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# Influence of Referral to a Combined Diabetology and Nephrology Clinic on Renal Functional Trends and Metabolic Parameters in Adults With Diabetic Kidney Disease

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## Abstract

**Objective:** To examine the impact of a diabetes renal clinic (DRC) on renal functional and metabolic indices in adults who have diabetes mellitus (DM) and chronic kidney disease (CKD).

**Patients and Methods:** All patients evaluated at a DRC in a single tertiary referral center from January 1, 2008, to December 31, 2012, were identified. Serial renal and metabolic indices from January 1, 2004, to December 31, 2014, were recorded, and trends over time were analyzed by linear mixed-effects models.

**Results:** A total of 200 patients who had DM and CKD were identified and subdivided into 3 categories based on presumptive CKD etiology: 43 (21.5%) with type 1 DM (T1D) only, 127 (63.5%) with type 2 DM (T2D) only, and 30 (15.0%) with DM and an additional CKD etiology. Average annual absolute (mL/min per body surface area per year) and percentage (%/year) changes, respectively, in Chronic Kidney Disease Epidemiology Collaboration estimated glomerular filtration rate before vs after first DRC attendance were:  $-1.59$  vs  $-3.10$  ( $P=.31$ ) and  $-1.22$  vs  $-9.39$  ( $P=.06$ ) for T1D;  $-5.64$  vs  $-3.07$  ( $P=.004$ ) and  $-10.88$  vs  $-9.94$  ( $P=.70$ ) for T2D; and  $-6.50$  vs  $+0.91$  ( $P<.001$ ) and  $-13.28$  vs  $-2.29$  ( $P=.001$ ) for DM with an additional CKD etiology. Glycemic control worsened in those who had T2D, whereas trends in total cholesterol levels improved in those who had T1D.

**Conclusion:** After first DRC attendance, the absolute rate of estimated glomerular filtration rate decline remained similar for those who had T1D, but it slowed for those who had T2D or DM with additional CKD etiology. Thus, benefits of combined diabetology and nephrology consultation may vary for different diabetic subpopulations.

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Diabetes mellitus (DM) is considered one of the primary challenges to health care delivery in the 21st century.<sup>1</sup> The International Diabetes Federation has estimated a global prevalence of 415 million cases of DM in 2015, with a projected rise to 592 million by 2035.<sup>2</sup> The increase in DM has been an important contributor to the increasing prevalence of chronic kidney disease (CKD).<sup>3</sup> A total of 43.9% of people who have end-stage renal disease in the United States have DM.<sup>4</sup>

Targeted control of blood pressure and glycemia can delay the onset of diabetic kidney disease (DKD) and slow its progression.<sup>5</sup> Diabetes renal clinics (DRCs), in which diabetology and nephrology care are delivered simultaneously to patients who have DM and CKD, hold promise in bridging the implementation gap between guidelines and clinical practice. Longitudinal studies examining the role of DRCs have revealed a reduction in the rate of renal functional decline, but the studies have been limited to subgroups of

patients who have rapidly progressing DKD and who attended DRCs serially.<sup>6-10</sup>

The primary aim of the current study was to determine the impact of DRC evaluation, at a single tertiary referral center in Western Europe, on renal functional and metabolic indices before and after attendance. The DRC cohort studied was stratified into 3 subgroups according to presumptive CKD etiology: type 1 DM (T1D) alone, type 2 DM (T2D) alone, and DM with an additional etiology for CKD.

## PATIENTS AND METHODS

### Study Design and Setting

All adults attending the DRC at Galway University Hospital in Ireland between January 1, 2008, and December 31, 2012, were identified from clinic lists, and the dates of first attendance were recorded. Clinical and laboratory information from January 1, 2004, to December 31, 2014, was extracted from paper and electronic medical records. The study was approved by the Galway University Hospital's Clinical Research Ethics Committee.

**Diabetes Renal Clinic.** The DRC at Galway University Hospital was established in 2004. Patients are jointly evaluated by a team consisting of either a consultant endocrinologist and specialist registrar in nephrology or a consultant nephrologist and specialist registrar in endocrinology. Individualized plans are agreed on for target-based control of blood pressure, glycaemia, lipids, and albuminuria. Referral criteria include T1D or T2D under active management along with one or more of the following:

- Current estimated glomerular filtration rate (eGFR) between 60 and 30 mL/min per body surface area (BSA) and a trend of declining eGFR;
- A trend of increasing albuminuria;
- Clinical features not typical of DKD, for which kidney biopsy might be considered; and
- Difficult-to-control hypertension in the setting of CKD.

On the basis of the outcome of the initial evaluation, those determined to have stable CKD are referred to the general diabetes clinic for continued follow-up; those with progressive CKD stage 3 (30-59ml/min per BSA) are

retained for ongoing DRC follow-up; and those with CKD stages 4 (15-29ml/min per BSA) and 5 (15ml/min per BSA) are referred to a CKD clinic run by the nephrology department, with separate DM follow-up in the general diabetes clinic.

