Epidemiology of Diabetic Kidney Disease

Anne T. Reutens, MBBS, PhD, FRACP,a,b,*

DEFINITION OF DIABETIC KIDNEY DISEASE

Diabetic kidney disease (DKD) refers to chronic kidney disease (CKD) presumed to be caused by diabetes.1 DKD is detected clinically by screening for persistent abnormal urine albumin excretion (defined as at least two abnormal specimens within a 3- to 6-month period) and by screening for a decreased estimated glomerular filtration rate (eGFR). In most cases, kidney biopsies are not used to establish the presence of diabetic glomerulopathy. Albuminuria has traditionally been divided into microalbuminuria (urine albumin creatinine ratio [ACR] of 30–300 mg/g, equivalent to timed collections of 20–200 μg/min or 30–300 mg/24 hours) or macroalbuminuria (ACR >300 mg/d, timed albumin excretion >200 μg/min or >300 mg/24 hours) (Table 1). Serum creatinine-derived estimates of GFR (previously calculated from the Modification of Diet in Renal Disease Study equation and now estimated using the Chronic Kidney Disease Epidemiology Collaboration formula) can be used to stage DKD, but eGFR alone can only accurately detect stages 3 or higher of CKD (eGFR <60 mL/min/1.73 m²) (Table 2).

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KEYWORDS

- Diabetes • Prevalence • Incidence • Microalbuminuria • Macroalbuminuria • End-stage renal disease

KEY POINTS

- Diabetic kidney disease is a leading cause of chronic kidney disease. This reflects the increasing prevalence of type 2 diabetes globally.
- In type 1 and type 2 diabetes, the presence of microalbuminuria and macroalbuminuria or decreased glomerular filtration rate confers increased risk of developing ESRD and of death.
- Increased risk of albuminuria has been identified in certain non-European ethnic groups.
- Renal impairment in diabetic kidney disease may occur in the absence of albuminuria.
The International Diabetes Federation Diabetes Atlas estimated that in 2011, there were 366 million patients with diabetes worldwide (8.3% of adults), and by 2030, this will increase to 552 million people. Forty-eight percent of this increase is predicted to occur in China and India. The increased diabetes prevalence will disproportionately affect low- and middle-income countries compared with high-income countries. To put the global increase in diabetes in perspective, the average annual growth in diabetes prevalence will be 2.7%, which is 1.7 times the anticipated annual growth in the world’s population. In the United States, 11.3% of people aged 20 years or older had diabetes in 2011 (25.6 million people), with prevalence increasing in older age groups (26.9% of people aged ≥65 years).

Increasing diabetes prevalence is already being reflected in high DKD prevalence. In 2006, the DEMAND study evaluated the presence of DKD in 32,308 patients with type 2 diabetes drawn from medical clinics in 33 countries. The global prevalence of microalbuminuria and macroalbuminuria was 39% and 10% respectively, with Asian and Hispanic patients having the highest prevalence of albuminuria. Twenty-two percent of patients had impaired renal function (eGFR <60 mL/min/1.73 m²). The results from the 2007 to 2010 nationally representative China National Survey of Chronic Kidney Disease give a glimpse of the magnitude of future challenges. The overall prevalence of CKD was 10.7%, affecting an estimated 119.5 million people in China. There was a low prevalence of people with renal impairment (1.7%) compared with albuminuria prevalence (9.4%). Zhang and colleagues noted that this may be because renal impairment from diabetes and other chronic diseases may take another 10 years to be reflected at the population level. A total of 19.1% of those with eGFR less than 60

### Table 1

<table>
<thead>
<tr>
<th>Category</th>
<th>Spot Collection (mg/g creatinine)</th>
<th>24-Hour Collection (mg/24 hours)</th>
<th>Timed Collection (µg/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normoalbuminuria</td>
<td>&lt;30</td>
<td>&lt;30</td>
<td>&lt;20</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>30–300</td>
<td>30–300</td>
<td>20–200</td>
</tr>
<tr>
<td>Macroalbuminuria</td>
<td>&gt;300</td>
<td>&gt;300</td>
<td>&gt;200</td>
</tr>
</tbody>
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### WORLDWIDE BURDEN OF DIABETES AND DKD

The International Diabetes Federation Diabetes Atlas estimated that in 2011, there were 366 million patients with diabetes worldwide (8.3% of adults), and by 2030, this will increase to 552 million people. Forty-eight percent of this increase is predicted to occur in China and India. The increased diabetes prevalence will disproportionately affect low- and middle-income countries compared with high-income countries. To put the global increase in diabetes in perspective, the average annual growth in diabetes prevalence will be 2.7%, which is 1.7 times the anticipated annual growth in the world’s population. In the United States, 11.3% of people aged 20 years or older had diabetes in 2011 (25.6 million people), with prevalence increasing in older age groups (26.9% of people aged ≥65 years).

