ORIGINAL ARTICLE

Long-term outcomes of patients with type 2 diabetes attending a multidisciplinary diabetes kidney disease clinic

> **Highlights**
> - The best model of care to retard diabetes kidney disease (DKD) in the clinic is currently underexplored.
> - Multidisciplinary endocrinology and nephrology care in the DKD clinic is associated with a lower risk of end-stage renal disease.

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Abstract

Background: The best model of care to retard diabetic kidney disease (DKD) in the clinic is underexplored. In this study we investigated the long-term renal outcomes of a joint endocrinologist–nephrologist clinic.

Methods: The present study was a nested case-control study derived from a cohort of patients with type 2 diabetes mellitus (T2DM) seen prospectively at a secondary care diabetes center (DC). Cases ("DKD clinic group") were patients seen at the CKD clinic after being referred by physicians in DCs for management of DKD. Controls ("non-DKD clinic group") were patients from the same DC (i.e. same source population) with the same inclusion criteria of Stages 3–4 chronic kidney disease (CKD) at baseline but not seen at the DKD clinic. The outcome was Stage 5 CKD, defined as an estimated glomerular filtration rate <15 mL/min per 1.73 m^2.

Results: During the median follow-up period of 3.0 years (interquartile range 1.2–5.1 years), 240 patients (28.7%) reached Stage 5 CKD, with 45.8% and 54.2% of those reaching Stage 5 CKD in the DKD and non-DKD clinic groups, respectively. Multivariable Cox regression revealed that the DKD clinic group had a lower risk of progressing to Stage 5 CKD (hazard ratio 0.55; 95% confidence interval 0.36–0.83; $P = 0.004$) compared with the non-DKD clinic group.

Conclusions: Multidisciplinary endocrinology and nephrology care in the DKD clinic is associated with a lower risk of end-stage renal disease. These findings may inform future management strategies targeted at patients with T2DM and CKD, especially with regard to joint specialist management involving endocrinologists and nephrologists.

Keywords: chronic kidney disease, diabetes mellitus, glomerular filtration rate.

Introduction

Diabetic kidney disease (DKD) is a major complication of diabetes mellitus (DM), occurring in 25%–40% of individuals with type 2 diabetes mellitus (T2DM).[1] It is also a leading cause of end-stage renal disease (ESRD) in many countries, with Singapore, Malaysia, and the Jalisco region of Mexico reportedly having the highest proportion of incident ESRD attributed to DM at 66%, 63%, and 58% respectively.[2] With a rising prevalence of

DM worldwide,[3] the morbidity, mortality, and economic burden posed by ESRD due to DM will potentially pose a significant public health problem. Therefore, there is a strong impetus to prevent or slow the progression to ESRD. Studies have looked into referral for nephrology care or multidisciplinary care in an effort to improve renal outcomes with chronic kidney disease (CKD).[4–13] For example, a study by Taskapan et al. showed that an improved slope of estimated glomerular filtration rate (eGFR) equal to or greater than +5 mL/min 1.73 m^2 was observed in 48%, 29%, and 15% of patients with Stage 2, 3, and 4 CKD, respectively, who were attending a nephrology clinic.[6] Another study by Borrelli et al. observed CKD regression in approximately one-quarter of patients under nephrology care.[7] These findings suggest that service dedicated to renal care may be associated with better outcome. Hitherto, there has been no study examining the effect of a renal management clinic on renal progression in patients with T2DM (a major cause of CKD). The aims of the present study were to examine the renal outcome of patients with T2DM who attended a joint nephrologist–endocrinologist DKD clinic in a regional hospital in Singapore and to compare these outcomes with those of patients with a similar renal burden who did not attend the DKD clinic.

Methods

Study population

This was a case-control study nested in a population of patients with T2DM seen at a secondary care diabetes center (DC). Cases ("DKD clinic group") were patients who attended the DKD clinic, having been referred by physicians in the DC for the management of DKD. These patients were first referred between November 2001 and April 2015, and were followed-up until March 2016. The inclusion criteria for referral to the DKD clinic were DM and Stages 3–4 CKD (i.e. eGFR 15–59 mL/min per 1.73 m^2 according to the Kidney Disease: Improving Global Outcomes (KDIGO) 2012 clinical practice guidelines for the evaluation of CKD[14]). Exclusion criteria for referral to DKD clinic were comorbidities that preclude renal retardation such as malignancies, severely limited life expectancy due to other advanced organ failure, inability to intensify risk factor control due to psychosocial issues or resource constraint, cognitive impairment or psychiatric illness, and Stage 5 CKD, where the patient is already on chronic renal-replacement therapy (RRT).

