


# Medication Adherence, Complementary Medicine Usage and Progression of Diabetic Chronic Kidney Disease in Thais

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**Purpose:** Non-adherence to medication is receiving more attention as a significant problem common to management of chronic diseases including diabetes and chronic kidney disease (CKD). This study was designed to assess the medication adherence and self-medication in a cohort of Thai patients with diabetic kidney disease, and its association with clinical outcomes.

**Patients and Methods:** Non-dialysis patients with diabetic CKD visiting outpatient's clinics of Siriraj Hospital, the largest tertiary care in Thailand, were asked for participation. Self-administered questionnaire was given to assess medication adherence (the 6-item-medication-taking-behavior measure in Thai), complementary medicine usage, and personal information. Clinical, pharmaceutical, and relevant laboratory data (at current and the last visit of around 12 months) were abstracted from the medical records.

**Results:** Of the 220 participants eligible (54.1% male, mean age 71.3), 50.9%, 24.1%, and 25% were classified as high-, medium-, and low-medication adherence, respectively. Overall, 24.1% reported self-usage of at least one type of herbal or complementary medicines. The most commonly identified items were cordyceps, cod liver oil, Nan Fui Chao, and turmeric (6 each), with unidentified Thai herbal mixture in 11. On multivariate analysis, late-stage CKD (stage IV–V) was the only independent predictor for low adherence (odds ratio (OR), 5.54; 95% confidence interval (CI), 2.82–10.88). Low adherence was associated with higher blood pressure, lower estimated glomerular filtrate rate (eGFR), and more eGFR decline with greater risk of being rapid CKD progressor (annual eGFR drop >5 mL/min/1.73 m<sup>2</sup>) [OR, 1.15; 95% CI, 1.06–1.25].

**Conclusion:** Medication taking behavior was a frequently encountered problem in Thai diabetic CKD patients. Increased medication non-adherence was independently predicted by stages of increasing CKD severity, and it was associated with poorer hypertensive control and kidney outcome. Targeting interventions to improve medication adherence should be an important strategy to slow CKD progression among patients with diabetic CKD.

**Keywords:** clinical outcome, complementary medicine, diabetic nephropathy, drug, eGFR, hypertension

## Introduction

Diabetic kidney disease (DKD) is one of the most frequent and serious complications in diabetic patients and is the leading cause of chronic kidney disease (CKD) worldwide.<sup>1</sup> It is usually accompanied by hypertension, albuminuria, and progressive decline in renal function, with excess morbidity and mortality due to macro- and microvascular complications. Effective management of DKD thus entails a comprehensive approach not only to slow kidney disease progression but also to minimize the risk of atherosclerosis and cardiovascular events including dietary control, lifestyle modification, and a wide array of medications for metabolic and hypertensive control.<sup>2</sup>

Based on the chronic and complex nature of the disease, patients with DKD are at risk to develop medication non-adherence and self-usage of complementary or alternative medicines (CAM).<sup>3</sup> The World Health Organization defines medication adherence as the degree to which a person's behavior, including taking medications, corresponds with the

agreed recommendations from a health-care provider. It has been shown that low adherence to prescribed anti-diabetes medicines is more common in developing countries and responsible for 30% to 50% of treatment failure to achieve adequate glycemic control.<sup>4</sup> In addition, many studies have reported that usage of CAM is common in these patients, while its efficacy and safety data remain in question.<sup>5</sup> Medication adherence is similarly important in CKD patients, given its potential impact on disease progression, its complications and quality of life.<sup>6,7</sup>

The number of patients with diabetes in Thailand was reported as 4.4 million in 2018, with the estimated prevalence of CKD of around 30%.<sup>8</sup> Similar to other countries worldwide, DKD is currently the most common cause of advanced CKD requiring renal replacement therapy (RRT) and its economic burden is a significant contributor to overall healthcare spending in Thailand.<sup>9</sup> Currently, the cost of treatment (including RRT) is covered by three national health-care schemes, which are the Civil Servant/State Enterprise Medical Benefit Scheme (CSMBS) for civil officers and dependents, the Social Security Scheme (SSS) for private employees, and the Universal Health Coverage Scheme (UCS) for the remaining citizens, respectively. Quantification of the problem with medication-taking behavior in the patients, and also identification of those who are at risk should be concerned as one important factor that may improve therapeutic effectiveness. We hypothesized that low medication adherence and CAM usage would also be common in Thai patients, and this might be associated with worse clinical outcome. To address this issue, we conducted a self-reported survey to identify the prevalence of medication non-adherence and self-usage of herbal or complementary medicines in Thais with pre-dialysis diabetic CKD, predictive factors, and their effects on the kidney disease progression.