### Participants

A total of 208 patients who attended the DRC on at least one occasion between January 1, 2008, and December 31, 2012, were identified. Of these, 3 were excluded from the analysis on the basis of inappropriate referral, 2 were excluded because they were already receiving renal replacement therapy at the time of first DRC attendance, 2 were excluded because of pregnancy during follow-up, and 1 was excluded because of underlying Wolfram syndrome. The final study cohort consisted of 200 participants who were subdivided into 3 groups based on presumptive CKD etiology: T1D alone, T2D alone, and DM with an additional CKD etiology. The additional CKD etiologies consisted of atherosclerotic renovascular disease, hypertensive nephropathy, interstitial renal disease, obstructive nephropathy, glomerulonephritis, and autosomal dominant polycystic kidney disease. Criteria used to define the presence of specific additional CKD etiologies are presented in [Table 1](#). Patients who did not meet these criteria were deemed to have CKD attributable to T1D or T2D alone.

### Data Collection

**Clinical Information.** Clinical information was extracted for each participant from an electronic health record for patients with DM (DIAMOND, Hicom, Woking, United Kingdom),<sup>11</sup> as well as from hospital discharge and outpatient records entered into medical charts. Clinical indices were assigned to a specific date. If the exact date of commencement/onset was not available (eg, prescription of certain medication classes, presence of macrovascular or nonrenal microvascular complications of DM), the indices were recorded as being either present or absent before the end of longitudinal follow-up in 2014. Results of the first renal ultrasonography, renal arterial imaging, and histopathological diagnoses obtained from kidney biopsy were recorded when present.

TABLE 1. Criteria for Definition of CKD Etiologies in Addition to Type 1 or Type 2 Diabetes Mellitus in the Cohort

CKD etiology	Diagnostic features	Diagnostic criteria
Atherosclerotic renal vascular disease	<ol style="list-style-type: none"> <li>1. Most likely CKD etiology, on review of the medical records</li> <li>2. <math>\geq 2</math> cm size discrepancy between left and right kidneys or bilaterally small kidneys (<math>&lt; 10</math> cm) on ultrasonography</li> <li>3. Radiographically confirmed unilateral or bilateral <math>\geq 50\%</math> renal artery stenosis by magnetic resonance or invasive angiography</li> </ol>	<ol style="list-style-type: none"> <li>1. Both diagnostic features 1 and 2 or</li> <li>2. Diagnostic feature 3 alone</li> </ol>
Hypertensive nephropathy	<ol style="list-style-type: none"> <li>1. Most likely cause of CKD, on review of the medical records</li> <li>2. Bilaterally small kidneys on ultrasonography (<math>&lt; 10</math> cm)</li> <li>3. Left ventricular hypertrophy on echocardiography</li> <li>4. Kidney biopsy—proven</li> </ol>	<ol style="list-style-type: none"> <li>1. <math>\geq 2/3</math> of diagnostic features 1-3 or</li> <li>2. Diagnostic feature 4 alone</li> </ol>
Interstitial renal disease	<ol style="list-style-type: none"> <li>1. Deterioration in renal function felt to be at least partly related to medication exposure, on review of the medical records</li> <li>2. Kidney biopsy—proven</li> </ol>	<ol style="list-style-type: none"> <li>1. Diagnostic feature 1 or</li> <li>2. Diagnostic feature 2 or</li> <li>3. Both diagnostic features 1 and 2</li> </ol>
Obstructive nephropathy	<ol style="list-style-type: none"> <li>1. Clinical suspicion of urinary tract obstruction contributing to deterioration in renal function, on review of the medical records</li> <li>2. Ultrasonography-confirmed hydronephrosis on at least one occasion</li> </ol>	<ol style="list-style-type: none"> <li>1. Both diagnostic features 1 and 2</li> </ol>
Glomerulonephritis	<ol style="list-style-type: none"> <li>1. Kidney biopsy—proven</li> </ol>	<ol style="list-style-type: none"> <li>1. Diagnostic feature 1 alone</li> </ol>
Autosomal dominant polycystic kidney disease	<ol style="list-style-type: none"> <li>1. Diagnosis confirmed by treating team, on review of medical records, on the basis of family history and ultrasonographic findings</li> </ol>	<ol style="list-style-type: none"> <li>1. Diagnostic feature 1 alone</li> </ol>

CKD = chronic kidney disease.

**Laboratory Data.** All recorded clinical biochemistry tests were analyzed in the clinical laboratories at Galway University Hospital. The method of creatinine measurement changed from a conventional Jaffé method to an isotope dilution mass spectrometry (IDMS)—traceable Jaffé assay on December 14, 2005, and subsequently to an IDMS-traceable creatininase assay on July 23, 2013. Owing to the limited concordance between creatinine values measured with the conventional Jaffé method and later IDMS-traceable assays and the validation of the CKD-Epidemiology Collaboration (CKD-EPI) eGFR equation with IDMS-traceable creatinine assays only,<sup>12</sup> creatinine values obtained before December 14, 2005, were excluded from analyses of renal functional trends. All creatinine assays were from Roche Diagnostics and were performed on Roche analytical platforms.

Glomerular filtration rate was estimated using both the 4-parameter Modification of Diet in Renal Disease (MDRD)<sup>13</sup> and CKD-EPI formulas.<sup>12</sup> With the IDMS-traceable Jaffé creatinine assay, the MDRD formula included a correction factor to account for the recognized overestimation of creatinine owing to chromogens such as proteins and

ketones.<sup>14</sup> This correction factor was removed for MDRD eGFR calculation based on creatinine values measured with the creatininase assay.

