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The Effect of Prevalence of Diabetes on the Epidemiology of CKD

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ABSTRACT

Increasing prevalence of diabetes around the world and changes in clinical practice have influenced the epidemiology of CKD in recent years. In many countries, including the United States, diabetes is responsible for over 40% of new cases of ESRD, surpassing other causes to become the single leading driver of incident kidney failure. Persons with diabetes-related CKD have lower survival relative to those without CKD, primarily because of the excessive risk of coexistent morbidity, particularly CVD, associated with CKD. Nonetheless, wide variation was observed in the epidemiology of CKD among populations with diabetes globally, largely because of the lack of high quality population-based studies with validated measures of CKD. Although considerable research is under way in search for better diagnostic means and more effective treatments, outside the research community and the realm of health care professionals, awareness of CKD has remained very low even among patients with diabetes.

KEYWORDS

Epidemiology; Prevalence; Incidence; Chronic kidney disease.

1. Introduction

Diabetes mellitus is a major public health challenge, both in developed and developing nations.1 In 2015, an estimated 8.8% or 415 million people were living with diabetes worldwide, nearly double the 4.6% (151 million) estimated in 2000, and this number is expected to increase to 10.4% (642 million) by 2040.2 The most commonly diagnosed forms of diabetes are type 2 and type 1. Other types of diabetes, including gestational diabetes, monogenic diabetes, and secondary forms of diabetes, are much less common. Type 2 diabetes accounts for 87% to 91% of the global burden of diabetes and is the most frequent cause of kidney complications.3 The onset of type 2 diabetes, unlike that of type 1 diabetes, often goes undetected and therefore both prevalence and incidence rates are generally underreported. The age-adjusted prevalence of type 2 diabetes is highest in North America, the Caribbean, Western Pacific, Middle East, and North Africa and lowest in subSaharan Africa.2,4 Most people with type 2 diabetes live in urban areas and in low- and middle-income countries, which are also projected to experience the highest increase in national prevalence of type 2 diabetes over the coming decades.2 The highest rates of type 2 diabetes are reported in certain ethnic groups across the globe, including the indigenous people of Nauru, American Indians in the United States, First Nations people in

Canada, and indigenous people in Australia and New Zealand.4-6 Type 1 diabetes accounts for 7% to 12% of the global burden of diabetes,2,3,7 its incidence varying substantially by geography,8 from around 60 cases per 100,000 people/ y in Finland9 and 40 cases per 100,000 people/y in Sardinia10 to about 0.1 cases per 100,000 people/y in China, India, and Venezuela.10 Half a million children aged ,14 years lived with type 1 diabetes worldwide in 2015, with the highest number residing in Europe, North America, and South-East Asia.2 In the United States, 1.25 million children and adults have type 1 diabetes11 and this number continues to increase.12 People with diabetes are at increased risk of developing a number of disabling and life-threatening complications, including cardiovascular disease (CVD), kidney disease, blindness, and lower-limb amputations.2 In this review, we will summarize the current evidence on the epidemiology of one of the most common complications associated with diabetes–CKD. Furthermore, we will explore trends in the incidence and prevalence of CKD in diabetes, mortality among those with CKD, and the level of awareness about kidney disease among patients with CKD.Many of the listed risk factors prevail in disadvantaged and displaced populations across the globe, predisposing to more frequent and earlier onset of diabetes and CKD.

2. Prevalence of Nonalbuminuric Kidney Disease in Diabetes

Albuminuria is considered an early indicator of diabetic kidney disease. However, a number of studies have documented that nonalbuminuric CKD (eGFR ,60 mL/ min/1.73 m2 in the absence of albuminuria) occurs relatively frequent in persons with diabetes and its prevalence is increasing. In NHANES 1988 to 1994,54 30% of participants 40 years and older with type 2 diabetes and low eGFR had no albuminuria or retinopathy. In more recent years, the National Evaluation of the Frequency of Renal impairment cO-existing with NIDDM (NEFRON) survey of primary care patients with type 2 diabetes found that 55% of those with low eGFR were persistently nonalbuminuric. This percentage was lower in Indigenous (17%) or Polynesian (,20%) patients.55 Although specific treatments were not explored in this study, the authors indicate that medicines known to reduce urinary albumin excretion (UAE) were commonly used in the care of these patients. Among 109 patients with type 2 diabetes attending a single tertiary referral center, nonalbuminuric CKD was reported in 39% of them.56 After excluding those patients whose normoalbuminuric status was possibly related to treatment with renin-angiotensin-aldosterone system (RAAS) inhibitors, the prevalence of nonalbuminuric CKD was 23%.56 This phenotype has also been reported in clinical trials. In the UK Prospective Diabetes Study, of the 1132 patients with type 2 diabetes and incident kidney dysfunction (Cockcroft-Gault estimated creatinine clearance ,60 mL/min or doubling of plasma creatinine),

575 (51%) were found not to have preceding albuminuria. Although albuminuria and low kidney function shared many of the same risk factors, certain nondiabetes-related factors specifically contributed to loss of kidney function (high systolic blood pressure, central obesity, female sex). Similarly, in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study, 24% of the 89 patients with type 1 diabetes who had sustained low eGFR did not have albuminuria.58 Those with initial albuminuria had significantly longer diabetes duration and experienced a steeper decline in kidney function than those without albuminuria.