## Materials and Methods

This cross-sectional questionnaire-based study was conducted at the outpatient clinics of Siriraj Hospital, the largest university-based tertiary care center in Thailand, from May 2018 to April 2021. The study was carried out in accordance with the guidelines of the Declaration of Helsinki, and approved by the Siriraj Institutional Review Board, Faculty of Medicine Siriraj Hospital, Mahidol University prior to the study (Si349/2018).

Patients were individually invited to participate in the study if they were more than 18 years old, had been diagnosed at our hospital with DM type 2 and CKD for more than one year without dialysis treatment. Patients will be excluded if they had any other significantly debilitating diseases, apparent cognitive or psychiatric problems, or were unable to communicate in Thai. A written informed consent was obtained from all participants who agreed to complete the study questionnaire and permitted for review of their electronic medical records. Relevant clinical data including the blood pressure, prescribed medicines and important laboratory results documented on the study date and the latest visit date in the period of approximately one year earlier were abstracted and recorded for further analysis.

The questionnaire used in the study consisted of three parts mainly to evaluate the prescribed medication adherence and the practice of self-medication. The first part obtained the demographic data of the participants, including age, gender, education level, monthly income, health-care scheme, disease duration, and home medicine management. The second was the Medication Taking Behavior in Thai (MTB-Thai) questionnaire of which has been developed and validated to use in Thai patients since 2016, with permission obtained from the original researcher.<sup>10</sup> The MTB-Thai questionnaire consists of 6 items relevant to medication adherence in the past 2 weeks with the response choices in a 4-point Likert scale. The total score for the MTB-Thai ranges from 0 to 24, and medication adherence is graded as high (24 score), medium (22–23 score) and low (<22 score) based on its original validation. The third part evaluated self-usage of herbal or complementary medicines using questions modified from a part of the international complementary and alternative medicine questionnaire (ICAM-Q).<sup>11</sup> In brief, the participants will be asked to list the non-prescribed products including the over-the-counter analgesics, herbs/herbal medicine, vitamins/minerals or other supplements that were taken in the past 12 months; the source of product information, and the reasons for self-administration.

## Statistical Analysis

The sample size was calculated using an estimating proportion of one group based on the report prevalence of 45.8% for medication misbehavior in Thai diabetic patients.<sup>12</sup> This would require the sample size to be around 200 to achieve the margin of error of 15% and a 95% confidence interval (CI).

Descriptive data for continuous variables were presented as median with interquartile range (IQR) or mean with standard deviation (SD) based on Shapiro–Wilk test for normality, and frequency distribution with percentage for categorical variables. Comparing the parameters from two-time points and difference between groups of defined medication adherence status was determined using chi-square test of categorical data, and *t*-test or non-parametric equivalent for continuous data with non-normal distribution, and a *P* value of less than 0.05 was considered statistically significant. To investigate determinants for medication adherence, we used a multivariate linear regression analysis as independent variables of aforementioned socio-demographic data (age, gender, education level, monthly income level, medical welfare scheme), vision problems, type of home medicine management, number of prescribed medicine, history of CAM usage, the level of glycemic or hypertensive control, and CKD staging were stratified. In addition, multinomial logistic regression was used to identify medication adherence and patient factors (age, sex, health-care scheme, the level of glycemic and hypertensive control, CAM usage) with the risk of being rapid CKD progressor (annual rate of eGFR decline greater than 5 mL/min/1.73 m<sup>2</sup>) as previously defined by the KIDGO consensus conference.<sup>13</sup>

## Results

**Table 1** details the demographic and baseline characteristics of survey participants. The final sample with adequate questionnaire responses for purpose of analysis comprised 220 pre-dialysis diabetic CKD participants, out of which 54.1% were male with the mean age of 71.3 years (older than 65 in 72.3%). In terms of educational background, 2.7% had received no formal education and nearly half of participants educated at the primary level or lower (47.4%). A substantial proportion were classified as having a low to middle income of less than 10,000 to 10,000–30,000 Thai baht per month (30.6% and 46.6% respectively). The medical service/drug expense was covered by the CSMBS in approximately half of the participants (54.5%), followed by the UCS (20.9%).

