Renal Outcome of Patients with Chronic Kidney Disease Stage 3-5 under a Multidisciplinary Care Program

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Abstract

BACKGROUND: A variety of factors are well-recognized as active in mediating the progression of chronic kidney disease (CKD). Multidisciplinary care programs (MDCPs) have been shown to be effective in retarding the progression of CKD. However, little is known regarding the progression of CKD in a cohort receiving MDCP. The objectives of this study were to identify factors associated with rapid decline of renal function among a CKD cohort and analyze their outcome.

METHODS: CKD patients (stage 3-5) who had been receiving MDCP for at least 24 months were analyzed retrospectively. Their demographic data, co-morbidities and biochemical data were reviewed and collected. Glomerular filtration rate (GFR) was estimated by the Modification of Diet in Renal Disease Study (MDRD) equation.

RESULTS: Of the total 343 patients, 32.1% were CKD stage 3, 23.0% were stage 4 and 44.9% were stage 5. Their mean age was 63.5 years and 36.7% were diabetic. Their baseline GFR was 24.5 mL/min/1.73 m^2 and biennial GFR change was -3.0 ± 6.4 mL/min/1.73 m^2. We further divided the patients into two groups according to the rate of GFR decline. Patients with biennial GFR change of more than -4 mL/min/1.73 m^2 were considered to have rapid progression. 133 patients with rapid progression were then compared with 210 patients with non-rapid progression. Patients with diabetes, hypertension, proteinuria, higher baseline systolic and diastolic blood pressure, and lower albumin level progressed more rapidly. During the follow-up, 30 patients (8.8%) reached the combined endpoint of the study. Logistic regression analysis disclosed that systolic blood pressure and serum albumin level were the independent factors of rapid renal progression. Patients with stage 4 or 5 experienced more rapid progression (stage 4: -3.4 ± 6.8; stage 5: -4.8 ± 5.0 mL/min/1.73 m^2) than those with stage 3 (0.1 ± 6.9 mL/min/1.73 m^2, P < 0.001).

CONCLUSION: The average annual rate of renal function decline in our MDCP cohort was slightly higher than the aging process. Baseline systolic blood pressure and serum albumin level were independent factors of rapid progression among moderate CKD patients under the MDCP.

KEY WORDS: chronic kidney disease, rapid progression, hypertension, albumin, multidisciplinary care program
of patients receiving dialysis therapy was 56,578 in 2009 and the prevalence rate was 2,447 per million people (1). It was estimated that approximately 12% of the adult population of Taiwan had CKD (2). A variety of factors were already identified as active factors in preventing the progression of CKD, including stringent control of blood pressure and sugar, use of renin-angiotensin system (RAAS) blockers and reduction of proteinuria (3, 4). There has been evidence of suboptimal CKD care provided by primary care physicians prior to referral to nephrologists (5, 6). Nevertheless, the outcome of this population is still unsatisfactory despite these therapeutic strategies. In order to retard the progression of kidney disease, multidisciplinary care programs (MDCPs) have been developed and introduced in many countries. In fact, it is not a new idea and was advocated by the NIH consensus group in the early 1990s (7). There is an extensive literature focusing on the effectiveness of MDCPs in promoting survival (8), reducing hospitalization (9), retarding renal disease progression (9) and prolonging time to renal replacement therapy (10). Still, the progression of the disease cannot be completely halted and some patients advance to ESRD rapidly despite all these efforts. Few studies have investigated the patients who are less responsive to MDCP. The objectives of this study were to characterize a group of CKD patients with rapid renal function deterioration and analyze the predictors for rapid deterioration of CKD in this population. Furthermore, we compared the change of GFR in different stages of CKD after MDCP intervention.