Controls ("non-DKD clinic group") were patients from the same DC (i.e. same source population), with the same inclusion and exclusion criteria as the DKD clinic group, who were not seen at the DKD clinic. This group was first seen at the DC in the same regional hospital between June 2002 and July 2003, and was followed-up until July 2014.

For analytical purposes, the following additional exclusion criteria were applied to both groups: fewer than three eGFR readings and <3 months follow-up. Eventually, 418 patients in the DKD clinic group and 419 patients in the non-DKD clinic group were identified as suitable for analysis. Ethics approval for the study was obtained from National Healthcare Group Domain Specific Review Board in Singapore. All patients who participated provided written informed consent.

Intervention at the DKD clinic

In the secondary care DC, six sessions of DKD clinic were conducted per month. The clinic was led by a regular dual-member team of a senior consultant nephrologist and an endocrinologist, providing joint consult face-to-face with the patient and caregiver in the same clinic room. The key therapeutic objectives included: (i) achieving control of major risk factors according to global clinical practice guidelines (i.e. HbA1c 6.5%–8% [set according to individualized needs like age and total comorbidities burden], blood pressure [BP] ≤130/80 mmHg, and low-density lipoprotein cholesterol [LDL-C] <2.6 mmol/L); and (ii) avoidance of adverse events (i.e. hypoglycemia, hypotension, and hyperkalemia).[15] The clinic was supported by a multidisciplinary team of advance practice nurses (APN), clinical pharmacists, dietitians, and social workers who helped reinforce lifestyle management plans, monitor the patients, and titrate medications between physician visits. There was ready access to 24-h ambulatory BP monitoring and a continuous glucose monitoring system. Monthly staff educational sessions were organized, in part, to facilitate cohesion of the multidisciplinary team.

Data collection

Data on demographics, duration of diabetes, and medication were obtained by trained nurses from patient case records or standardized questionnaires administered to the patients. Height and weight were measured by trained nurses. Blood pressure was measured with a standard automated sphygmomanometer in seated subjects after at least a 5-min rest (HEM-C7011-C1; OMRON, Kyoto, Japan). Spot urine and blood samples for serum creatinine, lipids, and HbA1c were collected and measured at the hospital laboratory accredited by the Royal College of American

Pathologists. Serum creatinine, LDL-C and triglycerides (TG) were quantitated using an enzymatic colorimeter test (Roche cobas c501; Roche Diagnostics, Mannheim, Germany), HbA1c was determined using a Tina-quant Hemoglobin A1c Gen.3 (Roche cobas c501; Roche Diagnostics), and urinary albumin was determined using an immunoturibidimetric assay (Roche cobas c 501; Roche Diagnostics). The corresponding intra- and interassay coefficients of variation (CVs) were as follows: serum creatinine, 0.6%–1.1% and 1.1%–1.4%, respectively; LDL-C, 0.7%–1.2% and 1.9%–2.5%, respectively; TG, 0.7%–1.1% and 1.6%–2.0%, respectively; and urinary albumin 0.7%–1.6% and 1.2%–2.8%, respectively.[16–20] Based on the 2014 American Diabetes Association (ADA) recommendations, lipid abnormalities were defined as follows: high LDL-C, ≥2.6 mmol/L; high TG, ≥1.7 mmol/L.[15] High BP was defined as systolic BP (SBP) ≥140 mmHg.[15] Obesity was defined as a body mass index (BMI) ≥30 kg/m^2 based on World Health Organization classification.[21] The Modification of Diet in Renal Disease (MDRD) formula was used to calculate eGFR rate.[22] We calculated the average HbA1c for each patient as the HbA1c intrapersonal mean. The HbA1c CV (%) was calculated by dividing the intra-individual HbA1c SD by the HbA1c intrapersonal mean.[23] In the present study, HbA1c CV was chosen as a normalized measure of HbA1c variability so as to correct for larger SD attributed to higher absolute values of HbA1c.[24,25]