Glycated hemoglobin (HbA<sub>1c</sub>) was measured by high-performance liquid chromatography (A. Menarini Diagnostics). The assay was switched from alignment with the Diabetes Control and Complications Trial to International Federation of Clinical Chemistry calibration in May 2011. Electrolytes and lipid parameters were measured using conventional Roche Diagnostics assays, except for low-density lipoprotein cholesterol, which was calculated using the Friedewald equation.<sup>15</sup> Urinary albumin was measured on a BN II nephelometer (Siemens Medical Solutions).

### Statistical Analyses

Data entry and analysis were conducted using SPSS version 22.0 for Windows (IBM). A *P* value of  $< .05$  was considered statistically significant for all analyses. Baseline characteristics at index DRC visit and clinical characteristics of the cohort during follow-up were summarized by descriptive statistics. One-way between-groups analysis of variance and Kruskal-Wallis tests, respectively, were

used to compare continuous variables that were and were not normally distributed across the CKD subgroups. Categorical variables across CKD subgroups were compared using  $\chi^2$  tests.

Linear mixed-effects models, incorporating subject-specific random intercepts and slopes for the time periods before and after first DRC attendance, were used to examine whether CKD subgroup-specific trajectories of laboratory indices changed after DRC attendance. Separate models were fit for MDRD and CKD-EPI eGFR, log-transformed MDRD and CKD-EPI eGFR, urine albumin to creatinine ratio, glycated hemoglobin (HbA<sub>1c</sub>), and lipid indices. Although data for urine albumin to creatinine ratio, HbA<sub>1c</sub>, and lipid indices were right-skewed, we present the results for these variables on their original scale to assist with interpretation from a clinical perspective. The *P* values for comparison of these variables are valid estimates, given the asymptotic considerations, on the basis of the relatively large sample size.<sup>16</sup>

Models fit to the original laboratory indices determine yearly decline in their native units, whereas models fit using log-transformed eGFR estimate their annual percentage decline. No serious violations of model assumptions were found on examination of the distribution of residuals. The function *lmer* (from the R package *lmerTest*, which calculates *P* values for fixed effects using Satterthwaite approximations) was used to fit and test the models.<sup>17,18</sup> Interactions between CKD subgroup and DRC attendance were tested via likelihood ratio tests.

For each participant, the first available laboratory result from January 1, 2004 (or in the case of eGFR, December 14, 2005), onward and the last available laboratory result up to December 31, 2014, were entered into the linear mixed-effects models. For example, if a participant first attended the DRC in 2009 and had longitudinal laboratory data available from 2005 to 2013, the 2005-2009 values would be considered pre-DRC attendance data, and the 2009-2013 values would be considered post-DRC attendance data. Second and subsequent eGFR values on a single day and eGFR values subsequent to renal replacement therapy initiation were excluded.

## RESULTS

Of the 200 eligible participants, 43 (21.5%) had T1D alone, 127 (63.5%) had T2D alone, and 30 (15.0%) were defined as having DM with an additional CKD etiology. Within the latter group, 1 individual (3.3%) had T1D, and 29 (96.7%) had T2D. The additional CKD etiologies consisted of the following: atherosclerotic renovascular disease (n=14; 46.7%); hypertensive nephropathy (n=7; 23.3%); interstitial renal disease (n=3; 10.0%); obstructive nephropathy (n=3; 10.0%); glomerulonephritis (n=2; 6.7%) (1 each with IgA nephropathy and membranous nephropathy); and autosomal-dominant polycystic kidney disease (n=1; 3.3%).

Regarding ethnicity, 2 patients (1.0%) were Asian, and 1 (0.5%) was black. The total number of attendance occasions at DRC varied, with 52 patients (26.0%) attending once, 36 (18.0%) attending twice, 29 (14.5%) attending 3 times, and 83 (41.5%) attending 4 or more times. At first DRC attendance (Table 2), no significant differences in blood pressure or smoking status were observed across the 3 subgroups. Body mass index was higher in those with either T2D alone or an additional CKD etiology compared with those who had T1D (*P*<.001). The group with T1D alone had a higher mean eGFR (*P*=.01) and a higher median albuminuria level than the other groups (*P*=.02). Higher levels of HbA<sub>1c</sub> (*P*<.001), total cholesterol (*P*<.001), and low-density lipoprotein cholesterol (*P*=.002) were also observed in the group who had T1D alone.

