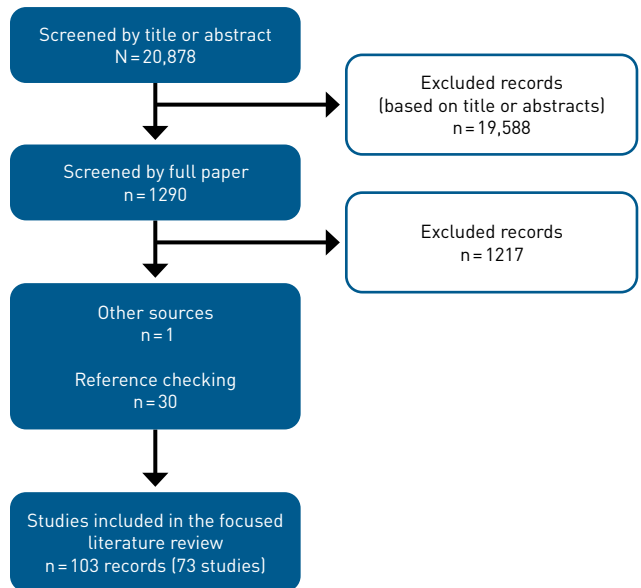
There is no defined standard or accepted methodology for conducting a targeted literature review; therefore, the initial stages of this review (ie, literature searching study selection, data extraction, and risk of bias assessment) followed methods recommended by the Cochrane collaboration handbook¹⁶ and the Centre for Reviews and Dissemination¹⁷ to reduce the risk of bias and errors.

The search was performed in Embase, Medline, Medline In-Process Citations, Daily Update and Epub Ahead of Print, and Iqaku Chuo Zasshi databases. Additionally, websites of the National Health Service, National Institute for Clinical Excellence, Guidelines International Network, National Guidelines Clearinghouse, FDA, European Medicines Agency, and Haute Autorité de santé were searched. Abstracts and full texts were screened by 2 independent reviewers to select relevant articles based on the inclusion criteria.

The review focused on the largest studies and the most recently published study results at the time of the literature review (March 2021). Studies were selected to cover all countries of interest (Canada, China, France, Germany, Italy, Japan, Spain, United Kingdom [UK], and United States). Studies with limited applicability due to highly selected population (eg, veterans; a single sex) and studies reporting minimal data were also excluded.

Data from included studies were extracted using templates created in Excel. One reviewer extracted the data while another validated the accuracy of the extracted information. A quality

FIGURE. Study Flow of Literature Selection and Inclusion



assessment was undertaken by using the Joanna Briggs Institute critical appraisal checklist for studies reporting prevalence data.¹⁸

Results

After removing duplicate studies, 20,878 records were identified, which were subjected to title and abstract screening. Of these, 1290 were selected to be checked at the full-paper stage. After the full-paper screening, 1217 additional records were excluded. Overall, after the study selection process and reference checking, 73 studies were included in the present targeted literature review. The study selection process is depicted in the **Figure**. The list of studies included in the review, along with reported variables, are presented in **Table 1**.¹⁹⁻¹²⁵

Profiles of Patients With CKD and T2D

The demographic and comorbidity profiles of patients with CKD and T2D were presented in 9 studies, providing adequate descriptions of eGFR and albuminuria.¹⁹⁻²⁶ Older age was associated with more severe disease and frequent comorbidities. Additional details regarding patient profiles are presented in **Table 2**.^{19-26,35}

Diagnosis and Screening Rates

There was a general lack of information about the rates of screening for and diagnosis of CKD in patients with T2D. No studies about rates of diagnosis were identified, and 3 studies reported information about screening rates.²⁷⁻²⁹ The results of a UK study indicated

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TABLE 1. Studies Included in the Targeted Literature Review¹⁹⁻¹²⁵