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### Table 2

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>GFR (mL/min/1.73 m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Kidney damage with normal or increased GFR</td>
<td>≥90</td>
</tr>
<tr>
<td>2</td>
<td>Kidney damage with mild decreased GFR</td>
<td>60–89</td>
</tr>
<tr>
<td>3</td>
<td>Moderately decreased GFR</td>
<td>30–59</td>
</tr>
<tr>
<td>4</td>
<td>Severely decreased GFR</td>
<td>15–29</td>
</tr>
<tr>
<td>5</td>
<td>Kidney failure</td>
<td>&lt;15 or dialysis</td>
</tr>
</tbody>
</table>

mL/min/1.73 m² had diabetes, and 17.3% of those with albuminuria had diabetes. The adjusted prevalence of diabetes in the total Chinese population was 4.9%, based on abnormal fasting plasma glucose or a history of diabetes. This prevalence may be an underestimate, because another recent Chinese representative survey that used an oral glucose tolerance test for diabetes diagnosis reported a prevalence of 9.7%. From India, the other country with an expected large increase in diabetes prevalence, a population-based examination of DKD in urban Chennai reported a prevalence of 2.2% for macroalbuminuria and 26.9% for microalbuminuria. These figures estimate that more than 850,000 people in India had overt DKD in 2007. Unfortunately, most would not be able to afford the cost of renal replacement therapy (RRT) after disease progressed to end-stage renal disease (ESRD).

The US Renal Data System reported high incidence rates of ESRD caused by diabetes in 2009 in certain countries: 58% to 60% in Malaysia and Mexico, and more than 40% in Thailand, New Zealand, Hong Kong, Republic of Korea, Japan, Taiwan, the United States, Israel, and the Philippines. In the United States in 2009, diabetes accounted for most incident cases of ESRD (154 per million patients with ESRD) and also caused most of the prevalent cases (647 per million patients). Since 1996, there has been a 35% decline in the age-adjusted incidence rate for ESRD caused by diabetes, a decline of 3.9% per year. This means that although the total number of ESRD cases caused by diabetes is increasing because of the increasing number of patients with diabetes, the likelihood of developing ESRD if a person is diabetic is decreasing. In the renal registry data from Australia and New Zealand (ANZDATA), the proportion of patients with DKD requiring RRT rose from 17% in 1980 to 35% of new ESRD cases in 2009, but the rate of increase seems to be leveling off since 2005.

The cost of DKD is considerable. The annual treatment cost in 2009 to 2010 for people with ESRD caused by diabetes in Australia was estimated to be $73,527 per person for RRT and $12,174 for conservative treatment. The total cost of DKD in Australia in 2009 to 2010 was $20.5 million for people with diabetes in CKD stages 1 to 4 and $446.3 million for people with ESRD and diabetes. This total cost is projected to double by 2020 in the United States in 2009, Medicare expenditure was $18 billion for people with CKD caused by diabetes. The cost of DKD progression was recently analyzed using information from the Kaiser Permanente Northwest health maintenance organization. Annualized cost increase was calculated for transition to higher stages of DKD. The costs of progression were $2764 from normoalbuminuria, $3618 from microalbuminuria, and $56,745 from macroalbuminuria. This demonstrated clearly that most of the increased cost is caused by development of ESRD. If the rate of GFR decline could be slowed by 10%, the saving to the US health budget would be approximately $9.06 billion.

In summary, the diabetes epidemic has led to substantial increases in numbers of people with DKD and ESRD. The costs for health care are immense. Unfortunately, increased diabetes prevalence will affect regions and populations that may be unable to bear these costs. Urgent attention is therefore needed to prevent DKD and to prevent progression of DKD. The following section will analyze the current epidemiology of diabetic kidney disease in greater detail.

**NEPHROPATHY IN TYPE 1 DIABETES**

*Early Studies*

The clinical significance of microalbuminuria in DKD

The concept of microalbuminuria arose with the development of a sensitive radioactive iodine assay for albumin and demonstration that increased albumin excretion
could be detected in people with diabetes without proteinuria. Several small studies in the early 1980s established that microalbuminuria was important for DKD prognosis in type 1 diabetes. A 14-year follow-up of a cohort from Guy’s Hospital, London (United Kingdom), showed that proteinuria and death occurred in 87.5% and 37.5%, respectively, of those with microalbuminuria compared with 3.6% and 9.1% of those with normal albumin excretion. When this cohort was followed for a further 23 years, 62.5% of those with initial microalbuminuria had died (50% from cardiovascular disease) and 25% had progressed to ESRD. The relative risk (in those with microalbuminuria compared with those with normoalbuminuria) was 9.3 for progression to proteinuria and 2.9 for cardiovascular death.

Mogensen and Christensen published a study of 44 patients with type 1 diabetes and no proteinuria, initially tested in 1969 to 1976 and restudied in 1983. In those who were initially normoalbuminuric, none developed proteinuria and 14% developed microalbuminuria, whereas 86% of those with microalbuminuria progressed to proteinuria. Similar results from Mathiesen and colleagues confirmed that those with albumin excretion at the higher end of the microalbuminuric range had the highest risk of developing proteinuria. Retinopathy, neuropathy, and hypertension were highly prevalent in those with microalbuminuria.

Incidence of proteinuria in DKD

Epidemiologic studies published in the mid 1980s showed a high incidence of ESRD, cardiovascular disease, and death in people with kidney disease caused by type 1 diabetes. For 25 years, Andersen and colleagues at the Steno Memorial Hospital followed 1475 people with type 1 diabetes diagnosed before 1953. A total of 41% developed persistent proteinuria. The cumulative incidence of DKD was 45% after 40 years of diabetes. Maximum DKD prevalence (21%) occurred after 20 years duration of diabetes and declined to 10% by 40 years. A total of 83% of those with proteinuria died (66% from uremia, 19% from cardiovascular disease), compared with 28% of the nonproteinuric patients. Those who developed proteinuria relatively early (<20 years from diagnosis of diabetes) were more likely to die from uremia and survived for approximately 7 years from onset of uremia. Those with later-onset kidney disease died more frequently from ischemic heart disease than uremia.