The median duration of known diabetes and CKD were 14 and 4.5 years with the mean number of 7.6 different prescribed medicines. Most patients received co-medication of both oral anti-diabetics and anti-hypertensive (95.4%) while lipid lowering medicines were prescribed in 84.8%. Sulfonylurea and metformin were two most commonly used anti-diabetic medicines (58.8% and 48.9%), while 57.2% received combination of medications including insulin. As for the anti-hypertensive agents, renin-angiotensin-aldosterone system inhibitors with angiotensin-converting enzyme inhibitors or angiotensin receptor blocker were most frequently prescribed (55.7%). The majority of patients reported self-administration of the prescribed medicine at home (80.3%).

**Table 2** shows comparison of clinical and laboratory results between the study visit and those in the previous visit of around one year earlier (10.2 ± 2.9 months). Overall, most patients were classified in CKD stage III (eGFR 30–59 mL/min/1.73 m<sup>2</sup>, 71.9% vs 73.1%) followed by stage IV (eGFR 15–29 mL/min/1.73 m<sup>2</sup>, 18.6% vs 15.0%) and stage II (eGFR 60–89 mL/min/1.73 m<sup>2</sup>, 4.5% vs 8.2%). There were no significant differences in the systolic blood pressure and the biochemical-metabolic parameters including blood sugar, HbA1C and cholesterol levels. However, compared to the previous year, the serum creatinine was significantly higher 1.5 (1.3, 2.0) vs 1.4 (1.2, 1.9) mg/dL and eGFR was lower 40.2 ± 14.4 vs 42.4 ± 14.2 mL/min/1.73 m<sup>2</sup> (*p* < 0.0001). The median average eGFR decline of patients in this study was 1.9 mL/min/1.73 m<sup>2</sup> per year.

Medication adherence level as measured by the sum score from MTB-Thai questionnaire and classified as having high, medium and low adherence was observed in 50.9%, 24.1% and 25.0% of survey participants, respectively. Considering the frequency of responses to the MTB-Thai-6 items, “not taking medicines as times prescribed”, “forget to take medicines” and “adjust dosage regimens” were three most commonly reported non-adherence practices (**Table 3**).

Self-medication with over-the-counter analgesics including non-steroidal anti-inflammatory drugs was reported in 4.8% (**Table 4**). However, usage of herb/herbal or complementary medicines in the past 12 months was more frequent in the participants (24.1%), mostly aimed to promote general health or to treat symptomatic conditions (**Table 4**). Commonly used products included unidentified Thai herbal mixture (11), Cordyceps (6), Cod liver oil (6), Nan Fui Chao leaf (6), Turmeric (6), Ginkgo (4), Ginseng (4), Ling Zhi mushroom (4), Bitter gourd extract (3), non-specified Chinese herb (3), Red seaweed (2), and River spiderwort leaf (2). Responses from the participant revealed that information about possible product benefit was primarily derived from personal source including friends or other patients

