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REVIEW ARTICLE

Epidemiological characteristics of diabetic kidney disease in Taiwan

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ABSTRACT

Diabetic kidney disease (DKD) is a critical microvascular complication of diabetes. With the continuous increase in the prevalence of diabetes since 2000, the prevalence of DKD has also been increasing in past years. The prevalence of DKD among individuals with type 2 diabetes in Taiwan increased from 13.32% in 2000 to 17.92% in 2014. The cumulative incidence of DKD among individuals with type 1 diabetes in Taiwan was higher than 30% during 1999–2012. DKD is the leading cause of end-stage renal disease (ESRD), with a prevalence of approximately 45% in a population on chronic dialysis in Taiwan. Among individuals with type 2 diabetes, the prevalence of ESRD in the receipt of dialysis also increased from 1.32% in 2005 to 1.47% in 2014. Risk factors for DKD development are age, race, family history, hyperglycemia, hypertension, dyslipidemia, dietary patterns, and lifestyles. Prognostic factors that aggravate DKD progression include age, family history, sex, glycemic control, blood pressure (BP), microvascular complications, and atherosclerosis. This review summarizes updated information on the onset and progression of DKD, particularly in the Taiwanese population. Translating these epidemiological features is essential to optimizing the kidney care and improving the prognosis of DKD in Asian populations.

INTRODUCTION

Diabetic kidney disease (DKD) is a devastating diabetic microvascular complication, leading to considerably high burdens on health care costs. With the global increase in the prevalence of diabetes, the number (prevalence) of people with chronic kidney disease due to type 2 diabetes has increased from 81,514,189 (1.39%) in 1999, 101,027,301 (1.52%) in 2009 to 129,560,073 (1.74%) in 2019[1], DKD has been increasing over past decades. According to a report of the Developing Education on Microalbuminuria for Awareness of Renal and Cardiovascular risk in Diabetes study[2], approximately 49% and 22% of patients with type 2 diabetes worldwide, respectively, had a urine albumin to creatinine ratio (UACR) of ≥30 mg/g and an estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73 m^2. In Taiwan, DKD is currently the leading cause of end-stage renal disease (ESRD), accounting for approximately 45% of the population on chronic dialysis[3].

Diabetic kidney disease is associated with high risks of cardiovascular diseases and mortality. In particular, it is a risk multiplier in people with hypertension and diabetes[4]. The United Kingdom Prospective Diabetes Study (UKPDS) disclosed that annually, 2.3% of people with type 2 diabetes and macroalbuminuria progressed to a plasma creatinine level of ≥1.98 mg/dL or received renal replacement therapy (RRT); these patients also had a 4.6% annual rate of all-cause death and 3.5% annual

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rate of cardiovascular mortality[5]. A study from Steno Diabetes Center indicated that annually, 2.7% of persons with type 2 diabetes and nephropathy progressed to ESRD, with a 2.6% annual rate of death and 7.5% annual rate of cardiovascular disease[6]. In an Asian study in Hong Kong, So *et al.* reported that annually, 3.5% of Chinese individuals with type 2 diabetes at stage 3 chronic kidney disease (CKD) progressed to renal end points (reduction in eGFR by >50%, progression to stage 5 CKD, dialysis, or death), with a 1.1% annual rate of all-cause mortality and 2.1% annual rate of cardiovascular diseases (Figure 1)[7]. Wen *et al.* investigated Taiwanese people with type 2 diabetes and early CKD (stage 1–3) and found a 2.8% annual rate of all-cause death and 0.6% annual rate of cardiovascular mortality[8]. According to the aforementioned epidemiological evidence, DKD deserves thorough investigation to enable the development of strategies for preventing serious health consequences.

Ethnicity has been shown to play a crucial role in the development and progression of diabetes and DKD. Compared with their Caucasian counterparts, Asians with diabetes usually exhibit a higher DKD prevalence, and those with DKD present a rapid deterioration and a high mortality rate[9–14]. The ethnic disparity may be caused by a distinct genetic predisposition, socioeconomic background, lifestyle patterns, and environmental hazard exposures; however, most published epidemiological studies have focused mainly on epidemiological features in Western countries. Therefore, this study delineated the unique epidemiological pattern of DKD in Asian populations, especially focusing on studies conducted with Taiwanese participants.

Diabetic kidney disease refers to kidney disease that is specific to diabetes mellitus. Although kidney biopsy is required to definitively diagnose diabetic glomerulopathy, it is an interventional procedure and cannot be used routinely to diagnose DKD. Therefore, the presence of UACR $\geq$ 30 mg/g or eGFR < 60 mL/min/1.73 m^2 for more than 3 months in patients with diabetes is used to define DKD[15]. The DKD outcome determinants include risk factors that promote the initiation of DKD development and prognostic factors that may aggravate the progression of DKD to worse renal dysfunction, ESRD, composite cardiovascular diseases risk, or even death. Most risk factors and prognostic factors of DKD are identical (e.g., poor glycemic control); however, some indicators have different mechanisms by which they initiate or worsen DKD status (e.g., obesity is a risk factor for DKD development but it may prevent those with late DKD/ESRD from deterioration). However, most review articles have not elucidated distinctions between risk factors for and prognostic factors of DKD, which make interpretation difficult. In this review, we discuss these two 'seemingly similar but not exactly the same' factors separately to aid clinical practice.