Table 3 presents additional clinical characteristics of the study cohort during longitudinal follow-up. Hypertension and peripheral arterial disease were more prevalent in those who had T2D and those who had an additional CKD etiology (*P*<.001 and *P*=.04, respectively), whereas diabetic retinopathy was more prevalent in those who had T1D and T2D (*P*=.001). Usage of renin-angiotensin-aldosterone system inhibitors was highly prevalent, with 156 (78.0%), 100 (50.0%), and 53 (26.5%) individuals, respectively, on a regimen of angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and dual renin-angiotensin-aldosterone system blockade at some point during follow-up. No difference was found in the usage rates of

TABLE 2. Baseline Characteristics of the Cohort at First Diabetes Renal Clinic Attendance Stratified by CKD Etiology (n=200)<sup>a,b</sup>

Characteristic	Data available [n (%)]	Total cohort (n=200)	Type 1 DM (n=43)	Type 2 DM (n=127)	Additional CKD etiology (n=30)	P value
Demographics	200 (100.0)					
Age (years)		63.6±15.5	44.8±15.9	68.8±10.6	68.7±11.3	<.001 <sup>c</sup>
Male		135 (67.5)	24 (55.8)	89 (70.1)	22 (73.3)	.17 <sup>d</sup>
Caucasian ethnicity		197 (98.5)	42 (97.7)	125 (98.4)	30 (100.0)	N/A <sup>e</sup>
DM type	200 (100.0)					<.001
Type 1		44 (22.0)	43 (100.0)	0 (0.0)	1 (3.3)	
Type 2		156 (78.0)	0 (0.0)	127 (100.0)	29 (96.7)	
DM duration (median [IQR]; years)	200 (100.0)	11.4 (13.9)	23.5 (18.3)	9.7 (12.1)	7.7 (6.4)	<.001 <sup>f</sup>
Source of referral	200 (100.0)					N/A
General diabetes clinic		182 (91.0)	41 (95.3)	113 (89.0)	28 (93.3)	
Inpatient services		9 (4.5)	1 (2.3)	7 (5.5)	1 (3.3)	
Primary care		9 (4.5)	1 (2.3)	7 (5.5)	1 (3.3)	
Blood pressure (mmHg)						
Systolic	198 (99.0)	134.9±19.5	129.3±19.5	136.4±19.0	137.2±21.0	.09
Diastolic	198 (99.0)	70.5±9.4	72.3±10.7	69.8±8.8	71.0±10.1	.31
Body mass index (kg/m <sup>2</sup> )	190 (95.0)	31.3±5.7	26.2±4.8	32.5±4.8	33.5±6.4	<.001
Smoking status	197 (98.5)					.09
Current smoker		36 (18.3)	14 (32.6)	19 (15.3)	3 (10.0)	
Ex-smoker		86 (43.7)	16 (37.2)	56 (45.2)	14 (46.7)	
Never smoker		75 (38.1)	13 (30.2)	49 (39.5)	13 (43.3)	
Laboratory results						
Estimated glomerular filtration rate (mL/min/body surface area)	197 (98.5)					
Modification of Diet in Renal Disease		48.7±23.4	58.2±30.3	47.0±21.1	42.5±17.9	.01
Chronic Kidney Disease-Epidemiology Collaboration		48.9±24.3	61.0±31.4	46.5±21.4	42.0±18.7	.001
Urine albumin-to-creatinine ratio (median [IQR]; mg/g)	198 (99.0)	141.6 (779.7)	367.3 (1338.9)	188.5 (775.2)	33.6 (427.4)	.02
International Federation of Clinical Chemistry glycated hemoglobin (mmol/mol)	186 (93.0)	63.4±19.0	77.8±24.6	59.3±15.0	60.2±15.4	<.001
Cholesterol (mg/dL)						
Total	168 (84.0)	162.4±50.3	201.1±77.3	150.8±34.8	158.5±38.7	<.001
Low-density lipoprotein	155 (77.5)	77.3±34.8	100.5±46.4	69.6±27.1	77.3±34.8	.002
High-density lipoprotein	167 (83.5)	46.4±15.5	58.0±19.3	42.5±11.6	46.4±15.5	<.001
Triglycerides (median [IQR]; mg/dL)	167 (83.5)	159.4 (132.9)	124.0 (88.6)	168.3 (150.6)	159.4 (79.7)	.13
DM therapy	200 (100.0)					
Diet-controlled DM		4 (2.0)	0 (0.0)	2 (1.6)	2 (6.7)	N/A
Oral hypoglycemics						
Metformin		84 (42.0)	0 (0.0)	71 (55.9)	13 (43.3)	<.001
Sulphonylurea		63 (31.5)	0 (0.0)	50 (39.4)	13 (43.3)	<.001
Meglitinide		2 (1.0)	0 (0.0)	2 (1.6)	0 (0.0)	N/A
Thiazolidinedione		3 (1.5)	0 (0.0)	2 (1.6)	1 (3.3)	N/A
Dipeptidyl peptidase-4 inhibitor		11 (5.5)	0 (0.0)	9 (7.1)	2 (6.7)	N/A
Glucagon-like peptide-1 analogue		7 (3.5)	0 (0.0)	6 (4.7)	1 (3.3)	N/A
Insulin therapy						
Multiple daily injection		60 (30.0)	37 (86.0)	21 (16.5)	2 (6.7)	<.001
Premixed insulin		37 (18.5)	4 (9.3)	27 (21.3)	6 (20.0)	.21
Long-acting insulin		18 (9.0)	0 (0.0)	13 (10.2)	5 (16.7)	N/A
Insulin pump		2 (1.0)	2 (4.7)	0 (0.0)	0 (0.0)	N/A

<sup>a</sup>CKD = chronic kidney disease; DM = diabetes mellitus; IQR = interquartile range; N/A = not applicable.

<sup>b</sup>Values are given as n(%), for categorical variables, or mean (±SD), for normally distributed continuous variables, unless otherwise indicated. Median (IQR) values are presented for continuous variables that are not normally distributed.

