

[ ORIGINAL ARTICLE ]

# Multidisciplinary Team Care Delays the Initiation of Renal Replacement Therapy in Diabetes: A Five-year Prospective, Single-center Study

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## Abstract:

**Objective** Although recent reports have highlighted the benefits of multidisciplinary team care (MTC) for chronic kidney disease (CKD) in slowing the progress of renal insufficiency, its long-term effects have not been evaluated for patients with diabetes mellitus (DM). We compared the renal survival rate between MTC and conservative care (CC).

**Methods** In this five-year, single-center, prospective, observational study, we examined 24 patients (mean age 65.5±12.1 years old, men/women 18/6) with DM-induced CKD stage ≥3 in an MTC clinic. The control group included 24 random patients with DM (mean age 61.0±12.8 years old, men/women 22/2) who received CC. MTC was provided by a nephrologist and medical staff, and CC was provided by a nephrologist.

**Results** In total, 10 MTC and 20 CC patients experienced renal events [creatinine doubling, initiation of renal replacement therapy (RRT), or death due to end-stage CKD]. During the five-year observation period, there were significantly fewer renal events in the MTC group than in the CC group according to the cumulative incidence method (p=0.006). Compared to CC, MTC significantly reduced the need for urgent initiation of hemodialysis (relative risk reduction 0.79, 95% confidence interval [CI] 0.107-0.964). On a multivariate analysis, MTC (hazard ratio [HR], 0.434, 95% CI 0.200-0.939) and the slope of the estimated glomerular filtration rate during the first year (HR, 0.429 per 1 mL/min/m<sup>2</sup>/year, 95% CI 0.279-0.661) were negatively associated with renal events.

**Conclusion** MTC for DM-induced CKD is an effective strategy for delaying RRT. Long-term MTC can demonstrate reno-protective effects.

**Key words:** chronic kidney disease, diabetic nephropathy, multidisciplinary team care, renal replacement therapy, urgent initiation of renal replacement therapy, end-stage renal disease

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## Introduction

Chronic kidney disease (CKD) is widely recognized as a powerful inducer of mortality due to various comorbidities,

such as cardiovascular events (1, 2), as well as progression to end-stage renal disease (ESRD). Furthermore, in ESRD, medical costs have been reported to increase sharply with the initiation of renal replacement therapy (RRT) (3) or comorbidity treatment by evolving medical technology. With

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the worldwide increase in the aging population, CKD has not only extensively threatened the health of individuals but also increased the economic burden in many countries. In particular, Japan has the highest concentration of elderly individuals worldwide (4); therefore, the establishment of an optimal strategy to delay the progression of CKD to ESRD is the most important issue in Japan.

Once diabetes mellitus (DM) has progressed from apparent proteinuria to the kidney dysfunction stage, fatal clinical outcomes may occur, such as heart disease, cerebral vessel disease, and even ESRD. Several meta-analyses and cohort studies have identified risk factors for the progression of DM to CKD/ESRD or death, such as female sex (5) and low (<6%) or high ( $\geq 9\%$ ) hemoglobin A1C (HbA1c) levels (6). DM also has a complicated pathology because of several critical comorbidities, such as hypertension, dyslipidemia, obesity, smoking, and overeating. In addition, pharmaceutical management of DM, even when DM was intensively controlled, only achieved limited improvement in clinical outcomes (7). Therefore, we recognize the need for multifocal support by multidisciplinary medical staff for patients with DM.

Recent reports have highlighted the benefits of multidisciplinary team care (MTC) for patients with CKD in slowing the progress of renal insufficiency and reducing medical costs (8-10). However, the long-term benefits and effects of MTC on patients with DM have not been reported. We presented our three-year results at the Japanese Society Dialysis Treatment conference in 2018, in which we demonstrated that, compared to conservative care (CC), three-year MTC had no significant effect on the renal survival.

Given that we evaluated the effect of MTC every year, in the present study, we evaluated the reno-protective effect of MTC for patients with DM-induced CKD over a period of five years and examined the risk factors for the progression of DM to renal dysfunction.

## Materials and Methods

This prospective cohort study analyzed patients with DM-induced CKD who received MTC at our Department of Nephrology to observe the progression of renal insufficiency. Our outpatient clinic accepts referral patients from practicing doctors and, together with them, we monitor these patients regularly. In this study, patients with DM started receiving MTC in April 2012. MTC was approved in 2012 for the first time in Japan as an additional medical expense for the medical team management of CKD induced by DM to prevent the initiation of RRT. The aim of this national strategy is to avoid initiating RRT. According to the regulation established by the Ministry of Health, Labor and Welfare, the MTC should consist of a nephrologist, a diabetes educator (clinical nurse or public health nurse) with education experience, and a nationally registered dietitian. The multidisciplinary team was required to report patients' estimated glomerular filtration rate (eGFR) maintenance, HbA1c lev-

els, and blood pressure (BP) once a year to the Ministry of Health, Labor and Welfare.