EPIDEMIOLOGY OF DIABETES AND DKD

The prevalence of diabetes has been increasing worldwide since 2000, with 463 million people aged 20–79 years having diabetes worldwide in 2019, corresponding to a prevalence of 9.3%[16]. These numbers, respectively, are estimated to reach nearly 700 million and 10.9% by 2045[16]. Among the 10 geographic regions of the world, the Western Pacific region has the highest number of people with diabetes[16]. The prevalence of diabetes among people older than 20 years in Mainland China was 9.7% in 2007–2008[17], and it increased to 11.6% in 2010[18]. According to

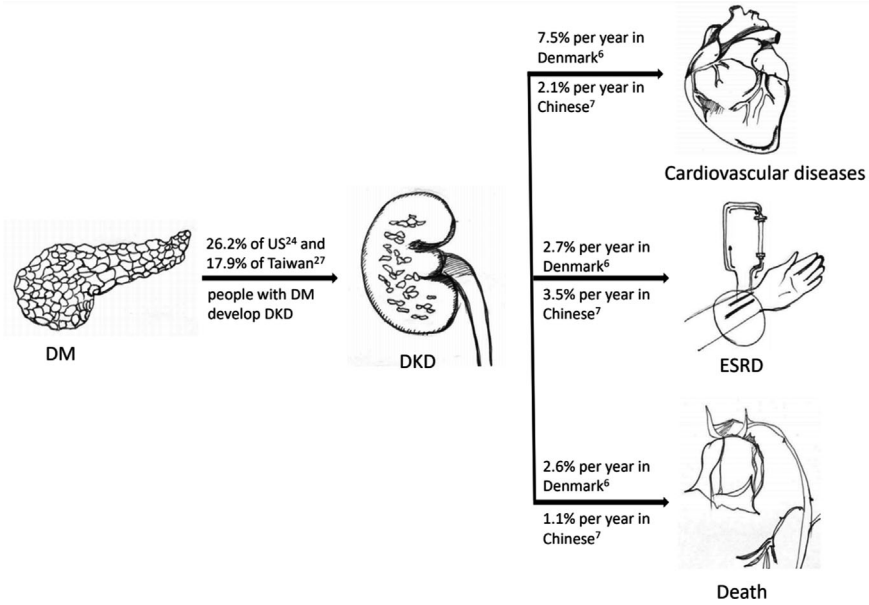

Figure 1| | Rates of progression from diabetes mellitus (DM) to diabetic kidney disease (DKD), end stage renal disease (ESRD), cardiovascular diseases, and death.

a recent analysis based on the National Health Insurance database, the incidence of diabetes in Taiwan among people aged 20–79 years showed a modest increase from 2005 (0.79%) to 2014 (0.88%)[19]. However, the prevalence of diabetes increased from 7.15% to 10.10% during the same period[19], possibly due to the prolonged life expectancy of the Taiwanese population. The prevalence of diabetes among adults (20–79 years) in Taiwan was estimated to be 10.0% and 10.9%, respectively, in the 2015 and 2017 IDF Diabetes Atlas[20,21]; however, it was reported as 6.6% in the 2019 IDF Diabetes Atlas[16]. From the study[19] that used the reliable national insurance database in Taiwan and the previous 2015 and 2017 IDF reports, the prevalence of diabetes in Taiwan may be underestimated in the 2019 IDF Diabetes Atlas.

Diabetic kidney disease is a chronic complication of diabetes and an important risk factor for CKD[22]. Because of the continual increase in diabetes prevalence in Taiwan, CKD and ESRD have become serious burdens on the national health care system. Taiwan has the highest incidence and prevalence of ESRD requiring chronic dialysis in the world, with a 52.5% increase in incidence for the past 18 years (from 331 in 2000 to 504 per million population in 2017) and a 140% increase in prevalence during the same period (from 1,448 in 2000 to 3,480 per million population in 2017). Of the nearly 90,000 patients under chronic dialysis, more than 46% had received a diagnosis of DKD as the primary cause of dialysis initiation[23].

According to several cross-sectional studies in the United States, no obvious change in the prevalence of DKD was observed from 1988–1994 (28.4%) to 2009–2014 (26.2%)[24]. Although a significant decrease in the prevalence of albuminuria was observed (from 20.8% to 15.9%) in the United States during the same period, the rate of renal dysfunction, defined as an eGFR of <60 mL/min/1.73 m^2, increased significantly from 9.2% to 14.1%[24]. Compared with Caucasians, the Chinese population had a higher risk (prevalence 27.6% vs 24.8%) of proteinuric DKD but a lower risk (6.3% vs 11.7%) of nonproteinuric DKD[25]. Based on the studies that used the National Health Insurance database, the prevalence of DKD among persons with diabetes in Taiwan increased from 13.32% in 2000 to 15.42% in 2009[26] and further increased to 17.92% in 2014[27]. The prevalence of ESRD requiring dialysis in patients with diabetes also increased from 1.32% in 2005 to 1.47% in 2014[27]. The cumulative incidence of DKD among patients with type 1 diabetes in Taiwan was even higher than 30% during 1999–2012[28]. Although the overall DKD prevalence among patients with diabetes was lower in Taiwan than in the United States (Figure 1), the increasing trend and the persistent burden attributable to ESRD requiring dialysis confirm that DKD is an urgent public health concern.