A study of 1134 patients with type 1 diabetes published 2 years later from the same hospital by Borch-Johnsen and colleagues showed that 40% of patients developed persistent proteinuria, with maximal incidence between 13 and 18 years of diabetes duration. This cohort of patients differed from the cohort in the previous study because the date of diagnosis of type 1 diabetes was limited to 1933 to 1952. Mortality increased after 3 years of proteinuria to 17% per year at 10 to 20 years after onset of proteinuria, after which it declined. Life expectancy was longer for those who were diagnosed later in 1950 compared with 1935. Those without proteinuria maintained a low relative mortality throughout the study.

At the Joslin Clinic, Krolewski and colleagues followed three cohorts of people with type 1 diabetes diagnosed in 1939, 1949, and 1959 for 20 to 40 years to determine if the natural history of nephropathy was changing. The cohorts were limited to whites from eastern Massachusetts who had diabetes less than 1 year before the first visit. The cumulative incidence of persistent proteinuria was 35% after 40 years of diabetes (67 patients), and 42 of these people developed ESRD. The median interval between appearance of persistent proteinuria and ESRD was 10 years. In this study, those who had been diagnosed with diabetes in 1939 had twice the risk of developing proteinuria compared with those in later cohorts.
Summary of early studies
These early studies set the historical context of type 1 DKD. By the 1980s, microalbuminuria had been identified as an early stage of renal damage, and as a predictor of the risk of death or DKD progression. A total of 80% to 90% of those with microalbuminuria progressed to proteinuria. Incident proteinuria occurred in 30% to 40% of patients with type 1 diabetes. Most patients developed ESRD within 10 years of proteinuria onset, and there was high mortality from uremia and cardiovascular disease.

Later Studies
The path from microalbuminuria to proteinuria is not inexorable
From the early studies, it seemed that after a patient developed microalbuminuria, he or she was committed to a path of proteinuria and premature death. However, recent observational studies have shown that microalbuminuria frequently remits. At the Steno Diabetes Center, 10-year follow-up of adult patients with microalbuminuria recruited in 1994 showed that 33% progressed to persistent proteinuria and 16% regressed to persistent normoalbuminuria. Of those who showed regression of microalbuminuria, in 55% it occurred after starting hypertension treatment.27 The Joslin Study of the Natural History of Microalbuminuria followed 386 patients recruited in 1991 to 1992. The 6-year cumulative incidence of persistent proteinuria was 19%. The cumulative proportion of people who regressed in their urine albumin excretion was approximately 60%. Factors independently associated with regression were shorter duration of microalbuminuria and better glycemic, lipid, and blood pressure control.28 These figures are similar to those obtained by Steinke and colleagues29 who followed patients from North America and France over a 5-year period. A total of 64% of patients with persistent microalbuminuria reverted spontaneously to normal albumin excretion during follow-up. In the Diabetes Control and Complications Trial (DCCT), an intensive glycemic treatment group of patients with recently diagnosed type 1 diabetes was compared with a standard diabetes care control group.30 Patients were enrolled from 1983 to 1989 and the trial terminated in 1993 after 6.5 years of treatment. The Epidemiology of Diabetes Interventions and Complications (EDIC) study continued observation of the participants after the end of the DCCT study. Reports from year 16 of the EDIC study (2008–2010) showed that in those who had developed persistent microalbuminuria, 40% regressed to normoalbuminuria.31 Of these, only 24.6% were using renin angiotensin system (RAS) inhibitors at the time of regression. Some patients regressed after more than 10 years of persistent microalbuminuria.

In summary, modern studies demonstrated that in DKD caused by type 1 diabetes, regression of microalbuminuria was more common than progression to proteinuria or ESRD.

Prevalence of DKD caused by type 1 diabetes
A cross-sectional study of people with type 1 diabetes from North Wales from 1999 showed a prevalence of 27.2% for microalbuminuria and 9.6% for overt DKD.32 Renal disease was reported for a large German and Austrian cohort of 27,805 children, adolescents, and adults with type 1 diabetes followed until 2007.33 After 40 years of diabetes, the calculated prevalence of microalbuminuria was 25.4% and calculated prevalence of macroalbuminuria and ESRD combined was 9.4%. Risk factors for development of microalbuminuria were diabetes duration, HbA1c, dyslipidemia, and blood pressure; and for macroalbuminuria, the risk factors were diabetes duration, HbA1c, dyslipidemia, and male gender. Onset of diabetes in childhood protected against development of microalbuminuria.
Incidence of proteinuria in DKD