Outcome measure

The primary outcome measure in the present study was Stage 5 CKD, defined as eGFR <15 mL/min per 1.73 m^2 according to KDIGO guidelines.[14]

Statistical analysis

The primary outcome was the occurrence of Stage 5 CKD (i.e. eGFR <15 mL/min per 1.73 m^2). Categorical variables are presented as numbers with percentages and continuous variables are presented as the mean ± SD or as median values with the interquartile range (IQR), as appropriate. Differences in patient characteristics stratified by DKD and non-DKD clinic groups were examined by Chi-squared tests for categorical variables, Student's t-test, or the Mann–Whitney test for continuous variables. An event was defined as the occurrence of Stage 5 CKD (i.e. eGFR <15 mL/min per 1.73 m^2).

The secondary outcomes included changes from baseline in HbA1c, diastolic BP (DBP), SBP, LDL-C, and the urinary albumin: creatinine ratio (ACR), where repeated measures were obtained over time for each patient. To compare changes in these parameters between the DKD and non-DKD clinic groups, linear mixed models were used that incorporated within-patient variation, between-patient variation, and the correlation structure of repeated measurements. We assumed that every patient had a different trajectory in the changes in outcomes. Specifically, we considered mixed models with random intercepts and slopes for observation times to accommodate within- and between-patient variation and with the unstructured assumption for the correlation structure by incorporating variables with fixed effects: age of onset, gender, race, eGFR, BMI, LDL-C, TG, and the corresponding baseline measurement of each outcome.

The changes in risk categories classified by KDIGO guidelines were compared at baseline and last follow-up using the Stuart–Maxwell (marginal homogeneity) test for three or more levels. A multivariable Cox proportional hazards regression model was used to estimate hazard ratios (HR) for the occurrence of CKD Stage 5, adjusting for covariates that were either tested to be significantly associated with outcome, biologically plausible, or proposed as risk factors based on the literature,[26] namely age of onset of DM, gender, race, urinary ACR, eGFR, BMI, SBP, LDL-C, TG, and use of a renin–angiotensin system (RAS) antagonist. The assumption of proportional hazard was tested for all covariates with a global test using scale Schoenfeld residuals. The assumption was not violated by the Cox regression model in our analysis ($P > 0.05$). All statistical tests were two-sided and $P < 0.05$ was considered significant. Statistical analyses were performed using STATA Version 14.0 (STATA Corp., College Station, TX, USA).

Results

Baseline characteristics are given in Table 1. Across the entire study population, the mean age was 48.9 ± 12.3 years, 53.4% were male, 67.3% were Chinese, 26.7% were Malay, 6.0% were Indians, the duration of DM was 15.1 ± 9.2 years, 23.4% were obese, 75.6% used an RAS antagonist, and 47.4% used insulin. At baseline, the proportion of patients with Stages 3b and 4 CKD and urinary ACR were higher in the DKD than non-DKD clinic group ($P < 0.001$). The DKD clinic group also had a poorer clinical profile in terms of BMI, SBP, and TG ($P < 0.05$ for all).

During a median follow-up period of 3.0 years (IQR 1.2–5.1), 240 (28.7%) of patients reached Stage 5 CKD (45.8% in the DKD clinic group, 54.2% in the non-DKD clinic group). Patients who progressed

Table 1 Baseline characteristics of patients all together and in the non-diabetic kidney disease (DKD) and DKD clinic groups separately