RISK FACTORS FOR DKD DEVELOPMENT

According to some systemic reviews[29–31], the risk factors for DKD development may be divided into two categories: unmodifiable risk factors such as age, ethnicity, family history, and genetic susceptibility and potentially modifiable ones such as hyperglycemia, hypertension, dyslipidemia, dietary patterns, and lifestyles (Table 1).

Demographic and hereditary factors

Older age, diabetes onset at young age, prolonged diabetes duration, and male sex are some globally recognized demographic factors related to DKD initiation[30]. Asians as well as black people, American Indians, Hispanics, and Pacific Islanders were reported to be more susceptible to DKD[30]. With regard to family history and genetic predisposibility[29], some hereditary markers have recently been identified in Chinese diabetic patients. Liao *et al.* conducted a case–control study to identify diabetic nephropathy-related susceptible variants in Han Chinese persons with type 2 diabetes. They indicated that some novel single-nucleotide polymorphisms (SNPs) and haplotypes located at the 16q22.1 region are involved in the biological pathways (these SNP polymorphisms are related to production of glucose, inflammation, cytokines, and transforming growth factor-beta and may lead to DKD) of DKD (Table 1)[32]. These SNP polymorphisms have not been reported for DKD in Han Chinese. The proportions of minor alleles of SNPs rs11647932 and rs6499323 among Taiwanese were similar to those of Han Chinese in China, but higher than those of Japanese, Europeans, and Africans[32]. Chang *et al.* examined IL-6 polymorphisms and the development of DKD in a prospective Taiwanese type 2 diabetes cohort and revealed that Taiwanese populations with type 2 diabetes and IL-6 gene polymorphisms [rs1800796 GG, adjusted hazard ratio (aHR) 1.98 (1.05–3.73); and rs1524107 CC, aHR 1.95 (1.03–3.68)] may be more likely to experience chronic inflammation and exhibit higher risks of incident DKD[33]. The evidence for the correlation between IL-6 polymorphisms and the risk of DKD has also been found in Japanese, Korean, and Caucasian patients[33]. Chung *et al.* also investigated the association of 18 ADIPOQ polymorphisms with DKD development in the same type 2 diabetes cohort. Their study revealed that ADIPOQ genetic polymorphisms rs2241766, rs1063537, rs2241767, and rs2082940 were correlated with the progression of incident DKD in Taiwanese men with type 2 diabetes[34]. The correlation of these SNPs with the progression of DKD in this study has also been reported among Korean, and European patients with some discrepancies[34].

Hyperglycemia

Persistently poor glycemic control is one of the most important risk factors for DKD. The reduction in the incidence of DKD in the United States since 1997 was attributed to the sustained improvement in diabetes care over the decades[35]. The benefit of better glycemic control in reducing DKD incidence was evident in both type 1 and type 2 diabetes cohorts. In the UKPDS, which recruited persons with new diagnoses of type 2 diabetes, after a 10-year intensive glycemic intervention targeted to achieve a hemoglobin A1c (HbA1c) of <7%, a 24%

Table 1| | Studies on the risk factors for DKD development

Authors (year)[reference]	Study design	Number of patients	Main findings
Hsu *et al.* (2010)[54]	Cross-sectional	509 men with type 2 diabetes	Dose-response effect of cigarette smoking on the development of proteinuria
Hsu *et al.* (2011)[55]	Prospective	738 patients with normoalbuminuric type 2 diabetes	Insulin resistance predicted the development of microalbuminuria in patients with type 2 diabetes
Hsu *et al.* (2012)[40]	Prospective	821 patients with type 2 diabetes and normoalbumiuria	HbA1c variability, even measured as early as 2 years, was independently associated with the development of microalbuminuria
Chang *et al.* (2013)[48]	Prospective	864 patients with type 2 diabetes	Stable and higher mean HDL-C levels were associated with lower risks of DKD development
Hsu *et al.* (2013)[56]	Prospective	851 patients with type 2 diabetes	Hyperferritinemia may be an independent risk factor of nephropathy in patients with type 2 diabetes
Liao *et al.* (2014)[32]	Case–control	217 diabetic nephropathy cases and 357 controls	SNPs rs11647932, rs11645214, and rs6499323 located at 16q22.1 were associated with 2-fold increased risk of DKD. 11 Haplotypes (4, 3, and 4 haplotypes in window size of 3-SNP, 4-SNP, and 5-SNP) located in the chromosome 16q22.1 region increased the DKD risk
Chung *et al.* (2014)[34]	Prospective	566 type 2 diabetes with normoalbuminuria	ADIPOQ genetic polymorphisms were correlated with incident DKD in Taiwanese men with type 2 diabetes
Sheen *et al.* (2014)[44]	Prospective	215 outpatients with type 2 diabetes	SBP is a powerful modifiable risk factor for incident albuminuria and a rapid renal function decline
Tsai *et al.* (2014)[49]	Case–control	6,406 patients with type 2 diabetes	A positive temporal relationship was found between nonsteroidal anti-inflammatory drug use and increased risk of DKD
Lin *et al.* (2014)[51]	Prospective	559 patients with type 2 diabetes without renal disease	Physical activity is a potential treatment for reducing incident DKD
Chang *et al.* (2016)[33]	Prospective	568 patients with type 2 diabetes and normoalbumiuria	IL-6 gene polymorphisms rs1800796 and rs1524107 can be used as predictors of the development of nephropathy in Taiwanese patients with type 2 diabetes
Yeh *et al.* (2017)[45]	Retrospective	789 patients with newly diagnosed type 2 diabetes	Variability in SBP and DBP was correlated with DKD
Chung *et al.* (2017)[53]	Prospective	1,187 patients with type 2 diabetes	Obese persons with excessive central fat, large weight gain (>10%), and increases in WC (>15%) were independently associated with incident DKD
Lin *et al.* (2020)[57]	Prospective	2,797 patients with type 2 diabetes	Higher intake of pickled foods was associated with renal function decline (≧40% drop in the estimated glomerular filtration rate)