In 2003, Hovind and colleagues\textsuperscript{34} from the Steno Diabetes Center published data from at least 20 years of follow-up of Danish patients with type 1 diabetes. The patients were divided into 5-year cohorts depending on year of diagnosis (Group A 1965–1969, through to Group D 1979–1984). Cumulative incidence of proteinuria was significantly reduced as the calendar year of diagnosis became more recent: 31.1% in Group A compared with 13.7% in Group D. In the later cohort, antihypertensive medications were started earlier after diagnosis, HbA\textsubscript{1c} and blood pressure were lower, and smokers were less prevalent. Similar results came from the Swedish Linköping study, which studied cohorts of patients diagnosed with childhood type 1 diabetes between 1961 and 1985.\textsuperscript{35} The cumulative proportion of persistent proteinuria occurring after 30 years of follow-up was 32% in those diagnosed between 1961 and 1965 compared with 10.8% in the next oldest cohort from 1966 to 1970. Prevalence of microalbuminuria was not statistically significantly different between the cohorts. Those with nephropathy had the highest mortality (33.3%) compared with 5.7% in those without nephropathy. In contrast to these promising Scandinavian results, in the Pittsburgh Epidemiology of Diabetes Complications Study, there was no decline in proteinuria incidence with calendar year.\textsuperscript{36} This study stratified participants into five cohorts according to year of diagnosis, ranging from 1950 to 1959, to 1975 to 1980. By 25 years, the cumulative incidence of persistent proteinuria was similar in all the cohorts, with a pooled incidence of 25%. However, there was a dramatic decline in 30-year incidence of ESRD, from the cohort diagnosed in the 1950s (31%) to the cohort from 1965 to 1969 (18%). Mortality also fell from 39% to 23% in the respective cohorts. A recent review of type 1 diabetes studies has proposed that the changing pattern of proteinuria may reflect a 5- to 15-year delay in onset of albuminuria due to improved management of glucose, blood pressure and cholesterol, reduced rates of cigarette smoking and increased use of RAS inhibitors, rather than a decrease in cumulative incidence of proteinuria.\textsuperscript{37}

Incidence of ESRD and death

A recent Swedish study showed a 3.3% cumulative 30-year incidence of ESRD in patients with type 1 diabetes.\textsuperscript{38} Onset of ESRD was delayed if the person was prepubertal when diabetes was diagnosed, or if female and 20 years and older at diabetes diagnosis. The Finnish Diabetes Register study of patients with type 1 diabetes diagnosed between 1965 and 1999 had a cumulative 30-year ESRD incidence of 7.8%, with declining risk in those diagnosed after 1969 compared with those diagnosed between 1965 and 1969.\textsuperscript{39} Those diagnosed with diabetes before 5 years of age had the lowest incidence of ESRD. The risk of dying with ESRD was 3.3% after 30 years. The prospective Finnish Diabetic Nephropathy (FinnDiane) study followed adults with type 1 diabetes recruited between 1997 and 2006 for 7 years.\textsuperscript{40} Mortality was compared with that of the age- and gender-matched general Finnish population to obtain a standardized mortality ratio. The standardized mortality ratio was 2.8 for people with microalbuminuria, 9.2 for those with macroalbuminuria, and 18.3 if people had ESRD. An eGFR less than 60 mL/min/1.73 m\textsuperscript{2} was also associated with increased mortality (adjusted hazard ratio, 1.7). Twenty-year outcomes were reported in Austrian patients with type 1 diabetes followed from 1983 to 1984.\textsuperscript{41} ESRD occurred in 5.6% (incidence rate 311 per 100,000 person-years) and mortality was 13% (mortality rate 708 per 100,000 person-years). Mortality risk was twofold higher in patients who originally had microalbuminuria and fourfold higher in those with macroalbuminuria compared with those who had normoalbuminuria.

After 23 years of follow-up in the DCCT/EDIC study, the cumulative incidence of sustained eGFR less than 60 mL/min/1.73 m\textsuperscript{2} was 11.4%.\textsuperscript{42} Of these people, 16%
had microalbuminuria and 61% had macroalbuminuria before developing a reduced eGFR. The rate of decline of eGFR was significantly greater in people with current macroalbuminuria (5.7% per year) or who previously had macroalbuminuria (5.1% per year) compared with those with a current or a previous history of microalbuminuria (1.8% and 1.4%, respectively). The rate of eGFR decline in those with normoalbuminuria was 1.2% per year. Renal outcomes were separately assessed for the 325 participants who developed incident microalbuminuria during the DCCT/EDIC study. Ten-year cumulative incidences were 28% for progression to macroalbuminuria, 15% for development of eGFR less than 60 mL/min/1.73 m², and 4% for ESRD.

A prospective study from the Steno Diabetes Center published in 2005 followed two groups of people with type 1 diabetes over 10 years, one group with persistent macroalbuminuria, the other with persistent normoalbuminuria. Median survival in the group with DKD was 21.7 years. A total of 30% in this group died, compared with 8% in the group with normoalbuminuria. In those with DKD, 42% died of cardiovascular disease and 50% of ESRD. The risk of ESRD in this study was 1.6 per 100 person-years. This low figure contrasts with higher figures from the FinnDiane study and the Joslin Clinic. In the competing-risk analysis of the FinnDiane study, 35.5% of patients with proteinuria developed ESRD and 9.5% died during the median follow-up time of 9.9 years. The incidence of ESRD was 5.1 per 100 person-years. From the Joslin Clinic, Rosolowsky and colleagues reported 15-year cumulative risks of 52% for ESRD and 11% for death before developing ESRD. The incidence rate for ESRD was 5.8 per 100 person-years and mortality rate was 1 per 100 person-years. The disparity between the Steno Diabetes Center results and the other two studies is puzzling, because all the studies were conducted after it became routine clinical practice to use RAS blockade and to treat hypertension and lipids aggressively.