<sup>c</sup>One-way between-groups ANOVA was used to assess for variation in normally distributed continuous variables across the CKD subgroups.

<sup>d</sup> $\chi^2$  analysis was used to analyze for variation in the incidence of categorical variables across the CKD subgroups.

<sup>e</sup>N/A indicates that the minimum expected cell frequency count for  $\chi^2$  not satisfied.

<sup>f</sup>Kruskal-Wallis test was used to assess for variation across the CKD subgroups in continuous variables that were not normally distributed.

**TABLE 3. Additional Clinical Characteristics of the Study Cohort (N=200)<sup>a,b</sup>**

Characteristic	Data available	Total cohort (N=200)	Type 1 diabetes mellitus (n=43)	Type 2 diabetes mellitus (n=127)	Additional CKD etiology (n=30)	P value
<b>Comorbidities<sup>c</sup></b>						
<b>Macrovascular complications</b>						
Coronary artery disease	200 (100.0)	63 (31.5)	9 (20.9)	42 (33.1)	12 (40.0)	.19 <sup>d</sup>
Cerebrovascular disease	200 (100.0)	27 (13.5)	4 (9.3)	17 (13.4)	6 (20.0)	.42
Transient ischemic attack		13 (6.5)	3 (7.0)	8 (6.3)	2 (6.7)	N/A <sup>e</sup>
Stroke		16 (8.0)	2 (4.7)	10 (7.9)	4 (13.3)	N/A
Peripheral arterial disease	200 (100.0)	71 (35.5)	9 (20.9)	53 (41.7)	9 (30.0)	.04
<b>Microvascular complications</b>						
Diabetic retinopathy	196 (98.0)	144 (73.5)	39 (90.7)	90 (72.6)	15 (51.7)	.001
Diabetic neuropathy	200 (100.0)	120 (60.0)	23 (53.5)	82 (64.6)	15 (50.0)	.21
<b>Other</b>						
Hypertension	200 (100.0)	175 (87.5)	29 (67.4)	118 (92.9)	28 (93.3)	<.001
Dyslipidemia	200 (100.0)	139 (69.5)	29 (67.4)	93 (73.2)	17 (56.7)	.20
Erectile dysfunction	200 (100.0)	14 (7.0)	3 (7.0)	9 (7.1)	2 (6.7)	N/A
Lower limb ulceration	200 (100.0)	39 (19.5)	10 (23.3)	27 (21.3)	2 (6.7)	.15
Lower limb amputation	200 (100.0)	12 (6.0)	1 (2.3)	11 (8.7)	0 (0.0)	N/A
<b>Usage of nondiabetic medications<sup>f</sup></b>						
<b>Renin-angiotensin-aldosterone system inhibitors</b>						
Direct renin inhibitor		3 (1.5)	0 (0.0)	1 (0.8)	2 (6.7)	N/A
Angiotensin-converting enzyme inhibitor		156 (78.0)	37 (86.0)	96 (75.6)	23 (76.7)	.35
Angiotensin II receptor blocker		100 (50.0)	22 (51.2)	64 (50.4)	14 (46.7)	.92
Mineralocorticoid receptor antagonist		10 (5.0)	0 (0.0)	8 (6.3)	2 (6.7)	N/A
Dual blockade		53 (26.5)	15 (34.9)	33 (26.0)	5 (16.7)	.22
Statin therapy		177 (88.5)	37 (86.0)	114 (89.8)	26 (86.7)	.76
Kidney biopsy	200 (100.0)					
Kidney biopsy during follow-up		10 (5.0)	1 (2.3)	5 (3.9)	4 (13.3)	N/A
<b>Biopsy findings</b>						
Diabetic nephropathy		6 (60.0)	1 (100.0)	5 (100.0)	0 (0.0)	N/A
Hypertensive nephropathy		1 (10.0)	0 (0.0)	0 (0.0)	1 (25.0)	N/A
Acute interstitial nephritis		1 (10.0)	0 (0.0)	0 (0.0)	1 (25.0)	N/A
IgA nephropathy		1 (10.0)	0 (0.0)	0 (0.0)	1 (25.0)	N/A
Membranous glomerulonephropathy		1 (10.0)	0 (0.0)	0 (0.0)	1 (25.0)	N/A
<b>RRT<sup>h</sup></b>						
Required RRT during follow-up	200 (100.0)	16 (8.0)	7 (16.3)	9 (7.1)	0 (0.0)	N/A
Time to RRT (y)		3.2 (3.9)	5.4 (4.4)	2.9 (2.9)	0 (0.0)	.32 <sup>g</sup>
<b>RRT modality</b>						
Hemodialysis		12 (75.0)	4 (57.1)	8 (88.9)	0 (0.0)	N/A
Peritoneal dialysis		2 (12.5)	1 (14.3)	1 (11.1)	0 (0.0)	N/A
Kidney transplant		1 (6.3)	1 (14.3)	0 (0.0)	0 (0.0)	N/A
Simultaneous kidney-pancreas transplant		1 (6.3)	1 (14.3)	0 (0.0)	0 (0.0)	N/A
<b>Death from any cause<sup>h</sup></b>						
Died during follow-up	200 (100.0)	34 (17.0)	5 (11.6)	26 (20.5)	3 (10.0)	.22
Time to death from any cause (y)		3.0 (3.8)	4.7 (2.2)	2.5 (3.7)	3.0 <sup>i</sup>	.22

<sup>a</sup>CKD = chronic kidney disease; N/A = not applicable; RRT = renal replacement therapy.