Country by continent	Population	Study identifier	Incidence	Prevalence	Mortality	Progression	Treatment patterns	Screening	CV events
Asia									
China	T2D	Gu 2016 ⁵¹	NR	NR	✓	✓	NR	NR	NR
		Huang 2014 ⁵²	NR	NR	✓	NR	NR	NR	NR
		Li 2015 ⁵³	NR	✓	NR	NR	NR	NR	NR
Hong Kong	T2D	Fung 2017 ⁴³	NR	✓	✓	NR	NR	NR	✓
		Kong 2014 ^{54,55}	NR	✓	✓	NR	NR	NR	✓
		Kung 2014 ³⁷	NR	✓	NR	NR	NR	NR	NR
		Luk 2013 ³¹	✓	NR	NR	NR	NR	NR	NR
		Luk 2017 ³⁴	✓	✓	NR	NR	NR	NR	NR
		Wan 2017 ⁵⁶	✓	✓	NR	NR	NR	NR	NR
		Yeung ⁵⁷	NR	✓	NR	NR	✓	NR	NR
Japan	T2D	Chida 2016 ⁵⁸	NR	NR	NR	✓	✓	NR	NR
		DDCRT ⁵⁹⁻⁶¹	✓	NR	NR	✓	✓	NR	NR
		Hanai 2018 ⁶²	NR	✓	NR	✓	NR	NR	NR
		Murayama 2019 ⁴¹	✓	✓	NR	NR	NR	NR	✓
		Tanaka 2015 ²¹	NR	✓	✓	✓	✓	NR	NR
		Wada 2014 ⁴⁸	NR	NR	✓	NR	NR	NR	✓
South Korea	T2D	Hong and Park 2018 ⁶³	NR	NR	NR	NR	✓	NR	NR
Europe									
Finland	T2D	Finne 2018 ⁶⁴	✓	NR	NR	NR	NR	NR	NR
		Metsärinne 2015 ¹⁹	NR	✓	NR	NR	NR	NR	NR
	ESRD	Kervinen 2018 ⁶⁵	NR	✓	NR	NR	NR	NR	NR
France	T2D	ALICE PROTECT ⁶⁶	NR	NR	✓	NR	NR	NR	✓
		GERODIAB ^{67,68}	NR	✓	NR	NR	NR	NR	NR
		Hadjadj 2016 ²⁰	NR	NR	✓	✓	✓	NR	NR
		OREDIA ⁶⁹⁻⁷²	NR	NR	NR	NR	✓	NR	NR
	ESRD	Lassalle 2017 ⁷³	NR	✓	NR	NR	NR	NR	NR
Germany	T2D	DIACORE ^{74,75}	NR	NR	NR	✓	NR	NR	NR
		Kostev 2018 ²⁷	NR	✓	NR	NR	NR	✓	NR
Italy	T2D	AMD-Annals (type 2) ⁷⁶⁻⁷⁸	✓	✓	NR	NR	✓	NR	NR
		De Cosmo 2015 ⁷⁹	✓	NR	NR	NR	✓	NR	NR
		De Cosmo 2016 ³²	✓	NR	NR	NR	NR	NR	NR
		Fabbian 2015 ³⁶	✓	✓	✓	NR	NR	NR	✓
		RAICE ^{80,81}	NR	✓	✓	NR	NR	NR	NR
		Trevisan 2014 ⁸²	NR	NR	NR	✓	✓	NR	NR
Netherlands	T2D	GIANTT ²⁹	NR	✓	NR	NR	✓	✓	NR
Spain	T2D	ESD2 2014 ⁸³	✓	NR	NR	NR	NR	NR	NR
		Franch-Nadal 2018 ^{84,85}	NR	✓	NR	NR	✓	NR	NR
		Gimeno-Orna 2015 ^{44,86,87}	NR	✓	✓	NR	NR	NR	NR
		MADIABETES ^{23,88}	NR	✓	✓	NR	✓	NR	NR
		PERCEDIME2 ^{22,89}	NR	✓	NR	NR	NR	NR	NR
		Romero-Aroca 2018 ⁹⁰	✓	NR	NR	NR	NR	NR	NR

(continued)