	All	Non-DKD clinic group	DKD clinic group	P-value
No. subjects	837	419	418	
Age of onset (years)	48.9 ± 12.3	50.0 ± 12.3	47.8 ± 12.2	0.009
Male	447 (53.4)	226 (53.9)	221 (52.9)	0.757
Race				0.028
Chinese	558 (67.3)	281 (67.1)	277 (67.6)	
Malay	221 (26.7)	104 (24.8)	117 (28.5)	
Indian	50 (6.0)	34 (8.1)	16 (3.9)	
Duration of DM (years)	15.1 ± 9.2	14.6 ± 9.4	15.6 ± 9.0	0.138
BMI ≥30 kg/m^2	152 (23.4)	72 (19.3)	80 (28.8)	0.005
HbA1c (%)				0.084
<7.0%	245 (29.3)	129 (30.8)	116 (27.8)	
7.0%–7.9%	225 (26.9)	124 (29.6)	101 (24.2)	
8.0%–8.9%	147 (17.6)	64 (15.3)	83 (19.9)	
≥9.0%	220 (26.3)	102 (24.3)	118 (28.2)	
SBP ≥140 mmHg	503 (60.7)	232 (56.5)	271 (64.8)	0.013
DBP ≥80 mmHg	396 (47.8)	178 (43.3)	218 (52.2)	0.011
TC ≥5.2 mmol/L	265 (33.0)	124 (30.0)	141 (36.2)	0.065
LDL-C ≥2.6 mmol/L	442 (55.3)	225 (54.6)	217 (56.1)	0.678
HDL-C (<1.03 mmol/L in men, <1.29 mmol/L in women)	358 (42.8)	192 (45.8)	166 (39.7)	0.074
TG ≥1.7 mmol/L	438 (54.6)	209 (50.6)	229 (58.9)	0.019
TC/HDL ≥4.5	295 (36.7)	157 (38.0)	138 (35.4)	0.440
Metabolic syndrome*	88 (10.5)	45 (10.7)	43 (10.3)	0.831
CKD stage[†]				<0.001
Stage 3a	287 (34.3)	181 (43.2)	106 (25.4)	
Stage 3b	311 (37.2)	137 (32.7)	174 (41.6)	
Stage 4	239 (28.6)	101 (24.1)	138 (33.0)	
Urinary ACR (mg/g)	279.5 [71.0–1424.0]	154.5 [38.0–758.0]	508.5 [120.0–2267.0]	<0.001
HbA1c CV[‡]				<0.001
Tertile 1	242 (33.4)	114 (30.0)	128 (37.1)	
Tertile 2	242 (33.4)	113 (29.7)	129 (37.4)	
Tertile 3	242 (33.4)	153 (40.3)	88 (25.5)	
Use of RAS antagonist	633 (75.6)	300 (71.6)	333 (79.7)	0.007
Use of insulin	379 (47.4)	168 (41.3)	211 (53.8)	<0.001

Unless indicated otherwise, data are presented as the mean ± SD, median (interquartile range), or n (%).
*Using the International Diabetes Federation[27] as a reference, metabolic syndrome is considered present if the following conditions are met: body mass index (BMI) >30 kg/m^2 plus any two of the following: triglycerides (TG) ≥1.7 mmol/L; high-density lipoprotein cholesterol (HDL-C) <1.03 mmol/L in males or <1.29 mmol/L in females, and systolic blood pressure (SBP) ≥130 mmHg or diastolic blood pressure (DBP) ≥85 mmHg.
[†]Chronic kidney disease (CKD) stages were defined using estimated glomerular filtration rate (eGFR) as follows: Stage 3a, eGFR 45–59 mL/min per 1.73 m^2; Stage 3b, eGFR 30–44 mL/min per 1.73 m^2; Stage 4, eGFR 15–29 mL/min per 1.73 m^2.
[‡]The HbA1c coefficient of variation (CV) tertiles were as follows (median [interquartile range]): Tertile 1, 6.7% (5.0%–8.1%); Tertile 2, 12.3% (10.9%–13.8%); Tertile 3, 20.8% (17.6%–25.8%).
DM, diabetes mellitus; LDL-C, low-density lipoprotein cholesterol; RAS, renin–angiotensin system.

to Stage 5 CKD had a younger age of onset of T2DM and were more likely to have a poorer clinical profile in terms of SBP, LDL-C, urinary ACR, and HbA1c variability ($P < 0.001$ for all). They were also less likely to use an RAS antagonist than those who did not progress to Stage 5 CKD ($P = 0.006$; Table 2).

Results from linear mixed models showed that reductions from baseline in terms of HbA1c ($\beta = -0.28$, $P = 0.036$), DBP ($\beta = -43.91$, $P < 0.001$) and log-transformed urinary ACR ($\beta = -0.39$, $P = 0.006$) were significantly larger in the DKD than non-DKD clinic group (Fig. 1). There were no significant differences

between the DKD and non-DKD clinic groups in SBP ($\beta = 30.93$, $P = 0.106$) and LDL-C ($\beta = -0.11$, p = 0.083; Fig. 1).