In this study, all procedures were carried out in accordance with the ethical standards of the institutional review board of our center and with the 1964 Declaration of Helsinki and its later amendments. Written informed consent was obtained from all participants included in the study.

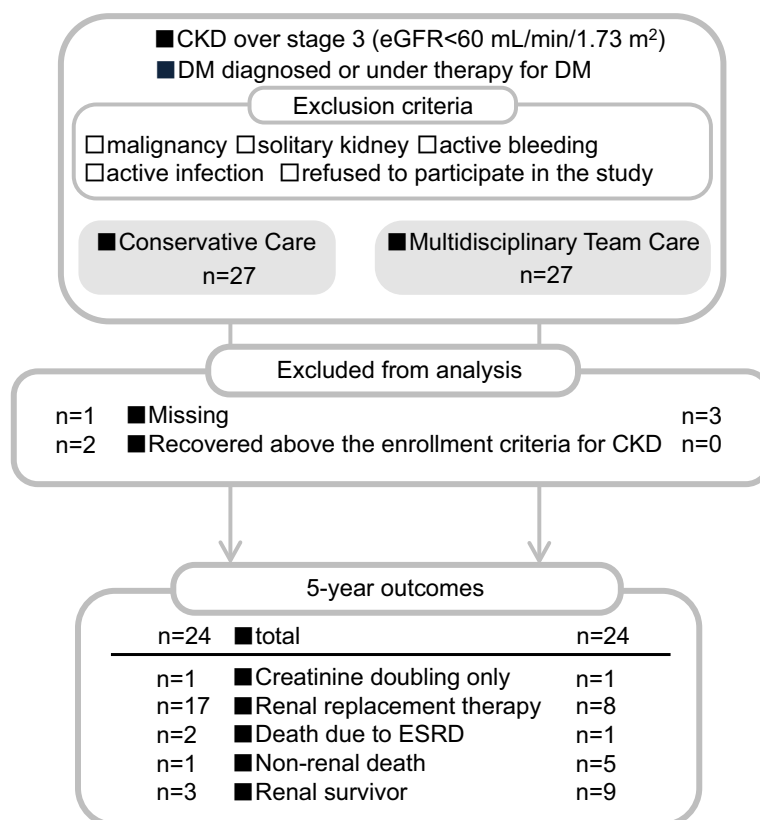
### Patients enrollment and study outcomes

We enrolled 27 patients with stage  $\geq 3$  CKD (eGFR <60 mL/min/1.73 m<sup>2</sup>) caused by DM without hemodialysis in the MTC outpatient clinic at our Department of Nephrology between April 2012 and March 2015. We analyzed the results of 24 patients after excluding the missing cases (n=3). The eGFR was calculated using the following equation:  $194 \times \text{serum Cr}^{-1.094} \times \text{age}^{-0.287}$  ( $\times 0.739$  in women). The MTC clinic only operated on fixed days of the week owing to shortages in medical specialists. As the control group (n=27), our medical staff selected one patient who received CC for every patient with DM who received MTC (1:1 ratio) according to our selection criteria. The selection criteria for the control patients receiving CC were (1) patients with a common background of DM with CKD and (2) patients who used to visit our clinic on days of the week other than the MTC clinic, and after receiving a notice about the MTC clinic, consented to visit the outpatient clinic on the same day of the week as before. We analyzed 24 patients in the CC group after excluding one patient who dropped out and two patients who recovered from CKD stage 3. The CC group received regular health checkups and medications from a nephrologist every one to three months and diet education by a dietician as needed. Patients were excluded when they met the following criteria: diagnosed with (1) malignancy, (2) solitary kidney due to kidney transplantation, (3) active gastrointestinal bleeding, (4) active infection upon enrollment; or (5) used to visit us on the MTC clinic days of the week and did not consent to receive their treatment in the MTC clinic (Fig. 1).

The end point of our observational study was the occurrence of a renal event, defined as serum creatinine doubling, the initiation of RRT, or death due to ESRD. We evaluated the effect of MTC on the occurrence of renal events every year until March 2019 for a total of five years.

### MTC clinic interventions

The multidisciplinary team consisted of a nephrologist, a clinical nurse as a healthcare educator, a nationally registered dietitian, and a pharmacist. At the beginning of MTC, the medical team prepared the original program (Fig. 2), which consisted of a series of six sessions of medical education for patients to enhance their comprehension and establish their overall knowledge of DM pathology; the sessions were conducted every two months for one year. MTC started after gathering information about the patients' lifestyle, including family structure, occupation, dietary habits, and fitness habits. Counseling was then continued to en-



**Figure 1.** Flowchart of the patient selection process and main outcomes. CKD: chronic kidney disease, DM: diabetes mellitus, eGFR: estimated glomerular filtration rate, ESRD: end-stage renal disease

hance the patients' understanding of the importance of measuring BP and body weight at home. In addition, the nurse observed the foot condition of each patient, the dietitian educated the patients on salt and protein intake restrictions, and the pharmacist provided information regarding drugs and explained the importance of adherence. At every visit, the medical staff reviewed the content of the previous session and assessed the current level of understanding among patients and their families before continuing to the next program. The consultation time with each staff member was approximately 10-20 min, and a flexible schedule was permitted as needed. At the end of the one-year MTC program, we decided to continue MTC depending on each patient's willingness and finally ended MTC when the patients requested to stop and return to CC.