DBP, diastolic blood pressure; DKD, diabetic kidney disease; HDL-C, high density lipoprotein-cholesterol; SBP, systolic blood pressure; T2D, type 2 diabetes; WC, waist circumference.

reduction was achieved in the development of microvascular complications, including DKD, compared with the conventional therapy[36]. After 12 years, the UKPDS group receiving intensive glycemic intervention exhibited a 33% reduction in the risk of proteinuria and a significant reduction in the proportion of patients with a doubling of the blood creatinine level (0.9% vs 3.5%) relative to the conventional therapy group[37]. Similarly, the Diabetes Control and Complications Trial (DCCT) recruited persons with early stage type 1 diabetes; intensive glucose intervention targeted to achieve a HbA1C level <7% reduced the 9-year risks of microalbuminuria and overt proteinuria by 34% and 56%, respectively, compared with standard care[38]. After a median follow-up of 22 years, the intensive intervention group in the DCCT exhibited approximately 50% lower risk of eGFR <60 mL/min per 1.73 m^2[39]. In accordance with the results of previous studies, Hsu *et al.* serially measured HbA1c over 5 years to assess the risk of microalbuminuria in Taiwanese patients with type 2 diabetes and found that in addition to the mean HbA1c values, HbA1c variability was independently and more significantly associated with the development of microalbuminuria[40].

Hypertension

High blood pressure is a crucial risk factor for DKD in individuals with both type 1 diabetes and type 2 diabetes. Persons with type 1 diabetes usually have a normal blood pressure at

diagnosis but exhibit hypertension near the onset of microalbuminuria[41]. The UKPDS trial treated persons with type 2 diabetes to a target blood pressure of 150/85 mmHg over a median of 15 years and revealed a significant 37% reduction in microvascular complications compared with those treated to a target blood pressure of 180/105 mmHg[42]. The Appropriate Blood Pressure Control in Diabetes trial randomly assigned 480 persons with type 2 diabetes to intensive (target BP of approximately 128/75 mmHg) and moderate (target blood pressure of approximately 137/81 mmHg) control. After a 5-year follow-up period, intensive control in normotensive type 2 diabetes persons delayed the progression to incipient and overt diabetic nephropathy but did not demonstrate any benefit for creatinine clearance reduction[43]. In line with the results of previous studies, Sheen *et al.* investigated 215 type 2 diabetes outpatients without symptomatic cardiovascular disease for 12 months in Taiwan and revealed that systolic blood pressure (SBP) is a powerful modifiable independent risk factor [adjusted odds ratio (OR) 1.023 (1.001–1.046)] for incident albuminuria and a rapid renal function decline[44]. Yeh *et al.* evaluated the relationship between the variability in blood pressure and the magnitude of renal function impairment in Taiwanese type 2 diabetes patients with normal renal function. They found that the visit-to-visit variabilities in SBP and diastolic blood pressure (DBP) were correlated with new-onset DKD in the first decade after type 2 diabetes diagnosis[45].

Dyslipidemia

Dyslipidemia, including high triglycerides, low-density lipoprotein (LDL) cholesterol, apolipoprotein-B-100, and low high-density lipoprotein (HDL) cholesterol levels, is independently associated with the development of DKD in both type 1 diabetes and type 2 diabetes cohorts[29]. However, which lipids play the most important role in the pathogenesis of DKD remain unclear. The Fenofibrate Intervention and Event Lowering in Diabetes[46] and Action to Control Cardiovascular Risk in Diabetes studies[47] have disclosed that the use of fenofibrate reduced albuminuria and attenuated eGFR decline. Chang *et al.* assessed the association of mean values and variability in metabolic parameters (blood pressure, blood glucose, and lipid levels) with the development of DKD in a Taiwanese type 2 diabetes cohort and demonstrated that persons with stable and higher mean HDL-C levels had lower risk [aHR 0.971 (0.953–0.989)] of incident DKD[48].

Renal injuries

Acute kidney injury, medications, toxins, smoking, and recurrent infections are potential initiators of DKD[29,30]. Tsai *et al.* investigated the temporal relationship between nonsteroidal anti-inflammatory drug (NSAID) use and the development of CKD in a type 2 diabetes cohort[49] and found that compared with persons who did not take any NSAIDs, those who took NSAIDs for at least 90 days had a 37% higher risk of DKD development.