Materials and Methods

Study Population and Design

This study enrolled Taiwanese patients with CKD stages 3-5. They had been visiting the nephrology outpatient clinics since December 2006 and joined the MDCP for at least 24 months, until ESRD, renal transplantation, or death. Patients were excluded if they were less than 18 years old, started to receive dialysis or underwent renal transplantation or died within the first 6 months after their entry into this program, or had incomplete laboratory data. Their demographic data, co-morbidities, and biochemical data were reviewed and collected according to medical records. GFR was estimated by the recalibrated 4-variable Modification of Diet in Renal Disease Study (MDRD) equation as 186 × (serum creatinine)\(^{-1.154}\) × age\(^{-0.203}\) × 0.742 (if women). Proteinuria was defined as having a positive dipstick urinalysis for proteinuria or urinary total protein to creatinine ratio ≥ 150 mg/gm in spot urine. Diabetes mellitus (DM) was defined as patients who were receiving oral anti-diabetic or insulin treatment; with fasting blood sugar ≥ 126 mg/dL or random blood sugar ≥ 200 mg/dL with associated symptoms. Hypertension was defined as systolic blood pressure (SBP) over 140 mmHg, diastolic blood pressure (DBP) over 90 mmHg, or a history of the use of antihypertensive medications for lowering blood pressure. Blood pressure was measured at every visit to the nephrology outpatient clinics with at intervals of approximately three months by trained medical staffs. The patients remained at rest in a sitting posture for at least 5 minutes before blood pressure was measured.

Definition of Decline in Renal Function and Combined Endpoint

Decline of GFR was calculated by subtracting the GFR after follow-up from the GFR at the time of entry. A negative GFR indicated a fall in GFR. According to NKF-K/DOQI guidelines, GFR normally reduces less than 1 mL/min/1.73 m\(^2\) in adulthood (11). Thus, patients with biennial GFR decline of more than 4 mL/min/1.73 m\(^2\) were considered to have rapid progression of renal function. The combined endpoint was defined as biennial eGFR decline ≥ 4 mL/min/1.73 m\(^2\), commencement of dialysis, renal transplantation or death.

MDCP

These patients joined the Pre-ESRD program of the National Health Insurance Bureau. The MDCP followed the guidelines in the instruction booklet of the Bureau of Health Promotion. The goals of the program included retarding progression of renal function, avoiding the renal insult of inappropriate medications and preventing of uremic complications. The MDCP team consisted of nephrologists, dietitians and case-management nurses who had background experience in renal replacement therapy. The program involved an integrated course comprising individual lectures on renal health and CKD related complications delivered by the case-management nurses. The lectures concentrated on nutrition, lifestyle modifications, nephrotoxin avoidance, dietary principles, and pharmacological regimens. We conducted standardized interactive educational sessions wherein all patients were interviewed according to their CKD stage at least once every three months. All patients received dietary counseling at least biannually from the dietitians. Additionally, the MDCP nurses often phoned the participants to ensure timely follow-up, encourage them to inform nephrologists about their symptoms and provide real-time counseling about the disease. When renal replacement therapy was started for these patients, the MDCP was discontinued.
Statistical Analysis

All analyses were performed with SPSS, version 17.0 (SPSS Inc., Chicago, Ill., USA). Data were presented as mean and SD for continuous variables and percentage for categorical variables. A Chi-square test was used for analyzing categorical variables. For the continuous variable, we used a paired t-test to investigate the effectiveness of the MDCP before and after the intervention. A student t-test was used for the comparison between the two groups and the difference of GFR decline between different CKD stages was analyzed by one way-ANOVA and then a Bonferoni Post-hoc test. A stepwise logistic regression test further identified the independent factors to predict rapid deterioration of renal function. To predict renal outcome of patients with different CKD stages, Kaplan-Meier analysis was applied. A P value < 0.05 was considered to be significant.

Results

Subject Characteristics

A total of 343 patients at CKD stages 3-5 without dialysis were enrolled in the study. Table 1 shows the baseline characteristics of the population. 204 (59.5%) patients were males and 139 (40.5%) were females. The mean age of the participants was 63.5 ± 13.0 years old. Among the patients, 66.2% had hypertension, 36.7% had diabetes mellitus, and 73.8% had proteinuria. 32.1% patients were at CKD stage 3, 23.0% were at stage 4, and 44.9% were at stage 5. Thirty patients (8.8%) had advanced to ESRD and received dialysis therapy or renal transplantation within 2 years of follow-up. Of the patients with hypertension, 40.8% achieved the blood pressure treatment target goal of less than 130/80 mmHg.
Table 2. Changes of biochemical data before and after entry in the MDCP