### Study parameters

Baseline vital signs and laboratory data were collected before starting the MTC program. In the MTC group, we used 24-hour urine samples to calculate the estimated daily salt and protein intake, using the following formula: 24-hour sodium excretion (mEq/day)/17 as a standard method (1 mEq of sodium=58.5 mg of NaCl) and [24-hour blood urea nitrogen excretion (g/day) + 0.031 × body weight (kg)] × 6.25 (11), respectively. After the one-year MTC program and CC observation, vital signs and laboratory data were collected again. We then evaluated the eGFR slope as the

annual decline in the eGFR, urine protein, HbA1c, and BP after the one-year MTC program or CC observation. We calculated the eGFR slope one year before and after our educational interventions using the following equation: (eGFR at outpatient clinic visit before study enrollment - eGFR at study enrollment)/months between the two measurement points × 12 as the baseline eGFR slope and (eGFR at study enrollment - eGFR at one year after study enrollment)/observational month × 12 as the one-year after eGFR slope. The target HbA1c level was below 7.0, which was based on the results of a randomized controlled trial conducted in Japan (12), and the target BP (below 130/80 mmHg), salt intake (below 6 g/day), and protein intake (0.6-0.8 g/kg/day) were based on the CKD guidelines in Japan (13).

### Statistical analyses

The Mann-Whitney U-test was used to analyze continuous variables with a normal distribution, and Fisher's exact test was used to analyze nominal variables to test the difference between CC and MTC. In the present study, as the survival analysis method, we applied the cumulative incidence function because non-renal death was a competing event whose independence from the renal event could not be proven. The risk of an event occurrence would be overestimated when competitive events that are undeniable related to the research event are treated as censored as in the Kaplan-Meier method with log-rank statistics, a classically

	Nurse	Dietician	Pharmacist
1 <sup>st</sup>	<ul style="list-style-type: none"> <li>✓ Interview of lifestyle</li> <li>✓ How to measure home BP and BW</li> </ul>	<ul style="list-style-type: none"> <li>✓ Interview of dietary habits</li> <li>✓ How to limit salt</li> </ul>	/
2 <sup>nd</sup>	✓ Review previous contents		<ul style="list-style-type: none"> <li>✓ Check drug contents</li> <li>✓ Did you forget to take medicine?</li> </ul>
	✓ Check for comorbidities	<ul style="list-style-type: none"> <li>✓ Interview of dietary habits</li> <li>✓ How to limit salt</li> </ul>	
3 <sup>rd</sup>	✓ Review previous content		
	✓ How to read CKD data	<ul style="list-style-type: none"> <li>✓ Interview of dietary habits</li> <li>✓ How to limit protein</li> </ul>	<ul style="list-style-type: none"> <li>✓ Risk of hypoglycemia</li> <li>✓ What are sick days?</li> </ul>
4 <sup>th</sup>	✓ Review previous content		
	✓ Points of daily life in CKD	<ul style="list-style-type: none"> <li>✓ Interview of dietary habits</li> <li>✓ How to limit protein</li> </ul>	✓ Importance of non-diabetic drugs
5 <sup>th</sup>	✓ Review previous content		
	✓ Importance of foot check	<ul style="list-style-type: none"> <li>✓ Interview of dietary habits</li> <li>✓ How to maintain energy</li> </ul>	✓ Over-the-counter drugs
6 <sup>th</sup>	✓ Review all content		

**Figure 2.** Education program for patients with CKD enrolled in the MTC clinic. This original MTC program consisted of a series of six sessions of medical education for patients to enhance their comprehension and establish their overall knowledge of diabetes mellitus pathology every two months for one year. BP: blood pressure, BW: body weight, CKD: chronic kidney disease, MTC: multidisciplinary team care

well-known survival analysis. Therefore, to assess the effect of MTC on renal events, we determined the cumulative incidence functions in the MTC and CC groups, taking into account the competitive risk, and compared the differences between the two groups using Gray's test.

To examine the risk factors for the renal events, we conducted a multivariate analysis using the Fine and Gray sub-distribution hazard competing risk regression model and calculated the hazard ratio (HR) and 95% confidence interval, which helped clarify the relationship between covariates and the cumulative incidence of renal events in the presence of competing events, such as non-renal death, in our study. Patients who did not experience renal events or non-renal death were censored at the end of the observational period. Covariates for the multivariate analysis were selected from previously known risk factors of CKD progression, such as HbA1c, BP, eGFR, and urine protein at baseline, as well as our target variate (performance of the MTC clinic). The multivariate model was adjusted for possible confounders, such as age and sex.