Lifestyles, dietary patterns, obesity, and insulin resistance

Sedentary lifestyle, high protein or sodium intake, obesity, and insulin resistance are associated with the development of DKD[29,30]. The Look AHEAD study revealed a significant reduction in incident albuminuria after a multifactorial diet and lifestyle intervention[50]. Several empirical studies have conducted in Taiwan illustrated a clear relationship between healthy lifestyle (physical activity, body weight loss, and abstinence of smoking) and DKD development in patients with type 2 diabetes. Lin *et al.* assessed the effect of physical activity [The questionnaire asked patients whether they had activities (Yes) such as walking, running, cycling, and so on, or not (No)] in persons with type 2 diabetes on the prevention of DKD. They demonstrated that physical activity reduced the probability of new-onset DKD by approximately 70%[51]. Obesity alone can promote the development of focal and segmental glomerulosclerosis, resulting in high proteinuria[52]. Chung *et al.* conducted a cohort study and indicated that obese persons with excessive central fat (measured by waist circumference) were more likely to have DKD; a weight gain of >10% and waist circumference increase of >15% independently predicted new-onset DKD[53]. In a cross-sectional study, Hsu *et al.* demonstrated a dose–response effect of cigarette smoking (especially those who smoked 15–30 or more than 30 pack-years) on the development of DKD and suggested that diabetic patients should quit smoking regardless of age, duration of diabetes mellitus, and status of blood pressure control[54]. Insulin resistance (IR) is also independently associated with DKD irrespective of its association with body weight, glucose, BP, and lipid control. Hsu *et al.* assessed the relationship between IR [homeostasis model assessment of insulin resistance (HOMA-IR)] and microalbuminuria in a prospective Taiwanese cohort of type 2 diabetes and confirmed that insulin resistance could significantly predict the development of microalbuminuria in persons with type 2 diabetes[55]. Hsu *et al.* surveyed 851 patients with type 2 diabetes and found hyperferritinemia, a chronic inflammatory marker with an impact on IR, was a predictor of incident DKD in Taiwan[56]. Lin *et al.* evaluated the relationship of unhealthy dietary behaviors with renal function decline in 2797 patients with type 2 diabetes and concluded that eating more pickled foods (The frequency of eating pickled foods was quantified as score 1: no eating, score 2: ≦1 time/month, score 3: 2–3 times/month, score 4: 1–2 times/week, score 5: 3–4 times/week, score 6: 5–6 times/week, score 7: 1 time/day, score 8: 2–3 times/day, score 9: 4–6 times/day) was associated with renal function decline defined as a ≥40% drop in the eGFR[57].

PROGNOSTIC FACTORS INFLUENCING DKD PROGRESSION OR MORTALITY

Identifying the prognostic factors of DKD and delaying DKD progression at early stages are crucial strategies for preventing the development of ESRD, cardiovascular complications, and premature death (Table 2)[58]. The bad outcomes of DKD included mortality, cardiovascular events, renal dysfunction

Table 2| | Studies on the prognostic factors of DKD

Authors (year)[reference]	Study design	Number of cases	Main findings
Hsu *et al.* (2014)[81]	Cohort	28,497 patients with type 2 diabetes and advanced CKD	ACEi or ARB were associated with 6% lower risk of long-term dialysis or death
Chung *et al.* (2014)[85]	Prospective	376 patients with type 2 diabetes	High PUFA concentrations, especially n-3 or higher n-3/n-6 PUFA ratio, may exert protection against renal function impairment
Hsu *et al.* (2014)[87]	Prospective	635 patients with type 2 diabetes	Frequent intake of fish and vegetables may be related to better kidney function
Hung *et al.* (2014)[88]	Prospective	105 patients with type 2 diabetes and CKD stage 3 or 4	BMI ≧ 25 kg/m^2 was a protective factor for renal function deterioration
Liao *et al.* (2015)[68]	Cohort	51,681 patients aged ≧30 years with type 2 diabetes	HbA1c level ≧ 7.0% and HbA1c < 6.0% were linked with increased ESRD risk
Chang *et al.* (2015)[75]	Prospective	362 type 2 diabetes and DKD patients	ABI < 0.9 was associated with higher risk of adverse events (mortality, CVD, and diabetic foot)
Lee *et al* (2015)[69]	Retrospective	101 patients with type 2 diabetes and DKD	Severe hypoglycemia was associated with deterioration of renal function
Chen *et al.* (2015)[70]	Prospective	2,632 haemodialysis patients with diabetes as comorbidity and 13,160 matched patients with DKD	Patients with diabetes as the primary kidney disease have worse survival than chronic hemodialysis patients with comorbid diabetes
Chen *et al.* (2015)[83]	Cohort	12,350 diabetic patients with advanced CKD	TZD users were associated with lower risk of ESRD and death than TZD nonusers
Kuo *et al.* (2016)[66]	Prospective	2,401 patients with type 2 diabetes with stage 3–5 CKD	Higher HbA1c level is associated with higher risks of clinical outcomes in diabetic patients with stage 3–4 CKD but not stage 5 CKD
Wen at al. (2017)[8]	Cohort	9,067 patients with type 2 diabetes with early DKD	Physical inactivity, smoking, alcohol drinking, and obesity could amplify the mortality risk
Hung *et al.* (2017)[71]	Cohort	1,330 patients with type 2 diabetes and DKD	Diabetic retinopathy was associated with poorer renal outcomes
Shen *et al.* (2017)[91]	Retrospective	196 patients with newly diagnosed type 2 diabetes	Intensive short-term multidisciplinary interventions may reduce coronary heart disease and nephropathy
Kuo *et al.* (2018)[67]	Cohort	1,558 patients with type 2 diabetes with stages 3–4 CKD	Higher HbA1c in patients with Hb ≧ 10 g/dL was associated with worse clinical outcomes (ESRD, all-cause mortality, and composite endpoint). The relationship did not exist in patients with Hb < 10 g/dL
Zhang *et al.*(2018)[73]	Cross-sectional	250 patients with type 2 diabetes and biopsy-proven DKD	Diabetic retinopathy remained an independent risk factor for progression to ESRD after adjustment for important clinical variables
Lin *et al.* (2018)[79]	Cohort	1,958 patients with type 2 diabetes and CKD stages 1–5	Hematuria was associated with an increased risk of ESRD
Chou *et al.* (2019)[61]	Cohort	55 patients with biopsy-proven DKD compared with 48 patients with glomerulonephritis and 82 patients with lupus nephritis	Patients older than 65 years and with lower serum albumin levels were independently associated with overall death
Lin *et al.* (2019)[74]	Cohort	4,050 patients with type 2 diabetes with CKD	Diabetic retinopathy was a risk factor for CKD progression
Chen *et al.* (2019)[81]	Cohort	125,490 patients with incident DKD	Traditional Chinese medicine users were associated with a 52% reduction of mortality risk and 19% reduction of ESRD risk
Chuang *et al.* (2019)[86]	Retrospective cohort	935 patients with type 2 diabetes	The presence of metabolic syndrome independently predicted DKD progression