Table 3 shows the change in CKD risk categories according to KDIGO classification from baseline to last follow-up. In the non-DKD clinic group, there was minimal change in the proportion of patients in the low to moderate risk categories combined (from 11.8% to 11.3%). However, there was a reduction in the proportion of subjects in the high risk category and an increase in the proportion in the very high risk category in the non-DKD clinic group (Table 3). In the DKD clinic

Table 2 Distribution of variables by occurrence of Stage 5 chronic kidney disease

| | Occurrence of Stage 5 CKD | | |
	No	Yes	P-value
No. subjects	597 (71.3)	240 (28.7)	
Age of onset (years)	50.4 ± 12.1	45.1 ± 12.1	<0.001
Male	323 (54.1)	124 (51.7)	0.523
Race			0.248
Chinese	407 (69.0)	151 (63.2)	
Malay	148 (25.1)	73 (30.5)	
Indian	35 (5.9)	15 (6.3)	
Duration of DM (years)	14.8 ± 9.2	15.9 ± 9.2	0.131
BMI ≥30 kg/m^2	106 (22.6)	46 (25.3)	0.469
HbA1c (%)			0.123
<7.0%	170 (28.5)	75 (31.3)	
7.0%–7.9%	167 (28.0)	58 (24.2)	
8.0%–8.9%	113 (18.9)	34 (14.2)	
≥9.0%	147 (24.6)	73 (30.4)	
SBP ≥140 mmHg	325 (55.1)	178 (74.5)	<0.001
DBP ≥80 mmHg	267 (45.2)	129 (54.2)	0.019
TC ≥5.2 mmol/L	154 (26.6)	111 (49.3)	<0.001
LDL-C ≥2.6 mmol/L	294 (51.0)	148 (66.7)	<0.001
HDL-C (<1.03 mmol/L in men, <1.29 mmol/L in women)	261 (43.7)	97 (40.4)	0.383
TG ≥1.7 mmol/L	306 (52.9)	132 (58.9)	0.127
TC/HDL ≥4.5	187 (32.4)	108 (48.0)	<0.001
Metabolic syndrome*	59 (9.9)	29 (12.1)	0.348
CKD stage[†]			<0.001
Stage 3a	243 (40.7)	44 (18.3)	
Stage 3b	249 (41.7)	62 (25.8)	
Stage 4	105 (17.6)	134 (55.8)	
Urinary ACR (mg/g)	154.0 [47.0–748.0]	1826.0 [324.0–3845.0]	<0.001
HbA1c CV[‡]			<0.001
Tertile 1	193 (37.8)	49 (22.9)	
Tertile 2	169 (33.1)	73 (34.1)	
Tertile 3	149 (29.2)	92 (43.0)	
Use of RAS antagonist	467 (78.2)	166 (69.2)	0.006
Use of insulin	267 (47.1)	112 (48.3)	0.761
DKD clinic group (%)	308 (51.6)	110 (45.8)	0.132

Unless indicated otherwise, data are presented as the mean ± SD, median (interquartile range), or n (%).

*Using the International Diabetes Federation[27] as a reference, metabolic syndrome is considered present if the following conditions are met: body mass index (BMI) >30 kg/m^2 plus any two of the following: triglycerides (TG) ≥1.7 mmol/L; high-density lipoprotein cholesterol (HDL-C) <1.03 mmol/L in males or <1.29 mmol/L in females, and systolic blood pressure (SBP) ≥130 mmHg or diastolic blood pressure (DBP) ≥85 mmHg.

[†]Chronic kidney disease (CKD) stages were defined using estimated glomerular filtration rate (eGFR) as follows: Stage 3a, eGFR 45–59 mL/min per 1.73 m^2; Stage 3b, eGFR 30–44 mL/min per 1.73 m^2; Stage 4, eGFR 15–29 mL/min per 1.73 m^2.

[‡]The HbA1c coefficient of variation (CV) tertiles were as follows (median [interquartile range]): Tertile 1, 6.7% (5.0%–8.1%); Tertile 2, 12.3% (10.9%–13.8%); Tertile 3, 20.8% (17.6%–25.8%).

DM, diabetes mellitus; LDL-C, low-density lipoprotein cholesterol; RAS, renin–angiotensin system.

group, there was an improvement in the low to moderate risk categories combined (from 2.3% to 5.5%), as well as in the proportion of subjects in the high risk group (Table 3), whereas there was minimal change in the very high risk category (Table 3).