**Table 1** Socio-Demographic and Baseline Characteristics of Survey Participants

Characteristics	n	%
Age – year (mean ± SD)	71.30 ± 9.8	
45–65	61	27.7
>65	159	72.3
Gender		
Male	119	54.1
Female	101	45.9
Education		
Primary and lower	102	47.4
Secondary	46	21.4
Bachelor and Higher	61	28.4
No formal education	6	2.8
Monthly Income		
<10,000 baht	67	30.6
10,000–30,000 baht	102	46.6
30,000–70,000 baht	36	16.4
>70,000 baht	14	6.4
Medical Welfare		
Civil Servant/State Enterprise Benefit Scheme	114	51.8
Universal Health Coverage Scheme	65	29.5
Social Security Scheme	28	12.7
Voluntary Payment	13	5.9
Duration of diabetes – year (median, IQR)	14 (10, 20)	
Duration of CKD – year (median, IQR)	5 (2, 7)	
Number of prescribed medicines (mean ± SD)	7.63 ± 2.73	
<5	45	20.5
≥5	175	79.5
Anti-diabetic (%): Metformin: SU: Glitazone: others*	48.9: 58.8: 22.9: 48.9	
Lipid lowering (%): Statins: Fibrate: others	79.4: 4.6: 8.4	
Anti-hypertensive (%): ACEI or ARB: CCB: Diuretics: others	52.7: 55.7: 20.6: 46.6	
Management of home medication		
Self	175	80.3
Caregivers	43	19.7

**Note:** \*Including Insulin.

**Abbreviations:** ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; IQR, interquartile range; SD, standard deviation; SU, sulfonylurea.

(19) and relatives (17); media source including television (11), radio (4) and social networks (2); self-perception (8); and providers in the drug store (2). No signs of toxicity or adverse events were observed at the visit.

In order to identify factors determining medication adherence, analysis of its association with the socio-demographic and selected clinical variables was conducted and shown in Table 5. As compared to the high- and medium-adherence group, individuals with low adherence were significantly more likely to be younger (<65), with lower educational status, vision problems, poorly controlled hypertension and lower eGFR value at the study visit by univariate analysis (Chi-

**Table 2** Comparison of the Clinical and Laboratory Results at the Study Visit and Earlier Period of Approximately One Year (Median, IQR)

Parameters	Current	Previous	P value
Systolic blood pressure – mm Hg	137.5 (128.0, 149.8)	141.0 (130.0, 151.0)	0.0538
Fasting blood glucose – mg/dL	129.0 (109.8, 159.0)	132.0 (114.8, 159.3)	0.2718
HbA1C – %	6.8 (6.4, 7.8)	7.0 (6.4, 7.8)	0.6119
Serum cholesterol – mg/dL	157.0 (137.0, 191.0)	162.0 (140.0, 199.0)	0.1121
Serum creatinine – mg/dL	1.5 (1.3, 2.0)	1.4 (1.2, 1.9)	<0.0001
Estimated GFR – mL/min/1.73 m <sup>2</sup>	39.7 (30.1, 49.7)	43.3 (34.1, 51.5)	<0.0001
Chronic kidney disease stage; n (%)			
II	10 (4.5%)	18 (8.2%)	0.1332
IIIa	70 (31.8%)	83 (37.7%)	
IIIb	86 (39.1%)	80 (36.4%)	
IV	41 (18.6%)	33 (15.0%)	
V	13 (5.9%)	6 (2.7%)	

**Table 3** Medication Adherence Analysis from the 6-Item MTB-Thai Questionnaire as Reported by Survey Participants

Items**	Response (N, %)*			
	1	2	3	4
1. Forget to take medicines	4 (1.8)	3 (1.4)	45 (20.5)	168 (76.4)
2. Not taking medicines as times prescribed	18 (8.2)	14 (6.4)	50 (22.7)	138 (62.7)
3. Stop taking medicines with because of adverse drug reactions	8 (3.6)	1 (0.5)	13 (5.9)	198 (90.0)
4. Stop taking medicines because of getting better	7 (3.2)	–	5 (2.3)	208 (94.5)
5. Stop taking medicines for other reasons	–	–	4 (1.8)	216 (98.2)
6. Adjust dosage regimens	13 (5.9)	2 (0.9)	8 (3.6)	197 (89.5)

**Notes:** \*1 = 5–6 times; 2 = 3–4 times; 3 = 1–2 times; and 4 = never within the past 2 weeks. \*\*Questionnaire items reprinted with permission from Springer Nature: Sakthong P, Sonsa-Ardjit N, Sukarnjanaset P, Munpan W, Suksanga P. Development and psychometric testing of the medication taking behavior in Thai patients (MTB-Thai). *Int J Clin Pharm*. 2016;38(2):438–445. DOI:10.1007/s11096-016-0275-8.<sup>10</sup> © Springer International Publishing 2016.