ABI, ankle brachial index; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; CKD, chronic kidney disease; CVD, cardiovascular disease; DKD, diabetic kidney disease; ESRD, end-stage renal disease; Hb, hemoglobin; PUFA, polyunsaturated fatty acid; T2D, type 2 diabetes.

progression, and ESRD. According to a meta-analysis, to better predict cardiovascular outcomes (such as cardiovascular mortality, heart failure, coronary disease, and stroke) in patients with CKD, researchers should include both eGFR and albuminuria in the study designs in addition to traditional risk factors. The outcome prediction power of eGFR and albuminuria was especially important in individuals with diabetes or hypertension[59].

Age, sex, family history, and ethnicity

The clinical and biochemical characteristics associated with the progression of DKD include older age, family history, male sex, diabetes onset at young age, glycemic control, BP control, duration of diabetes, baseline albuminuria, CKD stage, retinopathy, neuropathy, and increased pulse wave velocity of brachial-ankle or carotid-femoral arteries[60]. Chou *et al.* compared the mortality risks in a Taiwanese kidney biopsy cohort between patients with pathology-proven DKD (PP-DKD) and those with isolated crescentic glomerulonephritis (GN) or lupus nephritis (LN). They found a significantly higher overall death in PP-DKD than in patients with GN or LN if patients were aged above 65 years or had lower serum albumin levels[61]. In another Chinese cohort with 8301 diabetic participants with no CVDs with a median follow-up of 8.05 years, Wang *et al.* reported that diabetic women with proteinuria had a higher risk of all-cause mortality than diabetic men (HR: 3.96 vs 2.15)[62].

HBA1c, duration of diabetes, and complications

Glycemic control in patients with DKD was reported to be able to predict the risk of ESRD development[60]. The DCCT study revealed that intensified glycemic intervention did not reduce the rate of progression to macroalbuminuria in persons with type 1 diabetes and microalbuminuria[38]. For type 2 diabetes, positive results were found in the Kumamoto study and the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) study; in both, an approximately 21% risk reduction of conversion from micro- to macroalbuminuria was found in persons with type 2 diabetes receiving intensive treatments[63,64]. However, intensive glucose therapy (targeting low HbA1C 6–6.9%) in the ADVANCE study for persons with longstanding diabetes and DKD for 3.5 years increased the mortality and cardiovascular complications due to the risk of severe hypoglycemia[65].

Kuo *et al.* prospectively enrolled 2401 diabetic patients with stage 3–5 CKD and evaluated the changes of risks of adverse clinical outcomes (ESRD, all-cause mortality and combined CV events) with increasing HbA1c. They reported, in the group with a higher HbA1c (>9.0), the HRs for adverse clinical outcomes were 1.6 (95% CI, 1.07–2.38) for ESRD, 1.52 (95% CI, 0.97–2.38) for all-cause mortality, and 1.46 (95% CI, 1.02–2.09) for combined CV events with mortality, respectively. The results demonstrated the association between incremental HbA1c and hazard ratios was only in diabetic patients with stage 3–4 CKD but not with stage 5 CKD (Table 2)[66]. In follow-up research, the authors revealed that anemia modified the prognostic value of glycated hemoglobin in patients with DKD. They also reported that higher HbA1c in patients with hemoglobin (Hb) $\geq$ 10 g/dL was associated with worse clinical outcomes (ESRD, all-cause mortality, and composite endpoint). The relationship did not exist in patients with Hb < 10 g/dL[67]. Liao *et al.* recruited 51618 patients with type 2 diabetes aged $\geq$30 years without ESRD and followed them up for an average of 8.1 years. In addition, under a competing risk model against death, they evaluated the association between HbA1c levels and ESRD and reported that HbA1c levels $\geq$7.0 and <6.0% were associated with higher risks of ESRD. They emphasized that not only high HbA1c but also low HbA1c was associated with ESRD. The authors provided a possible explanation for the increased risk of ESRD for HbA1c < 6.0%; that is, diabetic patients with low HbA1c levels are likely to have hypoglycemia and increased risk of following hyperglycemia, which might worsen endothelial function, increase oxidative stress and inflammation. The results suggested that an appropriate glycemic level was essential for diabetes care[68]. Lee *et al.* conducted a retrospective cohort study to assess the impact of severe hypoglycemia on renal dysfunction in persons with type 2 diabetes and DKD and showed that severe hypoglycemia was associated with the deterioration of renal function and patients with higher baseline creatinine and longer duration of type 2 diabetes might present greater aggravation of renal function decline[69].