The Developing Education on Microalbuminuria for Awareness of renal and cardiovascular risk in Diabetes (DEMAND) study, a multinational cross-sectional clinic-based study conducted in 2003, found that 21% of the patients with an average duration of type 2 diabetes of 7.6 years had kidney dysfunction (assessed by the Cockcroft-Gault equation) with normal albuminuria.59,60 Overall, 12% of this cohort had diabetic retinopathy. In a 2007 cross-sectional survey of primary care patients in Catalonia, Spain, with 7 years of diabetes duration, 15% of the patients had nonalbuminuric CKD.33 These patients had better metabolic control, lower prevalence of smoking and macrovascular disease, and were more obese than those with albuminuria. On the other hand, CKD may be due to other causes than diabetes per se, particularly when diabetic retinopathy is absent. Few

studies, however, include information on retinal examination, a simple, noninvasive, ambulatory screening test that may help identify persons most likely to have kidney disease because of diabetes.

3. Incidence of CKD in Diabetes

Generally, the annual incidence of albuminuria is about 8% in type 2 diabetes or mixed diabetes type populations, and approximately 2% to 3% in type 1 diabetes.61 The incidence of low eGFR is approximately 2% to 4% per year regardless of type of diabetes; however, pooled incidence rates for CKD are not feasible because of substantial heterogeneity in population estimates. The UK Prospective Diabetes Study reported that 38% of persons with newly diagnosed type 2 diabetes developed albuminuria during a median follow-up of 15 years,57 29% developed renal impairment (Cockroft-Gault estimated creatinine clearance ,60 mL/min or doubling of plasma creatinine), and 14% developed both conditions. The risk of these outcomes increased with longer duration of diabetes, and the risk of developing albuminuria was higher among men than women. In the DCCT, the cumulative incidence of persistent moderate albuminuria (ACR 30300 mg/g) was 14%, 33%, and 38% at 10, 20, and 30 years duration of type 1 diabetes, respectively, among persons with conventional hypoglycemic treatment (mean A1c 9.6% [81 mmol/mol]). However, the incidence was lower, 10%, 21%, and 25%, respectively, with intensive diabetes treatment (mean A1c 8.9% [74 mmol/mol]). Eighteen years after the end of randomization in DCCT, those formerly assigned to intensive treatment had a 57% lower adjusted risk for moderate albuminuria and 84% lower risk for severe albuminuria (ACR $300 mg/g) compared with those who never received intensive therapy, suggesting a long lasting beneficial effect of tight glycemic control on the development of kidney damage.63 A long-term postrandomization effect was also observed with regard to kidney function, those in the intensive treatment arm having a 44% reduction in persistently low eGFR when compared with those who were treated conventionally. Other studies have shown that improving bodyweight, A1c, and systolic blood pressure reduces the incidence of advanced CKD (defined as eGFR ,30 mL/min/1.73 m2 regardless of ACR; eGFR ,45 mL/min/1.73 m2 and ACR $30 mg/g; eGFR ,60 mL/min/1.73 m2 and ACR.300 mg/g; or onset of dialysis) after a median followup of 8 years. An overall improvement in healthy lifestyle has a favorable effect on incidence of albuminuria over a short time period.

4. Secular Trends on CKD in Diabetes

A secular decline in the incidence of diabetes-related CKD has been described for type 1 diabetes but not for type 2 diabetes. The trends in type 1 diabetes coincide with a trend for earlier initiation of antihypertensive treatment after the onset of diabetes, expansion of RAAS inhibitor usage, and sustained improvements in glycemic and blood pressure control. In type 2 diabetes, Afkarian and colleagues44 reported that overall prevalence of diabetes-related CKD based on NHANES data has not changed significantly from 1988 to 2014. The prevalence was 28.4% in 1988 to 1994 and 26.2% in 2009 to 2014 (age-, sex-, and race/ethnicityadjusted prevalence ratio ¼ 0.95; 95% CI, 0.86-1.06; P¼.39 for trend). Specifically, the prevalence of albuminuria declined from 20.8% to 15.9% (adjusted prevalence ratio ¼ 0.76; 95% CI, 0.65-0.89; P,.001 for trend), largely because of declines among adults ,65 years and non-Hispanic Whites. The prevalence of low eGFR, however, increased from 9.2% to 14.1% (adjusted prevalence ratio ¼ 1.61; 95% CI, 1.33-1.95; P, .001 for trend), without differences in age or race/ethnicity–specific eGFR trends. This increase in the prevalence of low eGFR was despite increased use of glucose-lowering medications and RAAS inhibitors in people with diabetes. The SUrveillance, PREvention, and ManagEment of Diabetes Mellitus (SUPREME-DM) Data Link study in the United States, including 879,312 persons with diabetes, found that age- and sex-standardized prevalence of CKD diagnosis codes increased from 10.7% in 2005 to 14.3% in 2011 (an average relative increase of 4.1% per year, P, .001). However, ascertainment of low eGFR declined from 9.7% in 2005 to 8.6% in 2011 (an average relative decrease of 2.3% per year, P , .001). The discrepancy with the NHANES results likely reflects the poor concordance between laboratory measurements and diagnosis codes for CKD.