In summary, recent studies have confirmed the older findings relating the risk of eGFR decline, ESRD, and mortality with the level of urinary albumin excretion. In several studies, childhood onset of diabetes was associated with a lower risk of developing advanced DKD. The incidence of proteinuria, ESRD, and death varies considerably among centers. The reported 30-year cumulative incidence of proteinuria is 11% to 32%. The 30-year incidence of ESRD is 3.3% to 7.8%, which is considerably lower than previous reports. Patients with proteinuria are now more likely to proceed to ESRD than to die prematurely. However, cardiovascular disease remains an important cause of mortality.

Renal impairment can occur without albuminuria or without progression from microalbuminuria to proteinuria

From the DCCT/EDIC study, 24% of the patients who developed persistent GFR less than 60 mL/min/1.73 m² did not have any preceding microalbuminuria or macroalbuminuria. This uncoupling of renal impairment from albuminuria was found in previous biopsy studies. The eight renal biopsies reported by Lane and colleagues from women with type 1 diabetes and renal impairment but normal albumin excretion showed similar glomerular pathology to biopsies taken from diabetic women with microalbuminuria, or with microalbuminuria and low GFR. In the study by Caramori and colleagues of normoalbuminuric patients with type 1 diabetes, those with a reduced eGFR had more advanced glomerular lesions on electron microscopic examination. These subjects were more likely to be female, a finding confirmed in the study by Tsalamandris and colleagues.

A study from the Joslin Clinic tracked GFR and urinary albumin excretion in patients with type 1 diabetes and newly diagnosed microalbuminuria for 12 years. A total of 29% developed advanced renal disease (ESRD or stage 3–4 CKD) and these cases had a 50% to 75% decline in GFR over 12 years compared with a 20% decline in those
who did not develop severe renal disease. With regard to the urinary albumin excretion of the advanced renal cases, in those who developed stage 3 to 4 CKD, microalbuminuria had regressed in 18%, persisted in 47%, and 35% progressed to proteinuria. All the patients with ESRD had proteinuria, which developed only after or at the time that GFR began to decline (i.e. proteinuria did not usually precede the onset of GFR decline). In the other patients who did not develop advanced DKD, 50% regressed to normoalbuminuria, 34% had persistent microalbuminuria, and 16% had proteinuria.

In summary, these findings indicate that loss of renal function does not depend on prior development of proteinuria but can occur without any development of microalbuminuria or soon after microalbuminuria onset.

**NEPHROPATHY IN TYPE 2 DIABETES**

**Prevalence of Albuminuria**

The understanding of DKD associated with type 2 diabetes has evolved in parallel with the advances made in understanding DKD caused by type 1 diabetes. Cross-sectional studies of diabetes clinic patients from the 1980s showed a wide range of microalbuminuria prevalence. A Swiss study from 1982 reported a prevalence of 48%; 8.7% of these clinic patients had a GFR less than 60 mL/min.50 By contrast, Parving and colleagues51 from Denmark reported the prevalence of albuminuria in 1987 was 13.8% in adult patients with type 2 diabetes of approximately 10 years duration.

This paragraph presents prevalence of albuminuria from population-based studies. In the Wisconsin Epidemiologic Study of Diabetic Retinopathy, participants were selected from southern Wisconsin and serially evaluated.52 From the 1984 to 1986 examination, there were 840 participants with type 2 diabetes and in these people, the prevalence of microalbuminuria was 24.8% and 20.5% had proteinuria. In the 1988 Italian prevalence survey conducted in Casale Monferrato, 80% (1574) of the total population with type 2 diabetes was examined.53 The prevalence of microalbuminuria was 32.1% and prevalence of macroalbuminuria was 17.6%. Population-based cross-sectional analysis of adults with type 2 diabetes aged 40 years and older was done in the US Third National Health and Nutrition Examination Survey (NHANES III), which sampled the entire adult US civilian population between 1988 and 1994.54 Albuminuria was defined according to the study procedure of single assessment of urinary ACR. Prevalence of microalbuminuria was 35% and prevalence of macroalbuminuria was 6%. The Shanghai Diabetic Complications Study was a community-based sample of 3714 subjects, of which 930 people had type 2 diabetes.55 In those with diabetes, the prevalence of microalbuminuria was 22.8% and the prevalence of macroalbuminuria was 3.4%. A total of 29.6% had an eGFR less than 60 mL/min/1.73 m². The Australian Diabetes, Obesity, and Lifestyle Study (AusDiab study) was a population-based survey of 11,247 adults 25 years and older initially conducted in 1999 to 2000.56 Overall, the prevalence of microalbuminuria in participants known to have diabetes (with type 1 or type 2 diabetes) and participants newly diagnosed with diabetes was 25.3% (21% with microalbuminuria and 4.3% with macroalbuminuria). The prevalence of albuminuria increased with increasing glycemia, so that for the participants newly diagnosed with diabetes (of which most had type 2 diabetes) the prevalence was 17.8% and for participants known to have type 2 diabetes, the prevalence was 32.6%. Longer duration of diabetes increased the prevalence of albuminuria, from 20.9% if duration of diabetes was less than 4 years, to 54.1% if the duration was greater than or equal to 20 years.