The values in all the tables are expressed as the mean  $\pm$  standard deviation. Differences were considered significant with two-tailed p values  $<0.05$ . Statistical analyses were carried out using the JMP software program (SAS Institute, Cary, USA) and EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan).

## Results

A total of 54 patients were enrolled in this study, including 27 patients in the CC group and 27 patients in the MTC group. Of them, 1 in the CC group and 3 in the MTC group discontinued outpatient visits, and 2 in the CC group had a renal function that recovered to a value outside the enrollment criteria for CKD; both groups therefore ultimately included 24 cases each. During the five-year observational period, 20 patients in the CC group and 10 in the MTC group showed creatinine doubling, received RRT, or died due to ESRD, and 1 and 5 patients in the CC and MTC groups, respectively, died of causes other than kidney disease; consequently, 3 and 9 patients did not experience the aforementioned renal events in the CC and MTC groups, respectively.

The patient characteristics are shown in Table 1. In the Mann-Whitney U-test, no significant difference was found between the two groups in terms of the mean age ( $61.0 \pm 12.8$  years old in CC,  $65.5 \pm 12.1$  years old in MTC), mean eGFR ( $25.0 \pm 9.1$  mL/min/1.73 m<sup>2</sup> in CC,  $26.1 \pm 11.4$  mL/min/1.73 m<sup>2</sup> in MTC), mean systolic BP ( $141.4 \pm 18.2$  mmHg in CC,  $139.8 \pm 17.4$  mmHg in MTC), mean diastolic BP ( $74.9 \pm 14.5$  mmHg in CC,  $76.3 \pm 11.7$  mmHg in MTC), or mean HbA1c ( $6.5 \pm 1.1\%$  in CC,  $6.6 \pm 1.2\%$  in MTC). The number of current smokers and mean body mass index (BMI) were

**Table 1. Comparison of Characteristics between the Conservative Care Group and the Multidisciplinary Team Care Group.**

	CC group	MTC group	p value
n	24	24	
Age (years)	61.0±12.8	65.5±12.1	0.213
Male/female sex	23/2	18/6	0.097
CKD stage			
3 (eGFR<60 mL/min/1.73 m <sup>2</sup> ), n (%)	5 (20.8)	8 (33.3)	0.517
4 (eGFR<30 mL/min/1.73 m <sup>2</sup> ), n (%)	16 (66.7)	13 (54.2)	0.556
5 (eGFR<15 mL/min/1.73 m <sup>2</sup> ), n (%)	3 (12.5)	3 (12.5)	1.000
eGFR (mL/min/1.73 m <sup>2</sup> )	25.0±9.1	26.1±11.4	0.724
HbA1c (%)	6.5±1.1	6.6±1.2	0.760
Comorbidity			
Hypertension, n (%)	23 (95.8)	23 (95.8)	1.000
Dyslipidemia, n (%)	15 (62.5)	15 (62.5)	1.000
Hyperuricemia, n (%)	19 (79.2)	21 (87.5)	0.522
Systolic blood pressure (mmHg)	141.4±18.2	139.8±17.4	0.766
Diastolic blood pressure (mmHg)	74.9±14.5	76.3±11.7	0.719
Body mass index (kg/m <sup>2</sup> )	25.7±4.8	25.6±4.3	0.973
Current smoker, n (%)	11 (45.8)	6 (25.0)	0.129
Statin, n (%)	10 (41.7)	9 (37.5)	0.768
RAS blocker, n (%)	21 (87.5)	21 (87.5)	1.000
CCB, n (%)	20 (83.3)	15 (62.5)	0.101
β-blocker, n (%)	8 (33.3)	9 (37.5)	0.763
Insulin user, n (%)	8 (33.3)	8 (33.3)	1.000
CVD history, n (%)	13 (54.2)	11 (45.8)	0.564
Hemoglobin (g/dL)	11.5±1.7	11.2±1.6	0.637
Albumin (g/dL)	3.6±0.5	3.8±0.6	0.244
Uric acid (mg/dL)	6.7±1.5	7.0±1.3	0.456
Potassium (mEq/L)	4.7±0.4	4.5±0.6	0.210
Calcium (mg/dL)	8.7±0.5	8.7±1.0	0.924
Phosphate (mg/dL)	3.6±0.9	3.9±0.8	0.379
Intact PTH (pg/mL)	140.8±96.4	119.1±69.7	0.517
CRP (mg/dL)	0.28±0.47	0.15±0.14	0.263
LDL-cholesterol (mg/dL)	112.0±25.4	97.0±29.2	0.064
HDL-cholesterol (mg/dL)	49.4±25.7	50.5±18.0	0.863
Triglyceride (mg/dL)	152.7±104.4	148.0±79.1	0.864
Urine protein (g/gCre)	4.37±3.51	3.38±3.81	0.353
DM history (years)	14.5±10.7	16.9±10.7	0.437
Number of MTC clinics (n)	-	10.4±6.1	-
Duration of MTC clinic (months)	-	22.9±14.9	-
Intake of sodium (g/day)	-	10.6±5.1	-
Intake of protein (g/day)	-	51.6±20.4	-

Data are presented as mean±standard deviation.