5. ESRD in Diabetes

Globally, 80% of ESRD cases are caused by diabetes, hypertension, or a combination of the both. Compared with adults without diabetes, the incidence of ESRD is up to 10 times as high in those with diabetes. Even so, only a limited number of patients with diabetes-related CKD will ever receive renal replacement therapy, as 78% of these people are living in low- and middle-income countries where resources, coverage, and access to dialysis and kidney transplantation are limited. The proportion of diabetes-related ESRD varies greatly between countries around the world. In 2014, between 5% and 66% of new ESRD cases were primarily caused by diabetes, the highest proportion being reported in Singapore, Malaysia, and the Jalisco region of Mexico, and the lowest in Norway, Romania, and Iceland. Most countries at the upper end of this distribution experienced a steep increase in diabetes-related ESRD incidence over the past decade; between 2001 and 2015 top increases were by 1448% in Thailand, 981% in Russia, and 378% in the Philippines. Because these rates are reported for the overall countryspecific populations, they essentially reflect the increasing prevalence of diabetes in those populations, in part as a consequence of disease burdens moving away from infections toward chronic lifestyle-related diseases and increased life expectancy. Treated ESRD prevalence was highest, ranging from 1568 to 3219 per million population, in the Asian countries of Taiwan, Japan, Singapore, and the Republic of Korea, as well as the United States, Portugal, and the Jalisco region of Mexico.78 Although treated ESRD incidence rates have been quite stable or have declined in many countries during recent years, the prevalence has steadily increased in all 32 countries that provided data from 2001 to 2014.

6. Awareness of CKD

One in 3 adults with diabetes are estimated to have CKD and most of them are not aware of having kidney disease.95 Moreover, claims data indicate that testing for urine albumin, an early marker of kidney disease in diabetes, is being done in less than half of patients.96 Early detection and better management of CKD can slow its progression, prevent complications, and reduce cardiovascular outcomes. However, early kidney disease is asymptomatic and consequently most patients with CKD are unaware of their condition.

Globally, the level of CKD awareness is less than 10% in the general population of CKD patients. The NHANES101 collected data on the level of awareness among US patients with CKD by asking participants whether they had ever been told they had “weak or failing kidneys.” From 1999 to 2004, in the general population of CKD patients, only 6% reported being told that they had weak or failing kidneys (3.7%, 3.5%, 7.8%, and 41.8% for Stage 1, 2, 3, and 4, respectively). Participants at high risk of CKD reported better awareness: 17.8% of those with diabetes were aware of having CKD compared with 5.9% of those without diabetes.

Among participants with diabetes and CKD in the US Kidney Early Evaluation Program (KEEP), 9.4% were aware of their CKD; awareness level was 6% in those with CKD Stages 1 and 2 and 10.9% in those with later-stage CKD.102,103 In line with this study, the ADD-CKD study (Awareness, Detection and Drug Therapy in Type 2 Diabetes and Chronic Kidney Disease) in the United States reported that although more than half of participants with type 2 diabetes had CKD as manifested by changes in the urine protein excretion, a decreased eGFR, or both, only 12% had their CKD identified by the primary care practitioners. It also reported that clinicians were more likely to identify advanced than early CKD.106 Although regular physician visits were not associated with greater awareness in a Canadian study,107 they were in other studies from the United States and Canada.100,108 Studies in other populations reported similar CKD awareness, between 5% and 10%, with lowest values among people with low socioeconomic and educational statuses.104,105 In a single center study in Tanzania, mostly in patients with type 2 diabetes, more than three-quarters (83.7%) had CKD and 80% had significant albuminuria, however, none of them was aware of their illness.36

7. Conclusion

Increasing prevalence of diabetes around the world and changes in clinical practice have influenced the epidemiology of CKD in recent years. In many countries, including the United States, diabetes is responsible for over 40% of new cases of ESRD, surpassing other causes to become the single leading driver of incident kidney failure. Persons with diabetes-related CKD have lower survival relative to those without CKD, primarily because of the excessive risk of coexistent morbidity, particularly CVD, associated with CKD. Nonetheless, wide variation was observed in the epidemiology of CKD among populations with diabetes globally, largely because of the lack of high quality population-based studies with validated measures of CKD. Although considerable research is under way in search for better diagnostic means and more effective treatments, outside the research community and the realm of health care professionals, awareness of CKD has remained very low even among patients with diabetes.

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