Table 4 shows the results of the Cox regression for the occurrence of Stage 5 CKD. The DKD clinic group had a 45% lower hazard of Stage 5 CKD than the non-DKD clinic group (P = 0.004) after adjusting for demographic and clinical factors. The other independent risk factors associated with the occurrence of Stage 5 CKD were LDL-C ≥ 2.6 mmol/L, CKD Stages 3b and 4, increasing urinary ACR, and HbA1c -CV Tertile 3.

Discussion

In the present study, we observed that the DKD clinic group had a lower risk of progression to Stage 5 CKD
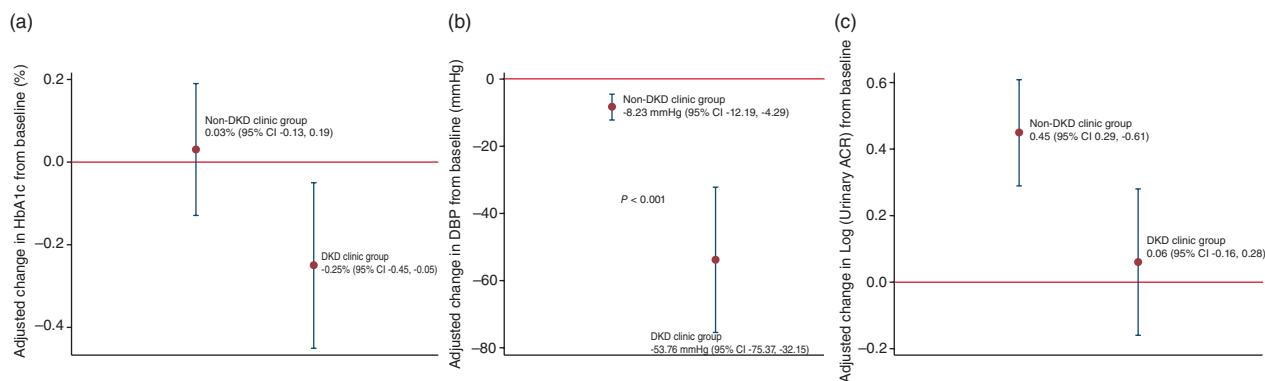
Figure 1 Adjusted changes (see text for details) in (a) HbA1c, (b) diastolic blood pressure (DBP) and (c) urinary albumin: creatinine ratio (ACR) from baseline in the non-diabetic kidney disease (DKD) and DKD clinic groups. Data show larger mean (± 95% confidence interval [CI]) reductions in the parameters of HbA1c, DBP and urinary ACR in the DKD clinic group than non-DKD clinic group. The horizontal lines represent no change from baseline.

compared with the non-DKD clinic group. The DKD clinic group also showed more marked improvement in CKD risk categories. One possible explanation is that the DKD clinic group had a higher proportion of subjects using an RAS antagonist (79.7% vs 71.6%; $P = 0.007$). This could reflect the more intensive treatment received by the DKD clinic group. Furthermore, a higher percentage of patients in which Stage 5 CKD did not occur were using an RAS antagonist compared with patients in whom Stage 5 CKD occurred (78.2% vs 69.2%; $P = 0.006$). This is in line with previous reports supporting the renoprotective effects of RAS antagonists in T2DM.[28–30] However, the association between RAS antagonist use and the occurrence of Stage 5 CKD lost statistical significance in the multivariable Cox regression model. "Reverse causation" may also account for the fact that patients with higher renal burden may not be able to the use an RAS antagonist for reasons such as hyperkalemia or excessive deterioration in eGFR upon initiation of RAS blockade. However, we lack high-resolution information on duration, dosage, and compliance with RAS antagonist use. Future studies need to take such information into

account in examining the effects of nephrology care on CKD progression. Nevertheless, the findings of the present study may inform future management strategies targeted towards patients with DM and CKD, especially with regard to joint specialist management involving endocrinologists and nephrologists.