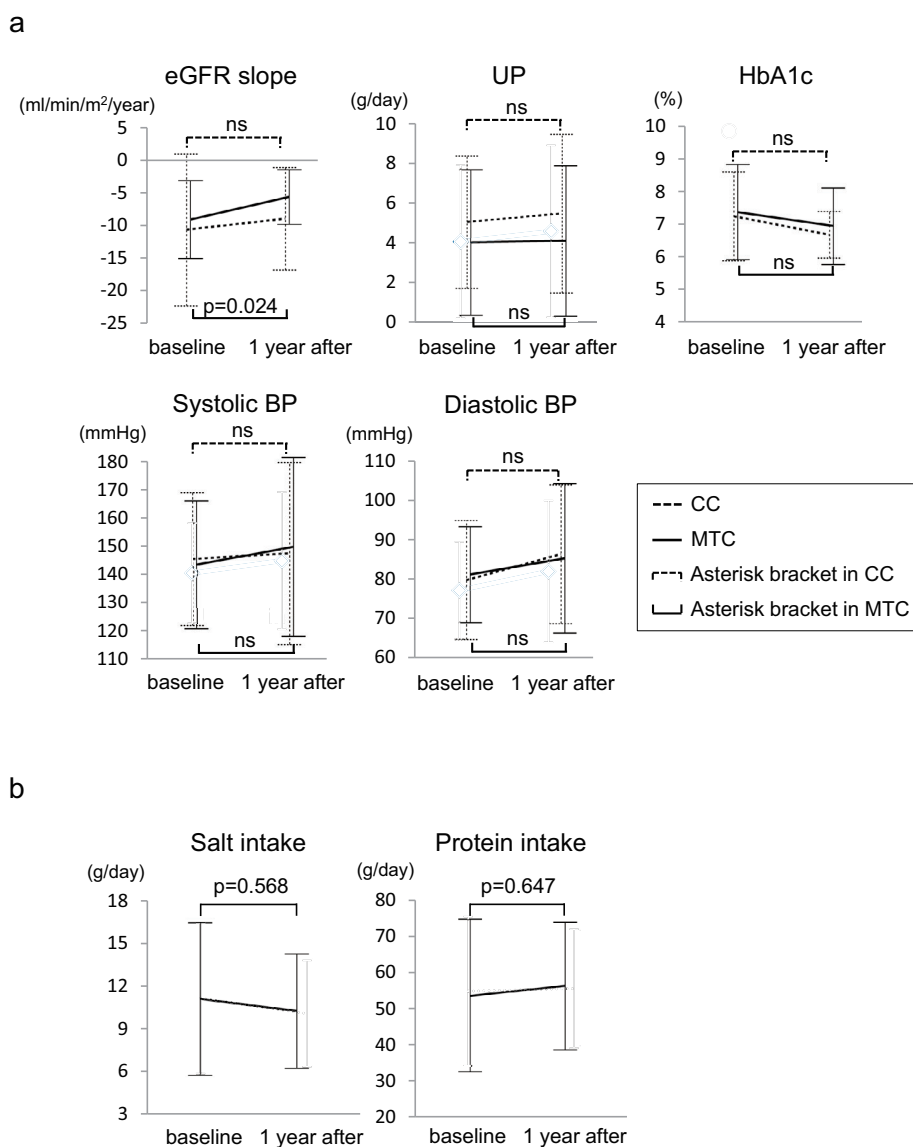
CC: conservative care, CCB: calcium channel blocker, CRP: C-reactive protein, CVD: cardiovascular disease, HDL-C: high-density lipoprotein-cholesterol, LDL-C: low-density lipoprotein-cholesterol, MTC: multidisciplinary team care, PTH: parathyroid hormone, RAS: renin-angiotensin system

also similar between the groups. The number of MTC sessions and MTC duration within five years were 10.6±5.1 times and 22.9±14.9 months, respectively.