**Table 4** Self-Medication in the Past 3 Months as Reported by Survey Participants

Items	N/Total	%
NSAIDs or other analgesics	10/207	4.8
Herbs/herbal or complementary medicines usage*	53/220	24.1
Aim:		
• To promote general health	37	63.7
• To treat symptomatic conditions	15	25.9
• To treat or prevent complications of underlying conditions	3	5.2
• Other reasons	3	5.2

**Notes:** \*Cordyceps (6), Cod liver oil (6), Nan Fui Chao leaf (6), Turmeric (6), Ginkgo (4), Ginseng (4), Ling Zhi mushroom (4), Bitter gourd extract (3), Chinese herb, non-specified (3), Red seaweed (2), River spiderwort leaf (2), Cinnamon cap (1), Clove tree (1), Coconut oil (1), Gluta (1), Karanda (1), Kariyat (1), Moringa seed (1), Ventilago denticulata (1), Unidentified Thai herbal mixture (11).

**Table 5** Association of Medication Adherence Level with Socio-Demographic and Relevant Clinical Parameters

Parameters	Medication Adherence Level			Chi Square	p value
	High (%)	Middle (%)	Low (%)		
Age (year)					
45–65	23 (39.0%)	22 (37.3%)	14 (23.7%)	8.13	0.0171
>65	89 (55.3%)	31 (19.3%)	41 (25.5%)		
Gender					
Male	62 (52.1%)	30 (25.2%)	27 (22.7%)	0.76	0.6836
Female	50 (49.5%)	23 (22.8%)	28 (27.7%)		
Educational level					
No formal, Primary and lower	50 (46.3%)	21 (19.4%)	37 (34.3%)	9.49	0.0500
Secondary	25 (54.3%)	14 (30.4%)	7 (15.2%)		
Bachelor and Higher	36 (59.0%)	14 (23.0%)	11 (18.0%)		
Monthly income (baht)					
<10,000	32 (47.8%)	17 (25.4%)	18 (26.9%)	9.26	0.1594
10,000–30,000	46 (45.1%)	27 (26.5%)	29 (28.4%)		
30,000–70,000	26 (72.2%)	4 (11.1%)	6 (16.7%)		
>70,000	8 (57.1%)	4 (28.6%)	2 (14.3%)		
Medical welfare					
Civil Servant/State Enterprise	63 (55.3%)	24 (21.1%)	27 (23.7%)	2.97	0.8131
Universal Health Coverage	28 (43.1%)	18 (27.7%)	19 (29.2%)		
Social Security	14 (50.0%)	8 (28.6%)	6 (21.4%)		
Voluntary Payment	7 (53.8%)	3 (23.1%)	3 (23.1%)		
Vision problems					
Yes	24 (32.9%)	29 (39.7%)	20 (27.4%)	17.00	0.0002
No	84 (58.7%)	24 (16.8%)	35 (24.5%)		
Controlled DM (HbA1C level <7%)					
Yes	63 (51.6%)	30 (24.6%)	29 (23.8%)	0.12	0.9416
No	47 (50.5%)	22 (23.7%)	24 (25.8%)		
Controlled HT (systolic BP <130 mmHg)					
Yes	36 (50.7%)	24 (33.8%)	11 (15.5%)	7.90	0.0193
No	76 (51.0%)	29 (19.5%)	44 (29.5%)		
CKD stage (current)					
IV–V	16 (29.6%)	10 (18.5%)	28 (51.9%)	37.73	< 0.0001*
III	86 (55.1%)	43 (27.6%)	27 (17.3%)		
II	10 (100%)	–	–		

(Continued)

**Table 5** (Continued).

Parameters	Medication Adherence Level			Chi Square	p value
	High (%)	Middle (%)	Low (%)		
Home medicine management					
Self	85 (48.6%)	44 (25.1%)	46 (26.3%)	1.97	0.3734
Non-self	26 (60.5%)	8 (18.6%)	9 (20.9%)		
Number of prescribed medicine					
<5	25 (55.6%)	11 (24.4%)	9 (20.0%)	0.81	0.6675
≥5	87 (49.7%)	42 (24.0%)	46 (26.3%)		
History of analgesics, herb or alternative medicine use					
No	84 (52.2%)	37 (23%)	40 (24.8%)	0.50	0.7783
Yes	28 (47.5%)	16 (27.1%)	15 (25.4%)		

**Note:** \*Significance with multivariate logistic regression analysis ( $p < 0.001$ ).

square test,  $p < 0.05$ ). Lower adherence was more frequently observed in diabetic CKD patients stage IV–V (51.9%) compared to stage III (17.3%) and stage II (none reported). On cross-sectional multivariate linear regression analysis, only CKD stage IV–V was found to be associated with low medication adherence (adjusted odds ratio 5.54, 95% CI 2.82 to 10.88,  $p < 0.001$ ).