TABLE 1. (Continued) Studies Included in the Targeted Literature Review¹⁹⁻¹²⁵

Country by continent	Population	Study identifier	Incidence	Prevalence	Mortality	Progression	Treatment patterns	Screening	CV events
Europe (Continued)									
Sweden	T2D	DISS ⁹¹	✓	NR	NR	NR	✓	NR	NR
		PRIDE 2013 ⁹²	NR	✓	NR	NR	NR	NR	NR
		Svensson 2013 ^{24,93-95}	NR	NR	✓	NR	NR	NR	✓
		Svensson 2017 ⁹⁶	✓	✓	NR	NR	NR	NR	NR
		Svensson 2017 ⁹⁷	NR	NR	✓	NR	NR	NR	NR
United Kingdom	T2D	Anyanwagu 2018 ²⁵	NR	✓	✓	NR	NR	NR	✓
		Bell 2015 ⁴⁰	NR	✓	NR	NR	NR	NR	NR
		Hill 2014 ⁹⁸	NR	✓	NR	NR	NR	NR	NR
		Liang 2015 ²⁸	NR	✓	NR	NR	NR	✓	NR
		MacLachlan 2018 ⁹⁹	✓	NR	NR	NR	NR	NR	NR
		Mathur 2018 ¹⁰⁰	NR	✓	✓	✓	NR	NR	NR
		Min 2018 ¹⁰¹	NR	✓	NR	NR	✓	NR	NR
		Owusu Adjah 2018 ³³	✓	NR	NR	NR	NR	NR	NR
		Ruzafa 2015 ¹⁰²⁻¹⁰⁴	✓	✓	NR	✓	✓	NR	NR
THIN ⁴⁷	NR	NR	✓	NR	NR	NR	✓		
North America									
Canada	T2D	Tonelli 2019 ³⁵	NR	✓	NR	NR	✓	NR	NR
USA	T2D	Arnold 2018 ¹⁰⁵	NR	✓	NR	NR	NR	NR	NR
		Blankenburg 2018 ¹⁰⁶	NR	NR	✓	✓	✓	NR	✓
		Burke 2012 ¹⁰⁷	✓	✓	NR	NR	NR	NR	NR
		Cressman 2018 ¹⁰⁸	NR	✓	NR	✓	NR	NR	NR
		Iglay 2016 ¹⁰⁹	NR	✓	NR	NR	NR	NR	NR
		NHANES ^{26,39,110-118}	NR	✓	✓	NR	✓	NR	✓
		Nichols 2018 ⁴⁵	NR	✓	NR	✓	NR	NR	NR
		Pantalone 2018 ¹¹⁹	✓	✓	NR	NR	NR	NR	NR
		Pawaskar 2017 ¹²⁰	NR	✓	NR	NR	NR	NR	NR
		Shen 2018 ¹²¹	✓	✓	NR	NR	NR	NR	NR
		Vupputuri 2014 ⁴⁶	NR	NR	NR	✓	✓	NR	NR
Zhou 2017 ³⁰	✓	NR	NR	✓	✓	NR	NR		
South America									
Brazil	T2D	Cardoso 2018 ¹²²	✓	✓	NR	✓	NR	NR	NR
Mixed									
Western Pacific region ^a	T2D	Kosiborod 2018 ¹²³	NR	✓	NR	NR	NR	NR	NR
Netherlands and Scotland		Eder 2018 ¹²⁴	NR	✓	NR	NR	✓	NR	NR
Denmark, Norway, and Sweden		Knudsen 2018 ¹²⁵	NR	✓	NR	NR	NR	NR	NR

✓, outcome reported by the study; CV, cardiovascular; ESRD, end-stage renal disease; NR, outcome not reported by the study; T2D, type 2 diabetes.

^aAustralia, China, Japan, Malaysia, South Korea, and Taiwan.