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>After 2 years</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP (mmHg)</td>
<td>133.7 ± 20.0</td>
<td>132.8 ± 14.7</td>
<td>NS</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>73.3 ± 11.9</td>
<td>72.6 ± 8.0</td>
<td>NS</td>
</tr>
<tr>
<td>GFR (mL/min/1.73 m²)</td>
<td>24.5 ± 13.9</td>
<td>21.5 ± 15.2</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>11.4 ± 2.4</td>
<td>11.4 ± 2.2</td>
<td>NS</td>
</tr>
<tr>
<td>BUN (mg/dL)</td>
<td>40.6 ± 19.7</td>
<td>51.2 ± 29.3</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Cr (mg/dL)</td>
<td>3.2 ± 2.0</td>
<td>4.3 ± 3.4</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>4.1 ± 0.5</td>
<td>4.1 ± 0.4</td>
<td>NS</td>
</tr>
<tr>
<td>LDL (mg/dL)</td>
<td>111.4 ± 40.6</td>
<td>99.9 ± 33.8</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Hemoglobin (%)</td>
<td>7.4 ± 2.1</td>
<td>7.0 ± 1.5</td>
<td>0.019</td>
</tr>
</tbody>
</table>

SBP, systolic blood pressure; DBP, diastolic blood pressure; GFR, glomerular filtration rate; BUN, blood urea nitrogen; Cr, creatinine; LDL, low density lipoprotein; HbA1c, glycated hemoglobin; NS, non-significant.

Table 3. Comparison of changes of clinical parameters between the rapid and non-rapid progression groups after MDCP

<table>
<thead>
<tr>
<th></th>
<th>Biennial GFR Change (mL/min/1.73 m²)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; -4 (n = 210)</td>
<td>≥ -4 (n = 133)</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>0.3 ± 16.6</td>
<td>-2.8 ± 20.9</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>0.1 ± 10.2</td>
<td>-2.0 ± 11.4</td>
</tr>
<tr>
<td>Biennial GFR decline rate (mL/min/1.73 m²)</td>
<td>0.9 ± 3.7</td>
<td>-9.0 ± 5.0</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>0.2 ± 1.6</td>
<td>-0.4 ± 1.5</td>
</tr>
<tr>
<td>BUN (mg/dL)</td>
<td>4.5 ± 15.1</td>
<td>20.0 ± 23.8</td>
</tr>
<tr>
<td>Cr (mg/dL)</td>
<td>0.3 ± 1.4</td>
<td>2.2 ± 2.5</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>0.0 ± 0.4</td>
<td>0.0 ± 0.5</td>
</tr>
<tr>
<td>LDL (mg/dL)</td>
<td>-7.6 ± 40.3</td>
<td>-17.5 ± 43.4</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>-0.2 ± 1.7</td>
<td>-0.6 ± 2.4</td>
</tr>
</tbody>
</table>

SBP, systolic blood pressure; DBP, diastolic blood pressure; GFR, glomerular filtration rate; BUN, blood urea nitrogen; Cr, creatinine; LDL, low density lipoprotein; HbA1c, glycated hemoglobin; NS, non-significant.

Changes of Parameters after MDCP

Table 2 shows the changes of biochemical markers after MDCP intervention. Blood pressure was comparable during the follow-up. Serum BUN and Cr level increased significantly and GFR declined from 24.5 ± 13.9 to 21.5 ± 15.2 mL/min/1.73 m² (P < 0.001). The mean annual change in GFR was -1.5 mL/min/1.73 m². Hemoglobin and albumin did not change with renal function deterioration. Low density lipoprotein (LDL) improved from 111.4 ± 40.6 to 99.9 ± 33.8 mg/dL (P < 0.001). For DM patients, their glycated hemoglobin (HbA1c) declined significantly from 7.4 ± 2.1 to 7.0 ± 1.5% (P < 0.05).

Comparison between the Rapid and Non-Rapid Progression Group

Two hundred and ten patients (61.2%) were categorized as being in the non-rapid progression group, whereas one hundred and thirty three patients (38.8%) were placed in the rapid progression group (Table 1). Patients in the rapid progression group had a much higher prevalence of DM (45.9% vs. 31.0%, P = 0.004), hypertension (72.9% vs. 61.9%, P = 0.023), and proteinuria (82.7% vs. 68.1%, P = 0.002). Although the baseline GFR in the two groups was not significantly different (25.5 ± 13.4 vs. 23.9 ± 14.2 mL/min/1.73 m², P = 0.291), patients in the rapid progression group had higher baseline Cr (3.5 ± 2.3 vs. 2.9 ± 1.4 mg/dL, P = 0.002). The percentage of patients at CKD stage 3 in the rapid progression group was less than in the non-rapid progression group but higher at CKD stage 5 (P < 0.001). Compared with the non-rapid progression group, patients in the rapid progression group had higher baseline SBP and DBP (both P < 0.05), lower albumin level (3.9 ± 0.5 vs. 4.2 ± 0.4 g/dL, P < 0.001), and higher baseline HbA1c (7.4 ± 2.3 vs. 6.8 ± 1.6 %, P = 0.032). 14 patients (10.5%) of the rapid progression group and 10 patients (4.8%) of the non-rapid progression group progressed to ESRD and received hemodialysis before the end of the observation (P = 0.036).