In summary, population-based cross-sectional studies show that the prevalence of microalbuminuria in type 2 diabetes is 25% to 35%. The prevalence of macroalbuminuria is 3.5% to 20.5%.
Incidence and Progression of Albuminuric DKD

In 1984, Mogensen\(^5^7\) published 10-year follow-up results of a group of adult patients with type 2 diabetes and found that 22% of those with microalbuminuria had developed proteinuria. Mortality was significantly associated with elevated albumin excretion and if proteinuria was present, mortality was 148% higher compared with normal control subjects. Two studies published in 1988, a 10-year follow-up of Danish patients with type 2 diabetes\(^5^8\) and the study by Nelson and colleagues\(^5^9\) in Pima Indians with type 2 diabetes, confirmed that mortality, particularly cardiovascular mortality, was significantly increased in those with increased urine albumin excretion. The Pima Indians with proteinuria had a relative mortality rate of 3.5 compared with those without proteinuria.\(^5^9\) The cumulative incidence of overt proteinuria in Pima Indians after 20 years of type 2 diabetes was 50%.\(^6^0\) Gall and colleagues\(^6^1\) from the Steno Diabetes Center followed patients who initially had normoalbuminuria for a median of 5.8 years, starting from 1987. A total of 20% developed persistent microalbuminuria and 3% developed persistent macroalbuminuria. Compared with those who remained normoalbuminuric, the patients with DKD tended to be older, male, with higher blood pressure, poor glycemic control, and associated retinopathy.

Results of the United Kingdom Prospective Diabetes Study (UKPDS) have helped to define the natural history of DKD caused by type 2 diabetes. In the UKPDS, 5102 patients with early type 2 diabetes were recruited between 1977 and 1991. These patients were mainly white, normoalbuminuric, and with normal serum creatinine. After a median of 15 years diabetes duration, 38% developed albuminuria (microalbuminuria or macroalbuminuria); 28% had renal impairment (eGFR ≤60 mL/min/1.73 m\(^2\)); and 14% had both albuminuria and renal impairment.\(^6^2\) Annual transition rates were 2% per year from no kidney disease to microalbuminuria, 2.8% per year from microalbuminuria to macroalbuminuria, and 2.3% from macroalbuminuria to elevated plasma creatinine (≥175 μmol/L) or RRT.\(^6^3\) Mortality was high in those who were in this last stage, at 19.2% per year. Similar transition rates were seen in a prospective Swedish National Register study of 3667 adult patients with type 2 diabetes and no baseline renal disease, followed from 2002 to 2007. The rate of transition to albuminuria (mainly to microalbuminuria) was 4% per year, and this occurred in 20% of patients. Of the patients who developed microalbuminuria, 16% developed renal impairment. The rate of development of an eGFR less than 60 mL/min/1.73 m\(^2\) was 2.2% per year (11% of all patients).\(^6^4\)

The prospective Casale Monferrato study followed a community-based sample of 1253 people with type 2 diabetes and normoalbuminuria or microalbuminuria who were recruited in 1991 to 1992.\(^6^5\) Median follow-up was 5.33 years, during which time 3.7% per year progressed to proteinuria (2.5% per year if normoalbuminuric and 5.4% per year if initially microalbuminuric). Microalbuminuria therefore conferred a 42% increased risk of developing overt DKD. Recent evaluation of the DIAMETRIC database derived from two large clinical trials of patients with type 2 diabetes and overt proteinuria at baseline found that over 2.8 years of follow-up, 19.5% developed ESRD.\(^6^6\) The incidence of developing ESRD was 2.5 times the incidence of dying from cardiovascular causes, and 1.5 times the incidence of all-cause mortality. Recently, a meta-analysis was published by the Chronic Kidney Disease Prognosis Consortium in which data were analyzed from 1,024,977 participants, of which 128,505 had diabetes.\(^6^7\) These participants came from cohorts followed for an average of 8.5 years (general population cohorts) or 9.2 years (high-risk cardiovascular cohorts). Across the ranges of eGFR and ACR, the hazard ratios for all-cause mortality and cardiovascular mortality were 1.2–1.9 times higher in those who had diabetes, compared to those without diabetes. When mortality was analyzed for fixed ACR and eGFR
categories and compared to reference ranges of ACR <10 mg/g or eGFR 90–104 ml/min/1.73 m², the hazard ratios for all-cause mortality and cardiovascular mortality increased with lower eGFR or higher ACR in individuals with diabetes.

The recent large glycemic control studies in type 2 diabetes have provided more information about predictors of renal events and cardiovascular outcomes. The Action in Diabetes and Vascular Disease: Preterax and Diamicron-MR Controlled Evaluation study enrolled 10,640 patients. At baseline, 69%, 27%, and 4% were normoalbuminuric, microalbuminuric, and macroalbuminuric, respectively. After 4.3 years of follow-up, 1% developed a renal event (defined as death from kidney disease, RRT, or doubling of serum creatinine >200 μmol/L). After adjusting for regression dilution, for each 10-fold increase in baseline albumin/creatinine ratio, the increase in risks for cardiovascular events, cardiovascular death, and renal events were 2.5-fold, 3.9-fold, and 10.5-fold, respectively. For every halving of baseline eGFR, the risks increased 2.2-fold, 3.6-fold, and 63.6-fold for cardiovascular events, cardiovascular death, and renal events. These data have allowed further refinement of predictors for onset of microalbuminuria (eGFR, urine ACR, systolic blood pressure, HbA1c, retinopathy, baseline antihypertensive medication, Asian ethnicity, and waist circumference) and of major renal events (eGFR, urine ACR, systolic blood pressure, HbA1c, retinopathy, gender, and level of education).