TABLE 2. Demographic and Comorbidities Profile of Patients With T2D and Diabetic Kidney Disease^{19-26,35}

Demographic Profile								Comorbidities ^a (%)	
Study identifier	Renal disease	eGFR: albuminuria status ^b	N	Mean age	SD	Male (%)	Diabetes duration (years)	Heart failure	Hypertension
Finland									
Metsärinne 2015 ¹⁹	CKD	G1: A2-A3	53	58.6	NR	69.8	11.8 ^c	NR	NR
		G2: A2-A3	275	70.3	NR	52	10.0 ^c		
		G3: A2-A3	93	75.4	NR	39.8	10.8 ^c		
		G4-G5: A2-A3	8	74.8	NR	62.5	18.4 ^c		
France									
Hadjadj 2016 ²⁰	DN	G1-G5: Proteinuria	942	66.3	8.7	71	16.2	NR	73
Japan									
Tanaka 2015 ²¹	CKD	G1-G2: A1	1827	57	12	59.8	13	NR	NR
		G1-G2: A2	598	59	12	61.2	15		
		G1-G2: A3	137	55	12	68.6	14		
		G3-G5: A1	270	68	8	55.9	17		
		G3-G5: A2	183	68	8	64.5	19		
		G3-G5: A3	216	61	11	74.1	18		
Spain									
PERCEDIME2 ²²	CKD	G1: A2-A3	40	62.8	10.7	62.5	9.5	NR	80
		G2: A2-A3	73	67.6	11.1	64.4	9.7		82.2
		G3: A1-A3	133	74.4	8.6	47.4	11.1		91
		G4: A1-A3	60	75.2	10	60	11		93.3
		G5: A1-A3	13	73.6	10.6	53.8	11.7		100
MADIABETES ²³	CKD	G3-G5: A1-A3	965	75.7	8.2	38.7	10.9	11.1	86.6
Sweden									
Svensson 2013 ²⁴	CKD	G3-G5: A1	12,028	NR	NR	36	9	0	NR
		G3-G5: A2-A3	5917			59	12	0	
United Kingdom									
Anyanwagu 2018 ²⁵	CKD	G1-G2: A1-A2	4631	56.8	13.5	56	3.7	9	NR
		G1-G2: A3	5511	57.7	13.5	56	3.9	10	
		G3-G5: A1-A2	2522	66.7	11.5	48	4.9	18	
		G3-G5: A3	5563	67.1	11.9	51	4.9	18	

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that in the T2D population, annual screening rates decline over time, with a rate of 75.6% at 1 year after the start of the diabetic treatment, stabilizing at around 57% after 5 years.²⁸ However, a study from Germany revealed that only 15.3% of patients underwent eGFR testing at least once in 2016.²⁷

Incidence

The definition of kidney disease associated with T2D varied among studies that reported incidence rates. When defined as the presence of an urine albumin test indicating microalbuminuria or macroalbuminuria or as a diagnosis of ESRD, dialysis, or renal replacement therapy, the 1-, 3-, and 5-year incidence of developing diabetic nephropathy were estimated at 5.3%, 12.3%, and 14.7%, respectively

(data from United States).³⁰ Similar results were obtained in a study that was conducted in China. Throughout a median follow-up period of 7.2 years, 19.7% of patients developed CKD, defined as stage 3 and above based on eGFR level; the incidence rate ranged from 21.5 to 54.4 per 1000 person-years, depending on the level of glycated hemoglobin (A1C).³¹ During a 4-year follow-up in another study, 37% of patients developed DKD (defined as diabetes with albuminuria, low eGFR, or both), 16% developed low glomerular filtration rate, and 27% developed albuminuria; of note, all patients had hypertension at baseline.³² Lower incident rates of CKD defined similarly were reported in a study in the UK (The Health Improvement Network), in which the incidence rate ranged from 4.23 to 14.39 per 1000 patient-years.³³

According to data from the included studies, the overall incidence rate of ESRD ranged from 3.48 to 22.46 per 1000 patient-years

TABLE 2. (Continued) Demographic and Comorbidities Profile of Patients With T2D and Diabetic Kidney Disease^{19-26,35}