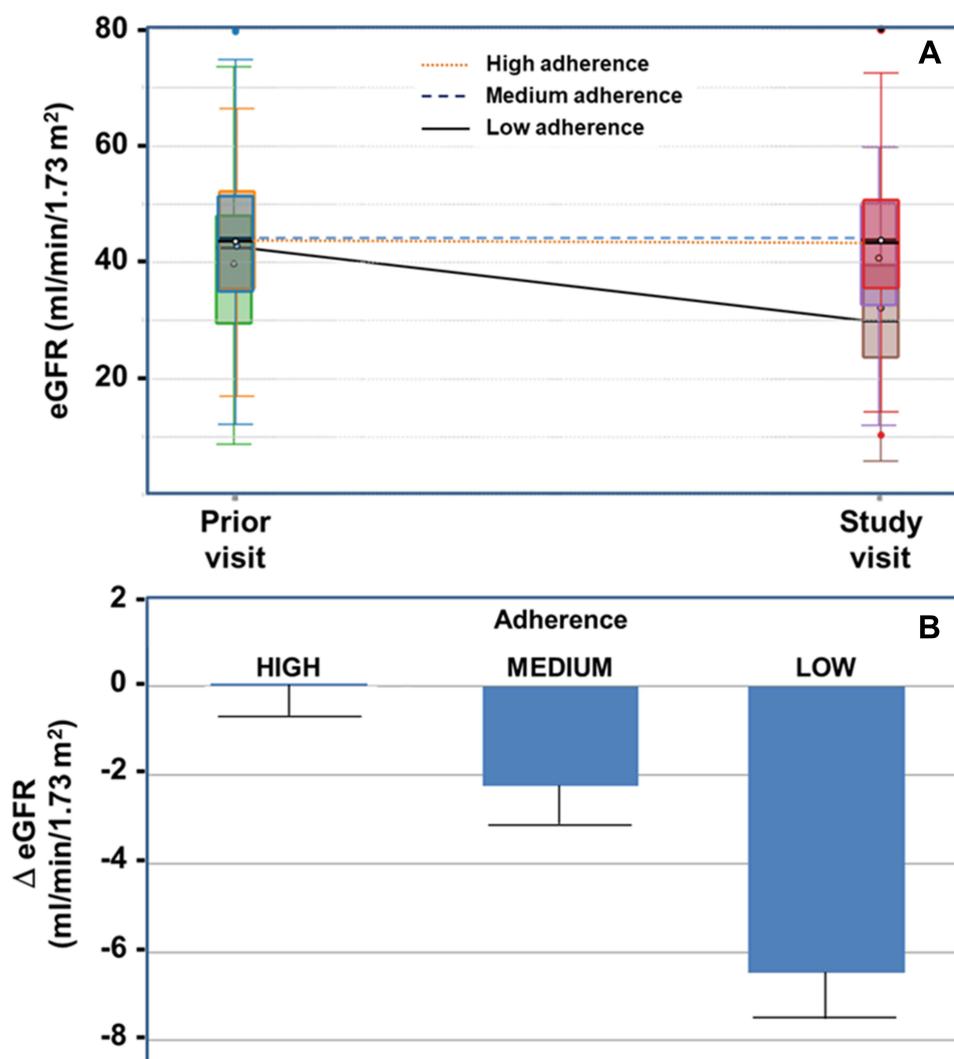
Considering the effect of medication adherence level on the clinical outcomes in particular of metabolic control and kidney function, we observed no differences in the FBS, HbA1C and cholesterol levels among group. However, patients with low medication adherence had higher systolic blood pressure (147 (134–164) vs 133 (122–143) and 137 (130–147) mmHg;  $p = 0.0004$ ) and lower eGFR (29.9 (23.6, 39.6) vs 43.9 (32.2, 51.2) and 43.4 (35.5, 50.8) mL/min/1.73 m<sup>2</sup>;  $p = 0.00001$ ) at the study visit. **Figure 1** shows that calculated annual eGFR change was significantly higher in the low medication adherence group (−6.48 vs −2.27 and 0.5 mL/min/1.73 m<sup>2</sup>;  $p = 0.00001$ ). In addition, the multinomial logistic regression analysis revealed that the only variable that represented a risk of being rapid CKD progressor was medication adherence, but not the age, gender, the level of glycemic or hypertensive control, or usage of herb/herbal or complementary medicines ( $p = 0.0002$ ). Calculation for the risk of rapid CKD progressor over 12 months by dividing the number of rapid CKD progressor by the total number of patients stratified by the medication adherence level showed a statistically significant odds ratio of 1.15 (95% CI 1.06 to 1.25) in patients with low medication adherence.