In addition to glycemic control, Chen *et al.* compared the survival of all patients on maintenance hemodialysis in Taiwan Renal Registry Database with DKD versus diabetes as a comorbid disease. They concluded that patients with DKD were associated with higher first-year and overall mortality than patients with diabetes as a comorbid disease[70]. Hung *et al.* evaluated whether clinical parameters favoring diabetic nephropathy could predict clinical outcomes in 1330 persons with type 2 diabetes and DKD and concluded that diabetic retinopathy (DR) was significantly associated with a higher risk of ESRD[71]. Zhang *et al.* assessed the relationship between DR and the progression of DKD to ESRD in 250 patients with type 2 diabetes with biopsy-proven DKD. The authors evaluated glomerular lesions according to the glomerular classifications of the Renal Pathology Society in 2010[72], which included (a) mild changes by light microscopy or glomerular basement membrane thickening by electron microscopy were both Class I; (b) mild mesangial expansion (Class IIa); (c) severe mesangial expansion (Class IIb); (d) Kimmelstiel–Wilson lesion (Class III); (e) global glomerulosclerosis (Class IV). Their results revealed that the severity of glomerular lesions was significantly associated with DR; DR may predict the renal prognosis of patients with type 2 diabetes and DKD[73]. Lin *et al.* investigated the relationship between DR and the progression of renal dysfunction in 4050 diabetic patients with CKD from 14 hospitals. They reported that the presence and severity of DR were risk factors for CKD

progression among Taiwanese CKD patients with diabetes[74]. Chang *et al.* retrospectively evaluated the influence of peripheral arterial disease (PAD) on 362 patients with type 2 diabetes with DKD. Patients with albuminuria plus ABI<0.9 were associated with a higher risk of composite events than those with albuminuria but normal ABI ($P < 0.05$). The only trend difference between the two groups was in the all-cause mortality. Albuminuria plus ABI < 0.9 was associated with a risk of composite events [aHR 4.20 (1.77–9.92)] and an all-cause mortality (aHR 17.77 (1.93–162.20)]. They concluded that patients with albuminuria and an ankle brachial index (ABI) < 0.9 had a higher risk of composite events (all-cause mortality, hospitalization for coronary artery disease, stroke, revascularization, amputation, and diabetic foot) and all-cause mortality than those with albuminuria but normal ankle brachial index[75].

Wang *et al.* evaluated the relationship between dipstick proteinuria and the risk of myocardial infarction (MI) and all-cause mortality in a cohort of 16,573 Chinese patients with diabetes or prediabetes, with a follow-up of 8.03 years. They concluded that the presence of trace dipstick proteinuria or worse was associated with increased risks of MI and all-cause mortality[76]. Based on a Chinese cohort of 8,301 diabetic participants with no CVD and a median follow-up of 8.05 years, Wang *et al.* reported that both lower eGFR and proteinuria were independent risk factors for all-cause mortality[77]. Focusing on proteinuria, Sun *et al.* reported increased mortality risks with elevated proteinuria (HR: 1.54) and decreased risks with reduced proteinuria (HR: 0.70) in 17,878 Chinese participants with diabetes mellitus or prediabetes, with a median follow-up of 6.69 years[78]. In a prospective Chinese cohort study with 17,380 participants with diabetes mellitus or prediabetes and a median follow-up of 6.9 years, the authors reported an increased stroke risk in participants with persistent, incident, and remittent proteinuria compared with those without proteinuria. Moreover, proteinuria reduction contributed to a 12% decrease in incident stroke[77].

Lin *et al.* investigated the prognostic value of hematuria in a cohort of 1958 patients with type 2 diabetes and CKD stages 1–5. The results revealed that hematuria was associated with an increased risk [aHR 1.39 (1.10–1.76)] of ESRD[79].

Hypertension and other medications

The 2021 Kidney Disease Improving Global Outcomes guideline recommends a SBP of <120 mmHg in most subgroups of high BP and CKD, including DKD, by using standardized office blood pressure measurement. Although medication with an angiotensin-converting enzyme inhibitor (ACEi) or an angiotensin II receptor blocker (ARB) was recommended, the combined use of ACEi with ARB or direct renin inhibitors was discouraged[80]. Hsu *et al.* assessed the effectiveness and safety of ACEi or ARB use for advanced (predialysis) CKD in patients with hypertension and anemia (approximately 50% of these patients have type 2 diabetes). They indicated that patients with advanced CKD using ACEi or ARB were associated with 6% lower risk of long-term dialysis or all-cause death[81].