<sup>b</sup>Values are presented as No. (percentage) for categorical variables. For continuous variables that are not normally distributed values are presented as median (interquartile range).

<sup>c</sup>Present by end-of-study follow-up on December 31, 2014.

<sup>d</sup> $\chi^2$  analysis was used to analyze for variation in the incidence of categorical variables across the CKD subgroups.

<sup>e</sup>N/A indicates that the minimum expected cell frequency count for  $\chi^2$  not satisfied.

<sup>f</sup>At any time during the study period.

<sup>g</sup>Kruskall-Wallis test was used to assess for variation across the CKD subgroups in continuous variables that were not normally distributed.

<sup>h</sup>Following first diabetes renal clinic evaluation.

<sup>i</sup>Interquartile range is not available because insufficient numbers had development of the outcome of interest.

TABLE 4. Number of Visits to DRC and Duration of Renal Functional Follow-up During Study Period<sup>a,b</sup>

Variable	Data available, No. (%)	Total cohort	Type 1 diabetes mellitus	Type 2 diabetes mellitus	Additional CKD etiology	P value
No. of visits to DRC during study period (n)	200 (100.0)	3.0 (4.0)	3.0 (6.0)	3.0 (4.0)	3.0 (3.0)	.84 <sup>c</sup>
Total No. of eGFR measurements <sup>d</sup> (n)	200 (100.0)	28.0 (40.0)	28.0 (45.0)	27.0 (37.0)	38.5 (59.0)	.09
Total duration of renal functional follow-up (y)	200 (100.0)	7.4 (3.4)	7.9 (3.4)	7.1 (3.4)	8.1 (2.2)	.03
Duration of renal functional follow-up before first DRC evaluation (y)	177 (88.5) <sup>e</sup>	2.7 (3.2)	2.7 (4.1)	2.6 (2.9)	2.8 (4.2)	.86
Duration of renal functional follow-up after first DRC evaluation (y)	198 (99.0) <sup>f</sup>	3.7 (3.6)	4.5 (4.5)	3.5 (3.6)	3.7 (4.5)	.29

<sup>a</sup>DRC = diabetes renal clinic; eGFR = estimated glomerular filtration rate.

<sup>b</sup>Median (interquartile range) values are provided for continuous variables that are not normally distributed.

<sup>c</sup>Kruskal-Wallis test was used to assess for variation across the chronic kidney disease subgroups in continuous variables that are not normally distributed.

<sup>d</sup>eGFR results based on creatinine values that were measured with a non-isotope dilution mass spectrometry traceable colorimetric creatinine assay between January 1, 2004, and December 13, 2005, were not included because creatinine values from this assay did not reliably correlate with results from later isotope dilution mass spectrometry traceable creatinine assays.

<sup>e</sup>A total of 23 patients had no available eGFR results before DRC evaluation.

<sup>f</sup>A total of 2 patients had no available eGFR results after DRC evaluation.

renin-angiotensin-aldosterone system inhibitors between the CKD subgroups. Rates of progression to renal replacement therapy (16 of 200 [8.0%]) and death (34 of 200 [17.0%]) during follow-up were relatively low.

The number of DRC visits and the duration of renal functional follow-up during the study period are presented in Table 4. The median (interquartile range) number of DRC visits was similar across all CKD subgroups: 3.0 (6.0) for T1D alone, 3.0 (4.0) for T2D alone, and 3.0 (3.0) for DM with an additional CKD etiology ( $P=.84$ ). Median (interquartile range) duration of renal functional follow-up for the total cohort was 7.4 (3.4) years overall: 2.7 (3.2) years before and 3.7 (3.6) years after first DRC attendance.

Annual absolute and percentage changes in CKD-EPI eGFR before vs after index DRC visit were (in mL/min in BSA per year and %/year, respectively):  $-1.59$  vs  $-3.10$  ( $P=.31$ ) and  $-1.22$  vs  $-9.39$  ( $P=.06$ ) for T1D;  $-5.64$  vs  $-3.07$  ( $P=.004$ ) and  $-10.88$  vs  $-9.94$  ( $P=.70$ ) for T2D; and  $-6.50$  vs  $+0.91$  ( $P<.001$ ) and  $-13.28$  vs  $-2.29$  ( $P=.001$ ) for DM with an additional CKD etiology. Similar results were observed for MDRD eGFR values (Table 5). Rates of change in albuminuria level did not differ before vs after index DRC visit in any group. After DRC attendance, the annual change in HbA<sub>1c</sub> remained similar in those who had additional

CKD etiologies ( $-0.89$  vs  $-0.37$  mmol/mol per year;  $P=.60$ ); in those with T1D, it showed a trend toward flattening ( $-2.66$  vs  $-1.30$  mmol/mol per year;  $P=.09$ ); and in those with T2D, it changed significantly from a negative to a positive trajectory ( $-1.26$  vs  $0.25$  mmol/mol per year;  $P=.003$ ). In the T1D subgroup, significant improvement was observed in the annual rate of change in total cholesterol ( $0.00$  vs  $-5.03$  mg/dL per year;  $P=.005$ ) but not for other lipid indices after index DRC attendance.