## Discussion

The behavior of patients for not adhering to medication and self-using of complementary or alternative medicines is a growing concern in many countries around the world. While the problem has been investigated in several chronic non-communicable diseases, not much is known about the prevalence of low medication adherence and its impact on the outcome specifically in diabetic patients with CKD. In this study, data obtained from self-reported survey revealed that 24.1% and 25.0% of Thai patients with diabetic CKD were medium- and low-adherent to prescribed medicine, and 24.1% used herb/herbal or complementary medicines. Our findings are in the same range as those of previous reports and reviews in diabetic patients from low to middle income and Middle East countries.<sup>14–17</sup> Moreover, our data showed that the adherence level was lowest in diabetic patients with stage IV–V of CKD with a significant odds ratio of 5.54, and low adherence was associated with an increased risk of being rapid CKD progressor. The study confirms that medication adherence is common and may result in poorer outcome in diabetic patients with CKD.

It is generally accepted that medication adherence in patients with chronic disease may be affected by various factors.<sup>4</sup> Recent systematic review and meta-analysis studies revealed that 67.4% of pre-dialysis CKD patients had the





**Figure 1** Box plot (median, lower and upper quartiles, and range) showing changes in estimated glomerular filtration rate (eGFR) from the study visit and prior visit of around one-year in participants with low-, medium- and high-medication adherence (A) and calculated difference (median + SEM) in annual eGFR decline rate among these patient group (B).

problems of medication adherence, and a total of 19 factors have been identified including socio-demographic, patient-related, therapy related, disease related and health care service related components.<sup>18,19</sup> Insights into the factors that may influence medication adherence are important for identification of patients at risk and also the adherence barriers that should be overcome. We found in this study that the factors of age, educational status, vision problems, poorly controlled hypertension and late CKD stage were statistically correlated by univariate analysis. The effect of age on medication adherence was similarly observed in another study in Thai CKD patients, but not other factors.<sup>17</sup> It is not surprising to us that medication adherence is higher in the elderly  $\geq 65$  years. The reason for this tendency has been explained by the health belief model in that older patients generally perceive greater severity of the illness and increase awareness in self-care.<sup>20,21</sup> Additionally, the patients who participated in this study do not have significant cognitive or functional impairment, including anxiety or depression problems, that may limit their understanding, implementation and adherence to therapy.<sup>19,21</sup> Low educational status is most likely related to insufficient health literacy (for example, specific purpose of each medicine, disease knowledge and management plan) which is known to be positively correlated with medication adherence.<sup>15,18</sup>

We found in this study that severity of CKD stage in the diabetic patient was the significant predictor for low adherence by multivariate analysis, the data which is similar to that published in a recent systematic review in pre-



dialysis CKD patients.<sup>19</sup> Earlier studies have reported 12–53% of patients with CKD stage III–IV and 21–74% with advanced kidney disease to be non-adherent.<sup>18,21</sup> A similar proportion was observed in our study when comparing among CKD stages. The low adherent percentage increased from null in stage 2 to 17.3% and 51.9% in CKD stage III and IV–V respectively. Another study also revealed that adherence to antihypertensive agents worsens with declining renal function, and poor adherence is associated with a greater risk of uncontrolled hypertension.<sup>22</sup> The major factors contributing to non-adherence in later CKD stage might include higher pill burden (and also costs), personal concern for drug interaction, and suspected efficacy of some prescribed medicines.<sup>23,24</sup> It is likely that these problems will be more apparent as the illness becomes longer and more severe. Further studies are needed to clarify to what extent these components influence medication taking behavior in diabetic CKD patients.