**Ethnic Background and DKD**

The effect of ethnic background was explored in a cohort of type 2 patients with diabetes of general practitioners in the United Kingdom. This study found that South Asian patients, when compared with white patients, had a higher prevalence of overt proteinuria and a lower prevalence of microalbuminuria. When duration of diabetes was taken into account, the South Asians had a lower risk of microalbuminuria early in the course of their diabetes, but also had an odds ratio (OR) of 2.17 versus whites for overt proteinuria. This suggested that DKD in South Asians, once it starts, more rapidly progresses to proteinuria. Ethnic differences in the prevalence of albuminuria in type 2 diabetes have also been documented in a New Zealand study of 65,171 patients with type 2 diabetes attending primary care doctors between 2000 and 2006. After controlling for multiple risk factor variables, compared with Europeans, the ORs for albuminuria were 3.9 for Maori, 4.7 for Pacific Islanders, 2 in Indo-Asians, and 4.1 for East-Asians. Ethnic differences in DKD incidence may reflect genetic predisposition and different access to care. To eliminate the effect of disparity of access, the Pathways Study in the United States was conducted in a setting of uniform access to good quality primary health care (in a large health maintenance organization in Washington state). In this cross-sectional study of 2969 patients with diabetes, ethnic differences in prevalence of albuminuria were found. In patients without hypertension, Asians had ORs of 2.01 for microalbuminuria and 3.17 for macroalbuminuria compared with whites. If patients had hypertension, Hispanics had greater odds of microalbuminuria (OR, 3.82) and blacks had greater odds of macroalbuminuria (OR, 3.32) compared with whites. From the 2009 ANZDATA renal registry data, examination of the incidence rate of RRT for DKD in Australia and New Zealand revealed that 35% of new patients had DKD, of which 92% was caused by type 2 diabetes. Australian indigenous people had a significantly higher incidence rate for RRT compared with nonindigenous Australians (particularly in the age group ≥60 years). Indigenous Australians made up 16.7% of the patients with DKD commencing RRT but only 2.5% of the Australian population in 2009.

In summary, in DKD caused by type 2 diabetes, there is a gradation of risk of ESRD and mortality depending on the level of urine albumin excretion, similar to what is seen
with type 1 diabetes. The range of annual transition rates from normoalbuminuria to microalbuminuria is 2% to 4%, from microalbuminuria to macroalbuminuria 2.8% to 5.4%, and from macroalbuminuria to RRT or high serum creatinine 2.3%. People from Hispanic, black, Asian, Indian, indigenous, Maori, and Pacific Island ethnic backgrounds have increased prevalence of albuminuric DKD compared with Europeans.

The Nonalbuminuric Pathway of DKD

As in type 1 diabetes, renal impairment often develops in those with type 2 diabetes without preceding abnormalities in urine albumin excretion. Maclsaac and colleagues determined the prevalence of impaired GFR in 301 people with type 2 diabetes attending a hospital clinic by using the gold standard of plasma isotopic marker disappearance. In this study, after excluding those taking RAS inhibitors because of their effect on urinary albumin excretion, 23% of the people with renal impairment of CKD stage 3 or worse had preceding persistent normoalbuminuria. In the UKPDS, after a median follow-up of 15 years, 28% of the people with type 2 diabetes developed renal impairment, defined as eGFR less than or equal to 60 mL/min/1.73 m². Of these, 51% had never had microalbuminuria or macroalbuminuria during the study and 16% developed albuminuria only after reaching an impaired eGFR. A total of 33% had albuminuria before onset of renal insufficiency. These results are similar to those obtained by the United States NHANES III. In those with type 2 diabetes and eGFR less than 60 mL/min/1.73 m², 30% had no retinopathy or microalbuminuria or macroalbuminuria. In the Swedish National Diabetes Register cohort studied by Afghahi and colleagues, 6% to 7% developed nonalbuminuric renal impairment within the 5 years of follow-up. Only one-third of those who developed renal failure had developed albuminuria.

A contemporary Australian study of patients attending general practitioners for type 2 diabetes management showed that 55% of those with stage 3 or lower CKD had persistent normoalbuminuria. The clinic-based, cross-sectional, global DEMAND study examined the prevalence of normoalbuminuric renal dysfunction in 11,573 adults with type 2 diabetes. The overall prevalence of normoalbuminuria was 51%. For CKD stages 3 to 5, those with normoalbuminuria formed 41%, 26% and 29% respectively of the total number of patients within each stage. A cross-sectional Italian study (The Renal Insufficiency and Cardiovascular Events [RIACE] study) of 15,773 adult patients with type 2 diabetes attending public hospital clinics in 2007 to 2008 showed that 56.6% of those with eGFR less than 60 mL/min/1.73 m² were normoalbuminuric. In this population, when those with nonalbuminuric renal impairment were compared with those with albuminuric renal impairment, the two groups had different clinical associations. The nonalbuminuric pathway had weaker associations with retinopathy, HbA₁c, and hypertension, but significant associations with female gender, nonsmoker status, and cardiovascular complications. The patients tended to have shorter duration of diabetes and were less likely to be on an angiotensin-converting enzyme inhibitor or on angiotensin receptor blocker treatment compared with those who had progressed down the albuminuric pathway. The two pathways had a similar association with age of the patient. Logistic regression analysis showed the OR of cardiovascular events was 1.52 for nonalbuminuric CKD and 1.90 for albuminuric CKD. For cardiovascular events, there was a stronger relationship between nonalbuminuric CKD and coronary events (OR, 1.514) than for cerebrovascular or peripheral events, and conversely, the association with cerebrovascular and peripheral events (OR, 1.69 and 1.88, respectively) was stronger for albuminuric CKD than for nonalbuminuric CKD.