## DISCUSSION

This study provides insight into potentially selective renal benefits of a DRC intervention as determined by CKD etiology. The group we describe is larger than previously reported DRC cohorts,<sup>6-10</sup> and this study is the first to compare trends in renal functional and metabolic indices among those with CKD adjudged to be caused by T1D, T2D, or DM with an additional established etiology.

Previous studies of the impact of DRC-based care differ from the current report in their focus on primarily severe DKD.<sup>7-10</sup> In absolute terms, individuals who had T2D or DM with additional CKD etiologies in this cohort had statistically significant reductions in the rate of renal functional decline after DRC attendance. This finding suggests that previously reported benefits of DRC attendance



**TABLE 5. Annual Changes in Renal Function, Albuminuria, Glycemic Control, and Lipid Indices Before and After First DRC Attendance, Stratified by CKD Etiology<sup>a</sup>**

Variable	Type 1 diabetes mellitus			Type 2 diabetes mellitus			Additional CKD etiology		
	Before DRC	After DRC	P value	Before DRC	After DRC	P value	Before DRC	After DRC	P value
Absolute change in renal function (mL/min/body surface area/year)	(n=34)	(n=43)		(n=115)	(n=125)		(n=28)	(n=30)	
Modification of Diet in Renal Disease eGFR	-1.14 <sup>b</sup>	-3.52	.10	-5.56	-3.31	.01	-6.40	0.68 <sup>c</sup>	<.001
Chronic Kidney Disease Epidemiology Collaboration eGFR	-1.59	-3.10	.31	-5.64	-3.07	.004	-6.50	0.91	<.001
Percentage change in renal function (%/year)									
Modification of Diet in Renal Disease eGFR	-0.95	-9.87	.04	-10.44	-10.06	.87	-12.82	1.95	.001
Chronic Kidney Disease Epidemiology Collaboration eGFR	-1.22	-9.39	.06	-10.88	-9.94	.70	-13.28	-2.29	.001
Absolute change in urine albumin to creatinine ratio (mg/g/year)	(n=41)	(n=42)	.97	(n=117)	(n=123)	.48	(n=28)	(n=30)	.73
Absolute change in International Federation of Clinical Chemistry glycated hemoglobin (mmol/mol/year)	(n=42)	(n=42)	.09	(n=120)	(n=123)	.003	(n=29)	(n=30)	.60
Absolute change in non-LDL-C lipid indices (mg/dL/year)	(n=41)	(n=40)		(n=119)	(n=110)		(n=27)	(n=27)	
Total cholesterol	0.00	-5.03	.005	-1.16	-1.55	.85	-1.16	-1.55	.84
High-density lipoprotein cholesterol	0.00	-0.77	.07	-0.77	-0.39	.06	-0.77	-0.39	.47
Triglycerides	0.00	-7.97	.09	0.00	-2.66	.40	2.66	-2.66	.33
Absolute change in LDL-C (mg/dL/year)	(n=41)	(n=40)	.16	(n=115) <sup>d</sup>	(n=107) <sup>d</sup>	.59	(n=27)	(n=27)	.86

<sup>a</sup>CKD = chronic kidney disease; DRC = diabetes renal clinic; eGFR = estimated glomerular filtration rate; LDL-C = low-density lipoprotein cholesterol.

<sup>b</sup>Negative integers represent an annual decline in laboratory indices.

<sup>c</sup>Positive integers represent an annual increase in laboratory indices.

<sup>d</sup>LDL-C values were calculated using the Friedwald equation. LDL-C values were not calculated for individuals with triglyceride readings >400 mg/dL, hence the lower number of individuals included in LDL-C analyses compared with non-LDL-C lipid analyses.

for patients who have rapidly progressing DKD also may apply to those who have moderate rates of eGFR decline. However, expressing ongoing renal functional loss as a percentage of existing renal function rather than as an absolute rate of decline may result in an exaggerated perception of benefit from an intervention.<sup>19</sup> In this study, the subgroup with T2D alone experienced stable but persistent proportionate decline in renal function of roughly 10% annually after DRC attendance. This finding suggests that the reduction observed in the absolute rate (mL/min in BSA per year) of renal functional decline after DRC attendance in this subgroup can be ascribed, at least in part, to a slowing effect that occurs as the finite value of eGFR approaches zero. Nonetheless, the lack of an

acceleration in the proportionate rate of renal functional deterioration, despite the advancement of DKD, may be considered a positive outcome of DRC attendance for this subset of patients.<sup>20</sup> In contrast, those who had additional CKD etiologies experienced decline in rate of renal functional loss, measured as either an absolute or proportionate change, after DRC attendance. Therefore, these patients plausibly experienced a benefit from encountering nephrology-led diagnosis and management at the DRC earlier in their CKD course than might otherwise have been the case. Although individuals with additional CKD etiologies have been excluded from previous studies examining DRC interventions,<sup>6-10</sup> biopsy-based studies have consistently found that a substantial proportion of patients with

diabetes and CKD have one or more non-diabetes-related kidney diseases.<sup>21</sup>