Study identifier	Renal disease	Demographic Profile					Comorbidities ^a (%)		
		eGFR: albuminuria status ^b	N	Mean age	SD	Male (%)	Diabetes duration (years)	Heart failure	Hypertension
Canada									
Tonelli 2019 ³⁵	CKD	G1: A2-A3	15,519	NR	NR	59.4	6.8 ^c	4.9	NR
		G2: A2-A3	19,168						
		G3: A1-A3	29,069						
		G4: A1-A3	14,698						
		G5: A1-A3	7529						
USA									
NHANES ²⁶	CKD	G1: A2-A3	201	52.9	NR	61.4	9	3.4	73.5
		G2: A2-A3	221	66.8	NR	56	13.1	19.5	90.7
		G3a: A2-A3	257	70.3	NR	50.3	13.1	16	90.7
		G3b: A2-A3	133	73.8	NR	38	15.8	29.4	94
		G4: A2-A3	48	73.2	NR	23.3	16	42.5	96.8
		G5: A2-A3	24	59.7	NR	40.6	8.7	44	97.9
		G2: A2-A3 ^d	693	56	15	63	11	NR	73
		G2: A2 ^d	608	57	13	61	11	NR	72
		G2: A3 ^d	169	55	16	63	14	NR	85

CKD, chronic kidney disease; DN, diabetic neuropathy; eGFR, estimated glomerular filtration rate; NR, outcome not reported by the study; T2D, type 2 diabetes.

^aData regarding hypercholesterolemia and anemia were not identified.

^bG1-G5—levels of eGFR, G1 the lowest level, G5 the highest one; A1-A3—albuminuria categories, A1 the lowest level, A3 the highest one.

^cMedian values; all others are means.

^dThis study includes microalbuminuria and macroalbuminuria as descriptions rather than identifying groups with mg/g range.

and was found to be associated with age, race, level of A1C, duration of diabetes, level of blood pressure, glycemic and lipid control, and retinopathy or macrovascular complications at baseline.^{31,34}

Prevalence

Diabetes affects more than 400 million people worldwide, and the prevalence is growing rapidly, especially for T2D. T2D is associated with a high risk of microvascular and macrovascular complications including CKD and CVD.³⁵ The definition of kidney disease associated with T2D varied among the included studies reporting prevalence rate, and data should be interpreted with caution. The prevalence of decreased eGFR in the T2D population (< 60 mL/min/1.73m²), regardless of albuminuria, ranged from 19.6% in Canada³⁵ to 29.6% in Italy.³⁶ The prevalence of albuminuria (UACR > 30 mg/g) ranged from 15.4% in Spain²² to 38.8% in China.³⁷ The prevalence of decreased eGFR and albuminuria was lower and ranged from 7.8% to 10.3% in Italy³⁸ and the United States,³⁹ respectively. In Italy, the prevalence was reported for different phenotypes: 18.9% for albuminuric DKD with preserved eGFR and 7.9% for albuminuric DKD with reduced eGFR. The prevalence of diabetic nephropathy in patients with T2D in China was 30.9% (defined as albuminuria category 2, UACR 30-299 mg/g) and 7.9% (defined as albuminuria category 3, UACR ≥ 300 mg/g). The prevalence of DKD (defined as albuminuria or decreased eGFR) among patients with

T2D in Japan was 43.5%. The prevalence of DKD (defined as G3-G5 < 60 mL/min/1.73m²) in T2D in the UK was 37.2%. The prevalence of CKD in patients with T2D in Brazil was 31.5%. The prevalence of CKD (defined as albuminuria or decreased eGFR) in patients with T2D in Canada was 33%. Among included studies, the prevalence of ESRD among patients with T2D seems to not exceed 1%.^{34,40,41}