After receiving the MDCP, the mean biennial
GFR change was \(-9.0 \pm 5.0\) mL/min/1.73 m\(^2\) in the rapid progression group and \(0.9 \pm 3.7\) mL/min/1.73 m\(^2\) in the non-rapid progression group through 24 months of follow-up (\(P < 0.001\), Table 3). Changes of BUN and Cr level were significantly higher in the rapid progression group. Hemoglobin increased in the non-rapid progression group and it declined in the rapid progression group (\(0.2 \pm 1.6\) vs \(-0.4 \pm 1.5\) g/dL, \(P = 0.002\)). Changes of SBP, DBP, albumin, LDL and HbA1c were similar between the rapid and non-rapid groups.

**Independent Variables for Predicting Rapid Decline of GFR**

Table 4 displays variables associated with rapid progression of CKD in different treatment modalities by using logistic regression analysis. Biennial GFR decline of more than \(4\) mL/min/1.73 m\(^2\) was entered as a binary dependent variable. Multivariate logistic regression analysis of associations between GFR decline and baseline characteristics showed that SBP (\(\beta = 0.016, 95\%\) CI 1.003-1.030, \(P = 0.013\)) and albumin (\(\beta = -1.151, 95\%\) CI 0.172-0.581, \(P < 0.001\)) were the significant independent predictors for rapid progression of renal function.

**Progression of Renal Disease in Different Stages of CKD**

At the end of this study, patients at CKD stage 3 had significantly better renal outcome compared with patients at CKD stages 4 and 5 (both \(P < 0.001\)) (Fig. 1A). Patients with stages 4 and 5 experienced more rapid progression (stage 4: \(-3.4 \pm 6.8\); stage 5: \(-4.8 \pm 5.0\) mL/min/1.73 m\(^2\)) than those at stage 3 (\(0.1 \pm 6.9\) mL/min/1.73 m\(^2\), \(P < 0.001\)). The renal outcomes between patients at CKD stages 4 and 5 were similar (\(P = 0.245\)). Kaplan-Meier analysis disclosed that CKD stage 3 had significantly a lower combined endpoint than did stages 4 and 5 (\(P < 0.001\), Fig. 1B).

Fig. 1. The change of GFR after two years of observation (A) and the prediction of combined endpoint in patients with different stages of CKD (B).

Compared to stage 5, there was no significant difference of combined endpoint achievement in stage 4.

**Discussion**

In this retrospective study, we demonstrated that annual decline of GFR was \(1.5\) mL/min/1.73 m\(^2\) in our
CKD cohort. LDL and HbA1c improved after MDCP intervention but albumin and hemoglobin remained stable as the renal function deteriorated slowly. There was significant higher prevalence of DM, hypertension, proteinuria and lower albumin in the rapid progression group. Also, the blood pressure and HbA1c of DM patients were significantly higher at the entry. Higher SBP and lower serum albumin level were the independent predictors of rapid renal deterioration. Moreover, patients at CKD stage 3 had better renal outcomes than patients at CKD stages 4 and 5.

The average annual GFR change in our study was slightly higher than that in the aging process of the normal population (11). In CKD patients without MDCP, a more rapid reduction of GFR, ranging from -12 to -2 mL/min/1.73 m², has been reported (12-14). A previous study showed that the annual GFR change in a MDCP[VAR1] for Taiwanese patients was 0.055 mL/min/1.73 m² but the follow up period was shorter (9). Also, lower prevalence of hypertension (5.2%) and nearly 30% of subjects progressing to ESRD were found. However, our findings were supported by another cohort study which disclosed that the mean annual change in GFR was -1.2 mL/min/1.73 m² in CKD stage 3 diabetic patients who received MDCP (15).