The trend toward acceleration in the rate of renal functional decline after DRC attendance in those with T1D was an unexpected finding. The mean CKD-EPI eGFR was 14.5 mL/min per BSA higher at the index DRC visit in the group who had T1D alone compared with those who had T2D. However, certain predictors of renal functional decline were more prevalent in those with T1D.<sup>22</sup> For example, the T1D group had DM for 14 years longer than their T2D counterparts. Additionally, patients with T1D had higher time-averaged HbA<sub>1c</sub> level, total cholesterol level, and low-density lipoprotein cholesterol parameters, had a greater degree of proteinuria, and were more likely to be active smokers when referred. The discordant trajectory in renal function after DRC attendance in those who had T1D compared with those who had T2D may also be related to recognized differences in the pathophysiology of type 1 and type 2 diabetic kidney disease.<sup>23</sup> Hyperglycemia is frequently more severe and of longer duration in type 1 diabetic kidney disease.<sup>23</sup> Recently, epigenetic changes in kidney cells have been identified as a mechanism by which periods of poor glycemic control may perpetuate ongoing renal functional losses.<sup>24-26</sup> Although patients with T1D experienced annual decline in HbA<sub>1c</sub> both before and after DRC attendance, the degree of decline lessened after DRC attendance, and baseline HbA<sub>1c</sub> values at the index DRC visit were much higher in this subgroup. Thus, adverse metabolic memory may have contributed to ongoing renal functional losses in those with T1D, despite improvement in glycemic control. In addition, some patients with T1D may have transitioned from the hyperfiltration phase of DKD to a period of persistent eGFR decline after DRC attendance,<sup>27</sup> accounting for some of the paradoxical worsening in renal function observed in this subgroup. Nevertheless, mean CKD-EPI eGFR was 61.0 mL/min per BSA at first DRC attendance, and annual trajectory in renal function was negative before DRC attendance for the T1D subgroup, suggesting that the influence of the hyperfiltration phase of DKD on the observed renal functional changes in this subgroup was likely modest.

Current treatment of DKD is relatively limited and focuses on minimizing the rate

of renal functional loss rather than reversing it.<sup>28</sup> However, an increasing number of novel therapies for DKD are in various stages of development,<sup>29,30</sup> with recent endeavors particularly focusing on inflammatory pathways in DKD.<sup>31</sup> In addition, emerging evidence reveals that hypoglycemic agents of the sodium-glucose cotransporter-2 inhibitor and glucagon-like peptide 1 receptor agonist classes exert renal protective benefits through hemodynamic alterations and modulation of inflammation.<sup>32-34</sup> A further benefit of DRCs may be that their referral criteria often broadly match characteristics of the target populations for novel therapeutic interventions in DKD and may facilitate the enrollment of higher-risk patients into clinical trials.

The observational nature of this study limits the conclusions that can be drawn regarding the direct role of decisions made at the DRC in the benefits observed.<sup>35</sup> The lack of a control group of patients who have DKD being managed in a general DM clinic also limits the strength of our inferences regarding the impact of DRC attendance on rate of eGFR decline. The multifactorial nature of CKD is often difficult to tease apart definitively without histopathological information.<sup>36</sup> However, despite the lack of biopsy proof of diabetic nephropathy for most of the patients in this cohort, we succeeded in creating 3 distinct CKD etiological groups through the use of strict criteria to define additional CKD etiologies—groupings that are supported by the higher degree of albuminuria in the T1D and T2D subgroups compared with those categorized as having DM with additional CKD etiologies.<sup>37</sup>

The predominance of white patients in our outpatient cohort limits the applicability of our findings to adults from other racial and ethnic backgrounds. The relatively small sample size limits statistical power. However, analyses of trends in renal function were made on the basis of a median of 28 eGFR values over a median of 7.4 years of longitudinal follow-up per participant. Owing to limitations in our electronic medical record system, start and stop dates for individual medications could not be recorded. Instead, the data given on medication usage are intended to provide an overview of various medication class exposures during study follow-up. Blood pressure measurements taken before first DRC

attendance were not available for comparison with post-DRC attendance values, further limiting interpretation of the clinical determinants of the renal functional trends.

## CONCLUSION

After DRC consultation, the absolute rate of eGFR decline was similar for those who had T1D but slower for those who had T2D and DM with additional CKD etiologies. Percentage loss of renal function was higher in those who had T1D, similar in those who had T2D, and lower in those with additional CKD etiologies. Our results provide evidence that, for patients who have T2D and documented stage 3 CKD (eGFR < 60 ml/min per BSA), medical care may be effectively optimized for renal functional preservation in an outpatient setting involving collaboration between diabetologists and nephrologists. We also conclude that DRC referral should not be restricted to those who have rapid renal functional decline, and it may provide particular benefit to diabetic patients who have additional CKD etiologies.

**Abbreviations and Acronyms:** BSA = body surface area; CKD = chronic kidney disease; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; DKD = diabetic kidney disease; DM = diabetes mellitus; DRC = diabetes renal clinic; eGFR = estimated glomerular filtration rate; HbA<sub>1c</sub> = glycated hemoglobin; IDMS = isotope dilution mass spectrometry; MDRD = modification of diet in renal disease; T1D = type 1 DM; T2D = type 2 DM

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