Conflicting findings have been reported by previous studies examining the effects of multidisciplinary care of patients with CKD.[5,10–13] For example, Jones et al. observed that patients referred to a shared care scheme comprising a nephrologist and a primary care physician experienced a lower risk of mortality or RRT compared with patients referred to a hospital nephrology clinic.[11] Other studies have observed improvements in eGFR in patients receiving multidisciplinary care.[5,13] Conversely, Harris et al. did not find any difference in renal function and mortality after enrollment between patients receiving intensive multidisciplinary case management and those receiving primary care from their usual physicians.[10] Of note, there was considerable heterogeneity in these studies in terms of study population (CKD with or without DM), components of multidisciplinary care, and outcomes, thus hampering direct

Table 3 Change in chronic kidney disease risk categories according to the Kidney Disease: Improving Global Outcomes (KDIGO) classification in the non-diabetic kidney disease (DKD) and DKD clinic groups from baseline to last follow-up

	Low risk	Moderate risk	High risk	Very high risk
Non-DKD clinic group				
Baseline	0 (0)	44 (11.8)	104 (27.8)	226 (60.4)
Last follow-up	11 (2.9)	35 (9.4)	66 (17.7)	262 (70.1)
DKD clinic group				
Baseline	0 (0)	8 (2.3)	42 (12.1)	298 (85.6)
Last follow-up	3 (0.9)	16 (4.6)	24 (6.9)	305 (87.6)

Data show the number of subjects in each group, with percentages in parentheses. Marginal homogeneity test (Stuart–Maxwell) $P < 0.001$ for the non-DKD clinic group and $P = 0.012$ for the DKD clinic group.

Table 4 Adjusted hazard ratios for the occurrence of Stage 5 chronic kidney disease

Baseline variable	HR (95% CI)	P-value
Age of onset (per year)	0.98 (0.96–0.99)	0.007
Male	0.89 (0.60–1.31)	0.541
Race		
Chinese	Reference	
Malay	0.92 (0.58–1.45)	0.723
Indian	1.21 (0.43–3.41)	0.723
BMI ≥30 kg/m^2	1.20 (0.77–1.88)	0.430
SBP ≥140 mmHg	1.04 (0.66–1.64)	0.854
LDL-C ≥ 2.6 mmol/L	1.55 (1.03–2.34)	0.037
TG ≥1.7 mmol/L	1.20 (0.80–1.80)	0.369
CKD Stage*		
Stage 3a	Reference	
Stage 3b	2.46 (1.48–4.08)	0.001
Stage 4	5.71 (3.51–9.29)	<0.001
Log urinary ACR	1.64 (1.43–1.88)	<0.001
HbA1c CV†		
Tertile 1	Reference	
Tertile 2	1.70 (0.99–2.92)	0.056
Tertile 3	2.54 (1.47–4.39)	0.001
Use of RAS antagonist	0.81 (0.53–1.24)	0.326
DKD clinic group	0.55 (0.36–0.83)	0.004

The multivariable model included age of onset, gender, race, body mass index (BMI) ≥30 kg/m^2, systolic blood pressure (SBP) ≥140 mmHg, low-density lipoprotein cholesterol (LDL-C) ≥2.6 mmol/L, triglycerides (TG) ≥1.7 mmol/L, CKD stage, log-transformed urinary albumin: creatinine ratio (ACR), HbA1c CV, use of renin–angiotensin system (RAS) antagonist, and DKD clinic group.
*Chronic kidney disease (CKD) stages were defined using estimated glomerular filtration rate (eGFR) as follows: Stage 3a, eGFR 45–59 mL/min per 1.73 m^2; Stage 3b, eGFR 30–44 mL/min per 1.73 m^2; Stage 4, eGFR 15–29 mL/min per 1.73 m^2.
†The HbA1c coefficient of variation (CV) tertiles were as follows (median [interquartile range]): Tertile 1, 6.7% (5.0%–8.1%); Tertile 2, 12.3% (10.9%–13.8%); Tertile 3, 20.8% (17.6%–25.8%).

comparisons with the present study. In contrast with most of these studies, the present study focused on patients with Stage 3–4 CKD and T2DM. To the best of our knowledge, the present is study the first to have looked at the effects of multidisciplinary care jointly provided by a nephrologist and endocrinologist supported by other healthcare professionals in nursing, pharmacy, nutrition, and sociology. Conversely, the multidisciplinary care in the other studies comprised a nephrologist who was involved to varying extents and other healthcare professionals in similar domains, but not an endocrinologist.[5,10–13] Nevertheless, the present study has added to the limited pool of information from these studies and supports the beneficial role played by multidisciplinary care in retarding the progression of CKD. We have also demonstrated that joint care provided by a nephrologist and endocrinologist lowers the risk of ESRD in patients with T2DM.