Changes in the mean values of the eGFR slope, urinary protein, HbA1c, and BP in patients who received CC or MTC for one year are shown in Fig. 3a. Although the eGFR slope after the one-year MTC intervention was higher than that at the baseline (−8.8±7.7 mL/min/m<sup>2</sup>/year to −4.3±5.4 mL/min/m<sup>2</sup>/year, p=0.024), the eGFR slope in the CC group

showed no significant difference between baseline and after the observations started (−10.8±15.0 mL/min/m<sup>2</sup>/year to −8.6±10.0 mL/min/m<sup>2</sup>/year, p=0.560). Furthermore, no significant difference was found in either group between baseline and after observation in terms of the urine protein (4.37±3.51 g/gCre to 4.90±4.15 g/gCre in CC, 3.38±3.81 g/gCre to 3.38±4.00 g/gCre in MTC), HbA1c (6.5±1.1% to 6.0±0.6% in CC, 6.6±1.2% to 6.3±0.9% in MTC), systolic BP (141.4±18.2 mmHg to 143.0±4.9 mmHg in CC, 139.8±17.4 mmHg

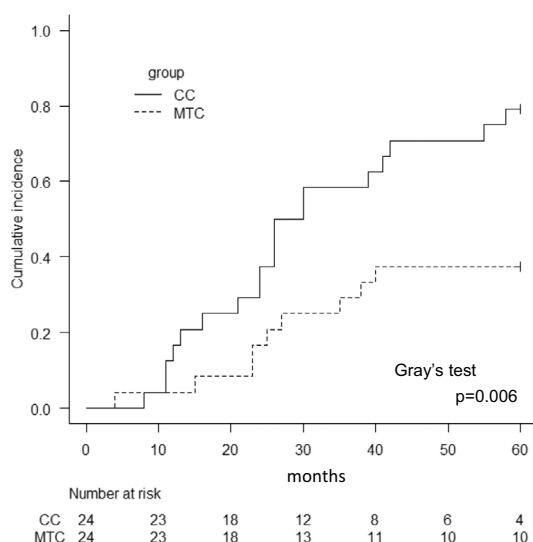




**Figure 3.** **a:** A comparison of main parameters in both MTC and CC groups before and after the one-year observation period. We compared the mean values of the main parameters related to the evaluation of MTC or CC for DM-induced CKD before and after the one-year observation period. The mean eGFR slope increased significantly in the MTC group but not in the CC group. Among other markers, urine protein, HbA1c, systolic blood pressure, and diastolic blood pressure showed no significant change in either group, indicating that the renal function was not associated with these main parameters, except for the eGFR slope, in the MTC or CC group. **b:** A comparison of the estimated salt and protein intake using 24-hour urine samples in the MTC group before and after the one-year MTC clinic. We compared the mean values of the estimated salt and protein intake in the MTC group before and after the one-year MTC clinic. Both parameters were evaluated by the Mann-Whitney U-test and showed no significant change during this period. Differences were considered significant when  $p < 0.05$ . BP: blood pressure, CC: conservative care, DM: diabetes mellitus, eGFR: estimated glomerular filtration rate, HbA1c: hemoglobin A1C, MTC: multidisciplinary team care, ns: not significant, UP: urine protein

to  $144.7 \pm 24.4$  mmHg in MTC), or diastolic BP ( $74.9 \pm 14.5$  mmHg to  $81.2 \pm 16.9$  mmHg in CC,  $76.3 \pm 11.7$  mmHg to  $80.2 \pm 18.2$  mmHg in MTC). Although we also analyzed the changes in other lifestyle parameters, such as the BMI, low-density lipoprotein, high-density lipoprotein, triglycerides, and uric acid, before and after the one-year observation period in each group, there was no marked improvement after

the introduction of the MTC clinic, and no significant differences in the change ratio of these parameters were noted during the one-year period between the groups (data not shown). In the MTC group, the change in the estimated daily salt intake ( $10.6 \pm 5.1$  to  $9.8 \pm 3.8$ ) and protein intake ( $51.6 \pm 20.4$  to  $54.2 \pm 17.0$ ) using 24-hour urine samples also showed no significant improvement despite constant educa-



**Figure 4.** Results of a survival analysis using the cumulative incident function for the occurrence of renal events. We used the cumulative incident function for renal events of the MTC and CC groups over five years. We represented the cumulative occurrence rate of the renal events, including creatinine doubling, initiation of RRT, and renal death. We performed a Gray test, and differences were considered significant when  $p < 0.05$ . CC: conservative care, MTC: multidisciplinary team care, RRT: renal replacement therapy

tion on salt and protein restriction (Fig. 3b). In addition, we investigated the serum potassium level before and after the MTC clinic. In the CC group, the potassium level increased significantly during the one-year observation period ( $4.7 \pm 0.2$  to  $5.1 \pm 0.2$ ,  $p = 0.003$ ), while there was no significant difference in the MTC group ( $4.5 \pm 0.5$  to  $4.8 \pm 0.4$ ,  $p = 0.09$ ).

Fig. 4 shows the results of the survival analysis using the cumulative incidence function for the occurrence rate of renal events during the five-year observation period. Compared with CC, MTC was associated with a significant reduction in the occurrence of renal events (Gray test  $p = 0.006$ ) (Fig. 4). Furthermore, compared with CC, MTC was significantly associated with a reduction in the urgent initiation of hemodialysis, defined as receiving temporary catheterization for dialysis (Fisher's exact test; relative risk reduction 0.79,  $p = 0.042$ ) (Table 2).