Mortality

The results of the identified studies demonstrated that the higher prevalence of kidney disease among patients with T2D contributes to the high mortality rates among this population.⁴² In a study conducted in United States based on the third National Health and Nutrition Examination Survey among individuals with both T2D and kidney disease, the standardized 10-year mortality rate was 31.1% (95% CI, 24.7%-37.5%), whereas a rate of 11.5% (95% CI, 7.9%-15.2%) was reported among patients without kidney disease. The same pattern was observed for CV mortality; the standardized 10-year mortality was estimated at 6.7% (95% CI, 4.2%-9.1%) and 19.6% (95% CI, 14.7%-24.4%) among patients with diabetes without CKD and with CKD, respectively.³⁹ Similar results were obtained in 2 other studies.^{25,43} In China, the results of a multivariable analysis showed that CKD was associated with an increased risk of all-cause death and CV death (HR, 1.63; 95% CI, 1.38-1.93 and HR, 1.54; 95% CI, 1.20-2.13, respectively).⁴³ These results were confirmed by a study conducted

in the UK, showing that the combination of reduced eGFR with increased UACR was associated with a higher risk of premature death (21.7 per 1000 person-years; 95% CI, 19.8-23.7) compared with patients who had reduced eGFR and normal albumin-to-creatinine ratio levels (19.5 per 1000 person-years; 95% CI, 17.0-22.4).²⁵ Additionally, according to results of a study conducted in Japan, the incidence rate of death was higher in patients with reduced eGFR (< 60 mL/min/1.73m²) than those with greater eGFR (≥ 60 mL/min/1.73m²).²¹ Those with more severe kidney disease (eGFR < 60 mL/min/1.73m²) were characterized by a mortality rate ranging from 7.7 to 11.8 per 1000 person-years, whereas the rate for those with less-advanced kidney disease (eGFR ≥ 60 mL/min/1.73m²) ranged from 1.3 to 4.8 per 1000 person-years.^{21,44}

CKD Progression

Most of the studies reported disease progression among patients with CKD and T2D as progression to ESRD, change in eGFR, or change in albuminuria occurred. It was found that higher levels of albuminuria at baseline significantly increased the risk of progression of eGFR-based kidney dysfunction.^{21,30,45} Additionally, patients with albuminuria were more likely to require dialysis in the future (HR, 4.23; 95% CI, 2.45-7.30; *P* < .05; and HR, 40.1; 95% CI, 25.3-63.6; *P* < .05 for micro- and macroalbuminuria, respectively).³⁰

In a study conducted in the United States, the progression rate from stage G1 to G5 increased from 0.8 to 8.8 per 1000 person years among patients with albuminuria levels from A1 to A3, respectively.⁴⁵ In another study, the progression rate was reported as 25.8, 74.2, and 78.2 per 1000 person-years for eGFR stages G1 and G2 (progression to stages G3-G5), G3 (progression to stage G4-G5), and G4-G5 (progression to ESRD), respectively (stage of albuminuria was not reported).⁴⁶ In Japan, at an eGFR stage of G3 to G5, the crude progression rate to renal replacement therapy at A1, A2, and A3 albuminuria stages were 0.0, 1.9, and 87.8 per 1000 person-years, respectively.²¹

CV Complications

The results of several studies demonstrated the risk of CV events among patients with CKD and T2D and highlighted the substantial effect of these conditions on morbidity and resource use. Although the methods varied considerably among the studies in terms of duration of follow-up and CV events that were evaluated, collective data from 5 studies showed an association among the stage of CKD (based on eGFR level or albuminuria) and incidence of CV events. The results from these studies showed that the risk of CV events progressed with CKD stage.^{5,25,36,43,47,48}

In China, it was found that the risks of coronary heart disease, stroke, or heart failure increased exponentially with the decrease in eGFR, with the HR increasing from 1.63 to 4.55, associated with stage G3 to G5 CKD, compared with stage G1 CKD.⁴³ Additionally, the level of albuminuria showed a positive linear association with CV

events. Microalbuminuria among men and women was associated with an HR of 1.58 and 1.48 for CV events, respectively, compared with normoalbuminuria.⁴³ Similar results were obtained in 2 other studies.^{36,47} Results from a single study showed that a lower eGFR was associated with an increased risk of both myocardial infarction (HR increasing from 1.27-2.34 among patients with CKD stage G3-G5, respectively) and ischemic stroke or transient ischemic attack (HR increasing from 1.09-1.78 among patients with CKD stage G3-G5, respectively) compared with stage G1 to G2 CKD.⁴⁷ In Italy, eGFR was found to be a risk factor for the development of CV events (including myocardial infarction and congestive heart failure) in patients with T2D of over 4.5 years' duration.³⁶