In summary, renal impairment without albuminuria has become the most common presentation of renal disease in type 2 diabetes. The recent RIACE Italian study
does not support previous conjecture that this change in presentation was caused by age-related GFR classification as stage 3 or higher CKD or because of widespread use of RAS inhibitors. The two pathways of developing DKD (albuminuric vs nonalbuminuric) have different risks of associated cardiovascular disease.

KIDNEY FUNCTION IN PREDIABETIC STATES

Changes in kidney function can be detected in the stages of impaired glucose tolerance (IGT) or impaired fasting glucose (IFG), collectively termed “prediabetes.” Prediabetes affects 35% of US adults. A total of 280 million adults worldwide were estimated to have IGT in 2011 (6.4%) and this is projected to reach 398 million (7.1%) by 2030. Even in these prediabetic stages, abnormalities are evident in pathways leading to kidney damage; for example, young adult African Americans with IGT had elevated urinary transforming growth factor-β levels compared with those with normal glucose tolerance. There has been a body of work examining the significance of abnormal GFR in people with prediabetes. Definition of an abnormal GFR, such as hyperfiltration, depends in part on identification of the age-appropriate GFR within a control healthy population. So far, there has been no consensus on the definition of hyperfiltration. A carefully conducted Japanese study by Okada and colleagues recently found that the prevalence of hyperfiltration increased as prediabetes worsened. In this study, hyperfiltration was defined as an eGFR greater than the 95th percentile of the age- and gender-specific eGFR, determined in 99,140 people in the Aichi prefecture. Prediabetes was diagnosed if the person had IFG. The ORs of hyperfiltration were 1.29 for stage 1 prediabetes (fasting plasma glucose 100–109 mg/dL) and 1.58 for stage 2 prediabetes (fasting plasma glucose 110–125 mg/dL). However, in this study, there was no association between prediabetes and decreased GFR. Similar results were found in a Norwegian study, the Renal Iohexol Clearance Survey. The OR for hyperfiltration in those with IFG compared with those with normal fasting glucose was 1.56. Decreased GFR has also been associated with prediabetes. In the 1999 to 2006 US NHANES, the prevalence of CKD stage 3 to 4 in people with IFG was 8.5%. Overall prevalence of CKD (defined by low eGFR or albuminuria) in prediabetes was 16.6%.

In summary, studies in people with prediabetes have shown evidence of early renal damage, demonstrated by albuminuria or abnormal GFR.

SUBCLINICAL CHANGES IN KIDNEY FUNCTION THAT OCCUR EARLY IN DIABETES

Nelson and colleagues assessed serial GFR changes in Pima Indians with normal glucose tolerance and IGT. Although at baseline there was no statistically significant difference in GFR between those with normal glucose tolerance and IGT, people who progressed to type 2 diabetes showed a 30% increase in GFR at onset of diabetes. A recent longitudinal study of people with type 2 diabetes and GFR greater than or equal to 120 mL/min/1.73 m² showed that those with persistent hyperfiltration had a hazard ratio of 2.16 for progression to albuminuria compared with those in whom hyperfiltration resolved or who did not have baseline hyperfiltration. Over 4 years, GFR decline was relatively rapid at 3.37 mL/min/1.73 m² per year. A meta-analysis of 10 studies in people with type 1 diabetes concluded that those with hyperfiltration had increased risk of progressing to DKD.

Measurement of serum cystatin C can improve detection of mild degrees of renal dysfunction. In a landmark study, Perkins and colleagues demonstrated that serial cystatin C measurements done over 4 years, when compared with iohexal clearance in Pima Indians with type 2 diabetes and GFR greater than 120 mL/min/1.73 m²,
could be used to detect early trends in renal function. Directly measured GFR declined at 4.4% per year. This technique was used to detect early renal function decline in people with type 1 diabetes from the Joslin Clinic, followed for 8 to 12 years. Early renal function decline was detected in 9% of people with normoalbuminuria and 31% with microalbuminuria. Skupien and colleagues have recently demonstrated that the slope of the early eGFR decline observed over 5 years predicted the risk of developing ESRD in people with type 1 diabetes.

In summary, subtle changes in GFR (hyperfiltration and rate of GFR decline) occurring early in the course of diabetes have been associated with DKD prognosis but these associations need to be confirmed.

SUMMARY

The increasing prevalence of diabetes has led to DKD becoming the leading cause of ESRD in many regions. The economic cost of DKD will grow to prohibitive amounts unless strategies to prevent its onset or progression are urgently implemented. In type 1 and type 2 diabetes, the presence of microalbuminuria and macroalbuminuria confers increased risk of developing ESRD and of death. Comparison of recent studies with earlier historical studies shows that the incidence of ESRD and death has decreased in DKD. Increased risk of albuminuria has been identified in certain non-European ethnic groups. However, the initial concept of progression of DKD as an albuminuric phenotype involving development of microalbuminuria, macroalbuminuria, and then ESRD has had to be modified. Albumin excretion frequently regresses, and GFR can decline without abnormality in albumin excretion. There is emerging evidence that changes in renal function occurring early in the course of diabetes predict future outcomes. The major challenges are to prevent DKD onset, to detect it early, and to improve DKD outcomes globally.

REFERENCES