There remains a limited and inconclusive data concerning the effect of medication adherence on the clinical outcomes in DKD. Prior studies from United States and our country showed that stage III–IV CKD patients with poor adherence were associated with increased risk of CKD progression,<sup>5,17</sup> while result from the African American Study of Kidney Disease and Hypertension did not verify this correlation.<sup>25</sup> It is interesting to note that the causes of CKD in these studies were diverse and not detailed. Our results indeed support the findings of an increased risk for diabetic patients with low medication adherence to have rapid CKD progression. The subtle but statistically significant risk should be primarily explained by uncontrolled hypertension since the parameters other than the systolic blood pressure (including the level of glycemic and lipid controls) were not different among group. Noteworthy, the concept of “healthy adherer” effect should also be considered since medication adherence may be just a surrogate marker for the personality or behavior relevant to motivation for healthy lifestyle and overall well-being.<sup>5</sup>

Finally, regarding self-usage of herbal or complementary products in nearly one-fourth of the patients, we observe no association with socio-demographic or clinical variables and no significant effects on the measured clinical outcomes. Slightly lower prevalence in our study compared to finding from previous Thai reports may be explained by the characteristics of our patients who mostly lived in the urban area.<sup>17,26</sup> Interestingly, our participants gained knowledge of potential product benefit from various sources, and it is likely that they will not disclose if the issue was not raised at the visit. It is known that such products may be harmful if its toxicity has not been properly investigated (particularly in CKD patients) or preparations may be contaminated with other toxic non-herbal compounds.<sup>27</sup> Moreover, interaction between a concurrently used medicine and these products may occur and result in adverse events or negative clinical outcomes.<sup>28</sup> It is thus important that health-care providers should recognize self-usage of herb, complementary or alternative medicine in their patients, so as to avoid any potential adverse effects or toxicity that may occur.

There are some limitations in our study. First, we used self-report questionnaire as a tool for measuring medication adherence which is known to be associated with over-estimation of adherence. Further study using a mixed-method approach that combines feasible subjective questionnaires and objective measurement of adherence will be valuable. Second, in our study, we selected patient-related and disease-related factors previously described to be associated with medication adherence by gathering data from the questionnaire and the electronic health record. Other predictors, such as psychological factors, factors of intention (motivation), medication knowledge, health care provider related factors, and other non-therapeutic factors were not accounted for. However, it is likely that these factors would not have had a major influence in this particular patient group and might not be much varied among our participants who were all treated in a single center. Third, we cannot clearly establish the temporal sequence of the estimated associations between low adherence and CKD outcome as these were measured at the same time. However, the clinical baseline of approximately one-year earlier was similar among group and adherence level was associated with a significant change in the last eGFR measurement at the study visit. It is thus suggested that diabetic CKD patients with low medication adherence are at risk for worse kidney outcome. Finally, similar to other observational studies, the possibility of residual confounding and bias cannot be ruled out.<sup>29</sup>

## Conclusion

To our knowledge, this study is the first to identify medication adherence and its association with clinical outcome, specifically in patients with pre-dialysis diabetic CKD. We show that a significant proportion of patients self-reported suboptimal adherence to their medications, and usage of herbal and/or complementary medicines. Late CKD stage is the

factor significantly associated with low adherence and it further heightened the risk for disease progression. Though we need more information to contextualize the adherence issue in diabetic CKD patients, our study underscores the urgent need for effective interventions to improve adherence and thus to improve clinical outcome in these high-risk group patients.

## Data Sharing Statement

The raw data of our study are in Thai and can only be made available upon request with modifications that will provide data security to the participants of our study.

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## Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

## Disclosure

The authors report no conflicts of interest for this work and declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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