Chen *et al.* compared, in a Taiwanese cohort of 125,490 patients with incident DKD, the risks of ESRD and mortality among patients who received traditional Chinese medicine (TCM) prescriptions under Taiwan National Health Insurance versus other patients who did not receive TCM prescription. There was a 52% risk reduction of mortality and a 19% risk reduction of ESRD in TCM users. Once the patients progressed to ESRD, the cumulative incidence of mortality increased rapidly compared with TCM users without ESRD. The TCM users who had used TCM longer or initiated TCM treatments after being diagnosed as having DKD were associated with a lower risk of mortality[82]. Chen *et al.* selected 12,350 diabetic patients with advanced CKD (serum creatinine levels greater than 6 mg/dL but not yet receiving renal replacement therapy) and compared the risk of ESRD in patients receiving thiazolidinediones (TZDs) with those who did not use TZDs. During a median follow-up of 6 months, among these diabetic patients with advanced CKD, the TZD users were associated with a lower risk of ESRD and death[83].

Dyslipidemia and metabolic syndrome

Lipid-lowering therapy is widely recommended in patients with DKD to reduce the risk of cardiovascular diseases and mortality[84]. However, whether lipid lowering treatment attenuates renal function decline remains controversial. Chung *et al.* analyzed the concentrations of erythrocyte polyunsaturated fatty acids (PUFA), including total PUFA, n-3 PUFA, n-6 PUFA and n-3/n-6 PUFA ratio, and inflammatory markers (interleukin-6) in 2008 and the eGFR changes in 2008 and 2012. The quartile levels of n-3/n-6 PUFA ratio were <0.277, 0.277–0.319, 0.320–0.368, and >0.368. The results revealed that high PUFA concentrations, especially n-3 or a higher n-3/n-6 PUFA ratio, may exert protection against renal function decline in patients with type 2 diabetes[85]. Chuang *et al.* conducted a retrospective cohort study for approximately 5 years including 935 patients with type 2 diabetes and reported that the presence of metabolic syndrome was an independent predictor of DKD progression[86].

Lifestyles, dietary factors, obesity, and insulin resistance

Intensive diet and lifestyle interventions are frequently recommended to persons with DKD, which include a low-protein diet, sodium restriction, body weight reduction, increased physical activity, and smoking cessation[30]. Wen *et al.* studied a cohort of 512,700 adults in Taiwan participating in a health surveillance program and identified that diabetic patients with early DKD were associated with high mortality risks. They found that patients with early DKD presented more lifestyle risks such as inactivity or obesity and were up to five times more vulnerable to mortality risks. Moreover, such patients exhibited a 3-fold increase in all-cause mortality (HR: 3.16) and

a 16-year loss in life expectancy, which is much worse than that in patients with early CKD (6-year loss) or diabetes (10-year loss) alone. They proposed that identifying early proteinuria among diabetic patients and realizing the importance of reducing lifestyle risks such as inactivity are crucial in increasing life expectancy[8]. Hsu *et al.* explored the relationships between dietary patterns and renal function in adults with type 2 diabetes. They revealed that healthy diet habits, such as a frequent intake of fish and vegetables, may be associated with better renal function[87]. Hung *et al.* prospectively observed the relationship between body mass index (BMI) and the progression of renal function decline in 105 patients with type 2 diabetes with CKD stage 3 or 4. They revealed that BMI $\geq$ 25 kg/m^2 was a protective prognostic factor for renal function decline in these patients[88]. In a retrospective study of 188 Chinese patients with type 2 diabetes and biopsy-proven DKD followed up for at least 1 year, Zhang *et al.* reported 6.2- and 7.37-fold increased risks of progression to ESRD in patients with moderate and severe hypoalbuminemia, respectively, independent of their histopathological characteristics[89].

Multifactorial intervention

The Steno-2 study randomized 160 persons with type 2 diabetes with microalbuminuria to multifactorial intervention (a low-fat diet, a light-to-moderate exercise program three to five times a week, smoking cessation, prescription of ACE inhibitors or ARBs and aspirin, achieved BP < 130/80 mmHg, fasting serum cholesterol < 175 mg/dL, fasting serum triglycerides <150 mg/dL, and HAB1c < 6.5%) and conventional treatment. The multifactorial intervention group exhibited a 61% reduction in the risk of macroalbuminuria and a 55% reduction in the risk of cardiovascular events[90]. Shen *et al.* retrospectively compared 196 persons with newly diagnosed type 2 diabetes receiving intensive multidisciplinary interventions with 206 persons receiving conventional treatment for 1 year. After 10 years of follow-up, they demonstrated that the initiation of earlier intensive short-term multidisciplinary interventions may reduce coronary heart disease and DKD progression[91].

PERSPECTIVES

Despite the advanced health care in the past decades, the prevalence of DKD in Taiwan is still increasing. Moreover, the incidence and prevalence of ESRD in Taiwan have been among the highest in the world for more than 10 years. Regarding the studies on the risk factors for DKD, Taiwan's studies (Table 1) echo the results of those from countries around the world; however, studies in Taiwan have also indicated unique genetic factors for the onset of DKD. Many comprehensive studies (Table 2) on the prognostic factors of DKD have been conducted in Taiwan, which provide empirical evidence for caring for Taiwanese patients with DKD. These results must be translated to other populations to optimize renal care and to modify national health policies. In persons who present susceptible factors of incident DKD, clinicians should regularly monitor the occurrence of DKD. Moreover, implementing early and optimal intervention is essential to reverse or attenuate disease progression. For persons who present modifiable risk factors for DKD development, adequate treatment must be given actively to reduce the probability of DKD development. For persons who present worsening factors of DKD, care providers must adopt intensive multifactorial intervention to delay the progression of DKD and even reduce the incidence of cardiovascular events and premature death.

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