At baseline, the DKD clinic group had a poorer clinical profile than the non-DKD clinic group in the present study. This reflects the appropriateness of referral to the DKD clinic. Despite the poorer baseline clinical profile, the DKD clinic group experienced comparable improvement in HbA1c, DBP, and urinary ACR, as well as a lower risk of progression to Stage 5 CKD than the non-DKD clinic group. This supports earlier findings in a recent study that intensive and multifactorial management is important in slowing or preventing ESRD in patients with T2DM with microalbuminuria.[31] However, the extent of improvement in SBP control was less marked in the DKD clinic group in the present study. Future studies need to take into account all the antihypertensive medications in the two groups in order to understand the intensity of BP management.

The findings of the present study showed that the risk of progression to Stage 5 CKD was higher in patients with Stage 3b CKD (eGFR 40–44 mL/min per 1.73 m^2) and Stage 4 CKD (eGFR 15–29 mL/min per 1.73m^2) compared with Stage 3a CKD (eGFR 45–59 mL/min per 1.73 m^2) at baseline. This could suggest that early referral of patients to the DKD clinic may improve CKD outcome. It was suggested that BP and RAS antagonist use may be more effective in individuals at earlier CKD stages, particularly in DM.[6]

The other risk factors affecting the progression to Stage 5 CKD are increasing urinary ACR, high LDL-C, and high HbA1c variability This is in agreement with our earlier finding that these factors were linked to CKD progression,[32] and hence highlight the importance of controlling these modifiable risk factors.

Strengths

To the best of our knowledge, the present study is the first to investigate the effects of joint management by a nephrologist and endocrinologist on renal outcome in patients with DM in Singapore. Previous studies have looked at nephrology care for patients with CKD, but scant attention has been given to patients specifically with DM receiving joint management from a nephrologist and endocrinologist. We speculate that improved communication between the nephrologist and endocrinologist and sharing of expertise in both fields in the same clinical consultation leads to better coordination of care and decision making in management. The strengths of the present study also include the use of a control group from the same source population for comparison with the DKD-clinic group to assess the effectiveness of the joint management with specialized nephrology and endocrinology care, availability of

information regarding RAS antagonist use, rich clinical data, and the use of serial eGFRs for analysis.

Limitations

The present study has several limitations. First, this study was confined to patients with T2DM attending a secondary care DC. This limits the generalizability of the results to the general population with diabetes. Second, there may be measurement errors using the MDRD equation to estimate GFR. However, it was shown that MDRD performed similarly or better than the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula in patients with DM,[33] especially when GFR is below 60 mL/min per 1.73 m^2. Third, the sampling time frame in the non-DKD clinic group differed from that in the DKD clinic group. Therefore, the contribution of some cryptic "cohort effect" has not been accounted for. The present study lacks high-resolution data on dosage and duration of RAS antagonist treatment, as well as the use of other antihypertensive medications. Such factors may affect renal disease progression. We also lack data on potassium and diuretic usage, and hence could not ascertain whether some patients experienced hyperkalemia and hence used more diuretics than RAS antagonists. We did not take into account other residual confounding factors, such as duration of follow-up at the DKD clinic, and behavioral factors such as self-care and medication compliance. In addition, we have not addressed cost-effectiveness issues associated with joint DKD management.

Future directions

Future studies can incorporate technical tools, such as ambulatory glucose profiles and telemonitoring, and behavioral modification strategies, such as motivational interviews, to evaluate the efficacy of these "enhanced" interventions over the present transdisciplinary model. Further research may also be needed to examine the effect of joint management with specialized nephrology and endocrinology care in patients in other care settings and for outcomes on mortality and cost-effectiveness. Information lacking in the present study, such as medication dosage and duration, could be incorporated in such future research.

Conclusions

Joint management with specialized nephrology and endocrinology care in the DKD clinic is associated with a lower risk of ESRD. More in-depth studies are needed to shed further light on mechanistic insights conferred by multidisciplinary care that directly affects renal outcome.

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Disclosure

The authors declare that they have no conflicts of interest.

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