Finally, we evaluated the major risks and beneficial factors associated with renal events in all patients using the Fine and Gray sub-distribution hazard competing risk regression model (Table 3). As a significant beneficial factor, the performance of the MTC clinic (HR, 0.434 vs. CC) and the eGFR slope during the first year (HR, 0.429 per 1 mL/min/ $m^2$ /year) were negatively associated with renal events. In contrast, the baseline urine protein level was an independent risk factor for renal events (HR, 1.314 per 1 g/gCre).

## Discussion

We performed a cohort follow-up study of patients with

DM-induced CKD to investigate the five-year effect of long-term MTC on the progression of CKD and initiation of RRT. In the study, we demonstrated that, in contrast to CC, multidisciplinary care provided by a medical team for patients with DM could delay the initiation of RRT and reduce the urgent initiation of RRT. To our knowledge, this is the first report to evaluate the long-term effect of MTC on DM-induced CKD using data collected over five years.

DM has been reported to cause fatal complications in various organs. Together with metabolic abnormalities (hypertension and/or dyslipidemia), hemodynamic overload, renin-angiotensin system activation, hyperglycemia, and the accumulation of advanced glycation end products, DM has the potential to induce histological damage in the kidneys (14, 15) through inflammatory and oxidative stress pathways (16, 17), which can result in the clinical progression of kidney dysfunction. Furthermore, DM-induced atherosclerosis may result in life-threatening complications, such as ischemic heart disease, cerebral vascular disease, and atherosclerosis obliterans. These fatal complications result from consistent poor lifestyle choices that affect not only the patients' health but also the medical economy. Therefore, medical experts worldwide have developed alternative strategies to break the cycle of poor lifestyle and DM pathology.

Previous studies have reported clinical evidence of improvements in CKD by increasing medical education through counseling to increase self-awareness (18, 19), maintain medication compliance (20), reduce protein (21) and salt (22) intake, and encourage habitual exercise (23). Recent cohort studies have revealed that the maintenance of the renal function may be a result of multidisciplinary medical team support or education for patients with CKD. In those studies, MTC maintained the eGFR, as confirmed by measurements of the eGFR slope during a two-year observation period for stage 3 (24), stages 4-5 (25), and stage 5 CKD (9). Furthermore, MTC was found to delay RRT initiation and decrease mortality as well as CKD progression (8), enable good control of anemia, allow a high rate of vascular access preparation (26), lessen urgent initiation of RRT, and shorten hospital stays (27). With a normal renal function, a meta-analysis revealed that MTC for patients with uncontrolled DM demonstrated significantly improved HbA1c and systolic BP levels without incurring excessive costs (28). In addition, a recent systematic review reported that, in cohort studies, MTC in patients with CKD was associated with lower all-cause mortality, a lower rate of dialysis initiation, and a lower rate of temporal catheterization for dialysis (29). In addition to the reno-protective effect of MTC based on our five-year observation data, we found that the effect was enhanced significantly by repeated programmed education in the MTC clinic and the maintenance or improvement of the eGFR slope in the first year, as shown in our analysis. This effect, which was observed in the long term after MTC ended, can be called the legacy effect. Regarding the residual effect, there has also been a negative report (30) describing no significant legacy effect

**Table 2. Association of MTC with Urgent Initiation of Renal Replacement Therapy.**

Parameter	Initiation of RRT		Relative risk	95% CI	p value
	urgent	scheduled			
MTC clinic	Yes	1	0.79	0.107-0.964	0.042
	No	10			

Fisher's test was used for all calculations.

CC: conservative care, CI: confidence interval, MTC: multidisciplinary team care, RRT: renal replacement therapy

**Table 3. Risk Factors for Renal Events over a Period of Five Years in All Patients.**

Parameter	Univariate Hazard ratio (95% CI)	Multivariate Hazard ratio (95% CI)
Performance of the MTC clinic (yes)	0.342 (0.157-0.748)	0.434 (0.200-0.939)
eGFR on baseline (per 1 mL/min/m <sup>2</sup> )	0.971 (0.932-1.011)	
eGFR slope at 1 year after MTC (per 1 mL/min/m <sup>2</sup> /year)	0.330 (0.110-0.588)	0.429 (0.279-0.661)
HbA1c on baseline (per 1%)	1.007 (0.724-1.400)	
Systolic BP on baseline (per 1 mmHg)	1.022 (0.998-1.044)	
Diastolic BP on baseline (per 1 mmHg)	1.036 (0.997-1.060)	
UP on baseline (per 1 g/gCre)	1.330 (1.208-1.465)	1.314 (1.210-1.428)

Fine and Gray sub-distribution hazards competing risk regression model was used. Adjusted for age and sex

BP: blood pressure, CI: confidence interval, eGFR: estimated glomerular filtration rate, MTC: multidisciplinary team care, UP: urine protein

after MTC intervention for patients with DM-induced stage 3-4 CKD during a two-year follow-up period. They attributed this result to the long duration of diabetes (15 years) and the short duration of intervention (2 years). Compared with their follow-up analysis, our patients had a similar duration of diabetes and exposure to MTC; however, our patients had better HbA1c control with less insulin usage and a lower BMI. We considered that not only the background and race but also a short observation period of two years may have had a large impact on whether or not the legacy effect of MTC would be obtained.