Discussion

This review highlights the burden of CKD among patients with T2D. The prevalence of CKD in patients with T2D has increased over the past 2 decades.⁴⁹ In part, this is an effect of the improved management of CV complications, resulting in increased life expectancy among these high-risk patients.⁵⁰ Moreover, the occurrence of CKD is expected to increase among patients with T2D, owing partially to an increase of the median age of the worldwide population, as well as the growing global prevalence of T2D.

CKD progression is associated with a range of complications, including increased risk of infections, anemia, pruritus, CVD, peripheral arterial disease, CV events, and all-cause mortality. In patients with T2D, the presence of CKD is clinically important given its effect on health care resource utilization and costs of care, as well as the burden of disease and reduction in health-related quality of life. In the late stages of CKD, patients may progress to ESRD, which requires renal replacement therapy via dialysis or kidney transplantation.

This review provides information regarding incidence and prevalence of CKD worldwide, as well as the current unmet needs for those with disease progression. In patients with T2D, CKD results in frequent complications and increased mortality; therefore, prevention and early, effective management of disease are the main challenges in clinical practice. Slowing the progression of CKD to ESRD is an urgent medical objective, and, unfortunately, it is still a major unmet need for patients with T2D. In patients with T2D, CKD is strongly associated with CVD, so the management of CV risk factors and careful monitoring of eGFR and albuminuria may represent opportunities to reduce the risks of CV events and mortality.

Limitations

There are 2 main limitations of this review. First, it was designed as a targeted literature review and, although the methods for conducting systematic reviews in health care are well established, there is no standard or accepted methodology for the conduct of a targeted literature review. Therefore, a structured method with

the aim of providing a transparent and reproducible process was developed and reported; we believe that our methods could be applied to increase the quality and credibility of targeted reviews in general. Although the approach is resource intensive, it represents the optimal strategy for reviewing large volumes of diverse data and producing a usable, readable overview. To ensure that this review would reflect current disease epidemiology and management, high-quality studies published in 2013 and after with large sample sizes that cover most outcomes of interests were included. The presented approach has resulted in reliable knowledge about the burden of CKD in T2D in the selected countries. Additionally, a quality assessment of all included epidemiological studies was performed using the Joanna Briggs Institute critical appraisal checklist for prevalence studies, in the absence of other validated tools.

Second, it is important to highlight that most of the identified studies were not designed to address the research questions defined for this review. For example, many studies focused on patients with T2D and reported the prevalence or incidence of CKD among them, limiting the details on CKD in T2D population. Another example is that the studies included different study populations as different definitions of kidney disease associated with T2D were used in the inclusion criteria (eg, CKD, DKD, diabetic nephropathy, ESRD, microalbuminuria, macroalbuminuria, proteinuria, dialysis, etc). Although this limited the comparability of results among studies, it ensured identification of all relevant studies about patients with renal complications of diabetes, regardless of the definition used by the authors.

Conclusions

This review of the burden of CKD in patients with T2D provides an overview of the latest estimates of incidence, prevalence, mortality, disease progression, and CV complications among patients, as well as information from the most up-to-date treatment guidelines. CKD is increasingly prevalent among patients with T2D; it progresses rapidly and is associated with increased mortality, with a large clinical and humanistic burden of disease, and with vast health care costs.

Thus, identification, prevention and early management of disease are critical. Slowing the progression of CKD, in particular to ESRD, is an urgent therapeutic challenge and, unfortunately, remains a major opportunity for patients with T2D. There is a need for new treatment alternatives for patients with CKD and T2D in order to reduce the burden of disease and healthcare resource utilization. ■

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