A previous study which enrolled patients with CKD stages 3 to 5 without MDCP disclosed cardiovascular disease (CVD), those with low BMI and high SBP were more likely to develop ESRD (14). In another study, the risk of dialysis increased in CKD stage 4 patients without MDCP with older age, higher baseline proteinuria, greater early decline in renal function, low baseline GFR and low hemoglobin (16). Our study has confirmed the role of SBP in the progression of CKD even in patients with MDCP. In our study, multivariate analysis showed that SBP, not DBP, was the independent predictor of rapid GFR loss. The mechanisms include glomerular hypertension with increased protein ultrafiltration (17) and endothelial dysfunction leading to vessel damage, atherosclerosis, and arterial stiffness (18,19). SBP has been reported to cause reduced intrarenal autoregulation and failure of accommodation to change in blood pressure (20). Because the relationship of SBP and arterial stiffness is more evident than that of DBP (21), it is reasonable that SBP, rather than DBP, may predict the rapid decline of GFR. Furthermore, our results are in accordance with those of previous studies (4,22).

The rapid progression group showed a higher prevalence of diabetes with significantly higher HbA1c level. However, diabetes was not found to be significant in the multivariate analysis. Possible reasons to explain this finding are given as follows. First, mean HbA1c level was 7.1 ± 2.0% in this cohort and the medications were adjusted for intensive blood sugar control during the follow-up. Second, there was evidence showing that the renal outcome of diabetes was not consistently the same in patients with and without proteinuria (23). Third, our study had a small scale patient number. Forth, the enrolled DM patients had different stages of CKD at the time of entry.

Proteinuria has been demonstrated to be deleterious for renal function in many previous studies. However, in our MDCP CKD patients, residual proteinuria after RAAS blockers treatment was not an independent predictor in our multivariate analysis. In a recent study, proteinuria strongly predicted ESRD at stages 3 and 4 but not at stage 5 (24). The diminished role of proteinuria when renal function progresses might rather indicate that mechanisms triggered by renal function loss per se, like uremic toxins accumulation (25), may be related to advanced stages of renal disease. In our study, there was no difference in the use of RAAS blockers between the two groups. However, 54.9% of patients in the rapid progression group were at CKD stage 5. In addition to that, dietary education provided by the MDCP to reduce proteinuria may also have contributed to the abrogated role of proteinuria and serum albumin which turned out to be another predictor of rapid GFR decline. Serum albumin level is also an indicator of inflammatory and general nutritional status and hypoaalbuminemia may indicate the existence of malnutrition syndrome, inflammation, and atherosclerosis complex in advanced CKD patients (26). Taken together, after RAAS inhibition and low protein dietary education to reduce proteinuria, the status of inflammation and nutrition may play an important role in affecting the prognosis of kidney disease rather than urinary protein excretion solely. Further studies are needed to confirm this view point.

Patients at CKD stage 3 had better renal outcomes than those at CKD stages 4 or 5 in this cohort. Chiu et al. (14) mentioned that the annual GFR decline was significantly greater for patients in stage 4 or 5 compared to those in stage 3. Their findings were similar to our observation. We further divided our CKD stage 3 patients into stage 3a and 3b with the cutoff value of 45 mL/min/1.73 m². Among the 110 patients, 30 patients were in CKD stage 3b. There was significant difference of GFR change when comparing the two groups after 2 years (stage 3a vs. 3b: 1.6 ± 5.6 vs. -3.8 ± 8.6 mL/min/1.73 m², P < 0.001). A possible “point of no return” in CKD has been proposed due to the unique structural features of the kidney, such as the inability of podocyte regeneration and transdifferentiation of epithelium to myofibroblast. This assumes a stage of progressive structural and functional damage independent of dietary measures and pharmacological treatment (27, 28). Although it is still uncertain about the definite threshold for the reversibility of kidney injury, the
benefit of MDCP in retarding GFR loss seems to be more prominent in earlier CKD according to our data. This is probably because of the severity of intrarenal fibrosis, inflammation, underlying disorder and uremic specific mechanism.

MDCP may promote kidney health through many facets. However, the renal function of some CKD patients still became progressive. As in the rapid progression group in this study, SBP, DBP, LDL and HbA1c showed improvement after MDCP but renal function deterioration could not be halted completely. The clinical implications here indicate that what we have provided CKD care involving intervention/treatment with currently known modifiable factors. Nonetheless, there is still space for further improvement, despite the success of CKD care in Taiwan under the government-initiated program.

In conclusion, the average annual change of renal function was slightly higher than the aging process in this cohort. Baseline SBP and serum albumin level were significant independent predictors of rapid progression. The effectiveness of MDCP in improving renal function or alleviating GFR loss was more prominent in CKD stage 3. Our study identified a subset of a high-risk population who might benefit from even more aggressive management.

References