Several limitations associated with the present study warrant mention. First, we were unable to clarify the elements of MTC education that most significantly contributed to delaying the initiation of RRT. Although previous reports pointed out the effect of salt or protein restriction on the maintenance of the renal function (21, 22), we found no marked change in the salt or protein intake during the first observation year despite continuous nutritional support. Furthermore, other main parameters, such as the BP, HbA1c, and urine protein, showed no significant improvement during the first observation year. Although previous randomized controlled trials of patients with DM indicated the reno-protective effects of optimal control of BP (31, 32) and HbA1c (33, 34), and proteinuria was reported as a definite aggravating factor of ESRD (35), we failed to establish the reason underlying the effect of MTC support on the expected parameters at the beginning of our MTC program. This is because we were unable to conduct a sufficient evaluation of the behavior changes with and without MTC intervention,

and insufficient comparisons were made with the CC group since we did not perform 24-hour urine collection or evaluate drug adherence in CC. However, at the very least, HbA1c can be considered less markedly associated with the effect of MTC, as its level was normal at baseline. Although the maintenance of the eGFR during one-year MTC may be the ideal target of MTC for long-term reno-protection, we need to ascertain the optimal medical education parameters to determine the reno-protective effects of MTC other than restrictions on the salt and protein intake. Second, DM nephropathy has been recently re-defined as diabetic kidney disease (DKD), which includes atypical cases, such as cases with renal dysfunction progression without proteinuria, in addition to the typical clinical features (36). As the elderly population has increased, DM accompanied by nephrosclerosis or improvement of proteinuria (atypical DKD) has demonstrated a better prognosis than typical DKD with long-term DM treatment. Although our study might have included some patients with atypical DKD, we could not distinguish patients with DM having primary pathology (typical DKD) from those with coexisting pathology (atypical DKD) mainly because no clinical indicators exist to distinguish between typical and atypical DKD. We speculate that it would be difficult to differentiate these patient populations at this time; therefore, we hope that a new parameter will be established to separate these pathologies in the future. Third, there might have been a lack of social support for patients with a low income or living alone and psychological support to motivate patients or address worries in those indicated for DM treatment. The relationship between income and mortal-



ity in patients with DM has previously been highlighted; however, social disparities inevitably persist despite universal access to care provided by the national healthcare system (37). Patients with DM were subjected to DM type-specific stress (38), and patients with DM experience psychological distress differently and have different personality traits from patients without DM (39). Although no study has evaluated DM care according to social or psychological parameters, we also were unable to assess and evaluate all aspects of patient demographics in the present study given the limited clinical time and shortage of medical specialists. This is the most important problem to be solved not only in our facility but also at a regional and national level. Fourth, our approach lacked an assessment of the need to strengthen collaboration with general physicians (GPs). Recently, it has been reported that strengthening the cooperation with GPs as well as behavioral changes in patients through patient education might be associated with a delay in the progression of CKD (40). We are also making an effort to keep updated with medical information documents as well as creating a CKD notebook, where we describe each other's medical care, and we are searching for ways to allow every doctor to perform such tasks for every patient; however, such an approach has not been established yet. The multi-target strategy for CKD needs to be enhanced in all respects. Fifth, this was an observational cohort study including a small number of study participants from a single center. Therefore, our study may have selection bias, and the generalization of our results to other populations (e.g., possible ethnic differences, differences in habits, and care protocols) may be challenging. Furthermore, the lack of a multivariate analysis to identify the predictive parameters for renal events within the MTC group owing to the limited number of renal events, in addition to the insufficient evaluation described above as the first limitation, may make it difficult to identify the case group likely to receive the greatest benefit from MTC, i.e., the true target of MTC intervention. In the future, we plan to employ an intervention protocol or conduct a prospective comparative study of patients with CKD induced by DM nephropathy to determine which aspect of the team support is the most effective.

## Conclusion

In this study, we demonstrated the long-term benefits of repeated MTC for patients with DM on delaying the progression of CKD and initiation of RRT and reducing the urgent initiation of RRT. In the management of DM-induced CKD with complicated and fatal pathology, we should consider total support through an MTC program to enhance patients' awareness and maintenance of self-healthcare, which will help inhibit the occurrence of ESRD and reduce medical costs. For this purpose, we need to enhance medical knowledge and ensure the cooperation of all medical staff members in delivering care. In the future, we will refine the contents of our MTC program and provide further support

to patients with DM.

**The authors state that they have no Conflict of Interest (COI).**

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