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Association Between Serum Uric Acid and Depression in Patients with Chronic Kidney Disease not Requiring Kidney Dialysis: Cross-Sectional and Longitudinal Analyses

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Background: Depression is the main problem of psycho-nephrology. We aimed to investigate clinical risk factors for depression in patients with non-dialysis chronic kidney disease (CKD).

Material/Methods: A non-dialysis CKD cohort study was conducted with 223 patients. Information on demographic and clinical parameters was collected at baseline. Beck Depression Inventory (BDI) and Pittsburgh Sleep Quality Index (PSQI) questionnaires were used to estimate depression and sleep quality in the patients. The questionnaires were repeated in 158 patients after 6 months. Logistic regression was performed to identify independent factors associated with depression and any longitudinal changes in BDI scores.

Results: At baseline, 17 patients (7.72%) in the CKD cohort presented with depression. Multivariate logistic regression revealed that being female (odds ratio [OR] 0.319, 95% confidence interval [CI] 0.108 to 0.944, *P*=0.039) and having lower levels of serum uric acid (SUA) (OR 0.675, 95% CI 0.469 to 0.970, *P*=0.034) were independent risk factors for depression. A decrease in PSQI score (OR 0.873, 95% CI 0.777 to 0.981, *P*=0.022) and an increase in SUA level (OR 1.383, 95% CI 1.115 to 1.715, *P*=0.003) were independently associated with decline in BDI scores in the patients in the 6-month follow-up group.

Conclusions: Lower SUA levels and being female were independent risk factors for depression in non-dialysis CKD patients. Improving sleep quality and increasing SUA levels may relieve depression to some extent.

MeSH Keywords: Depressive Disorder • Quality of Life • Renal Insufficiency, Chronic • Uric Acid

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Background

Depression is a common comorbidity among patients with chronic kidney disease (CKD) patients and it is one of the main research components of psychonephrology [1]. The prevalence of depression is significantly higher in patients with CKD regardless of disease stage compared with that in the general population [2,3]. In patients with pre-dialysis CKD, the estimated prevalence was 21% to 27%, whereas in patients with stage 5d CKD, the prevalence was higher at 39.3% (95% confidence interval [CI] 36.8 to 42.0). In transplant recipients, the rate was 26.6% (95 CI 20.9 to 33.1).[4] In the CKD cohort, depression was associated with increased mortality, faster decline in estimated glomerular filtration rate (eGFR), frequent hospitalization, and impaired quality of life (QoL) [5–7].

Because it is difficult to treat psychological disorders and improve QoL with medical therapy alone, urgent attention should be given to identifying risk factors for depression, particularly in patients with CKD. Early identification of patients with CKD who are at high risk for depression will allow for integrated patient management comprising intense supportive psychological care, targeted interventions for risk factors, and appropriate medical treatment and can prevent and ameliorate psychological comorbidity. Previous studies have shown that economic and social factors are associated with depression and health-related QoL in patients with CKD [8]. Other studies have found that nutrition and inflammation also impact psychological disorders in patients with CKD and other patient populations [9–13].

As a secondary analysis of our previous study, which explored the effects of depression on sleep disturbances in patients with CKD [14], the aims of the present report were to evaluate the prevalence of depression in our non-dialysis CKD patients and to investigate associated clinical risk factors.

Material and and Methods

Study population

This cohort study was conducted in patients with CKD who were followed at outpatient clinics in the Nephrology Department from November 2017 to December 2018. Patients with stages 1 to 5 non-dialysis CKD were eligible. The exclusion criteria were: (1) age younger than 18 or older than 80 years; (2) current use of hypnotics or sedatives; (3) unwillingness to participate; and (4) inability to fill out the questionnaire.

Clinical data collection

The participants were followed for 6 months from the beginning of the study. Demographic and biochemical data and information medications were recorded as mentioned in our previous study [14].

Measurement of depression, sleep quality, and quality of life

Enrolled patients were required to answer 3 questionnaires. A specially trained nurse explained the questionnaires to all the patients before the questionnaires were filled out. We used the Beck Depression Inventory (BDI) questionnaire [15] to estimate depression. Depression was defined as BDI score ≥14. Sleep quality was assessed with the Pittsburgh Sleep Quality Index (PSQI) questionnaire. In addition, QoL was evaluated with the validated Chinese population version of the Short Form-36 (SF-36) questionnaire [16,17], which comprises 8 components and 2 component summary scores of physical health (PH) and MH domains. A higher total score indicates better QoL. BDI and PSQI scores were estimated at baseline and measured again at the 6-month follow-up.

Statistical analysis

Normally distributed continuous variables were presented as mean±standard deviation (SD), not-normally distributed continuous variables (BDI score, Charlson comorbidity score, UB score of spot urine and 24-hour urine protein) as medians and interquartile ranges, and categorical variables as frequencies and percentages. A comparison of continuous variables between 2 groups was performed using an independent sample *t* test or Mann-Whitney U test, as appropriate. A chi-squared test was employed for categorical variables. Univariate and multivariate logistic regression analyses were performed to derive the odds ratios (ORs) of clinical predictors for depression. Parameters with $P<0.05$ in a univariate model were included in a multivariate model. By setting a smaller P value (using $P<0.05$ instead of $P<0.2$) in multivariate model selection, we avoided including weak covariates or non-covariates. The parameters predicting depression were subjected to receiver operating characteristic (ROC) analysis, showing the area under curve (AUC) with its 95% confidence interval (95% CI) and cut-off point. The association between BDI and SF-36 scores was analyzed using linear regression. The longitudinal changes in BDI scores, PSQI scores, and biochemical parameters from baseline to the sixth month were calculated. Based on the change in BDI scores at the 6-month time-point, the primary outcome was set as BDI decline (score change <0) and BDI non-decline (score change ≥0). Logistic regression was performed to evaluate factors predictive of longitudinal changes in BDI scores. All statistical analyses were conducted using

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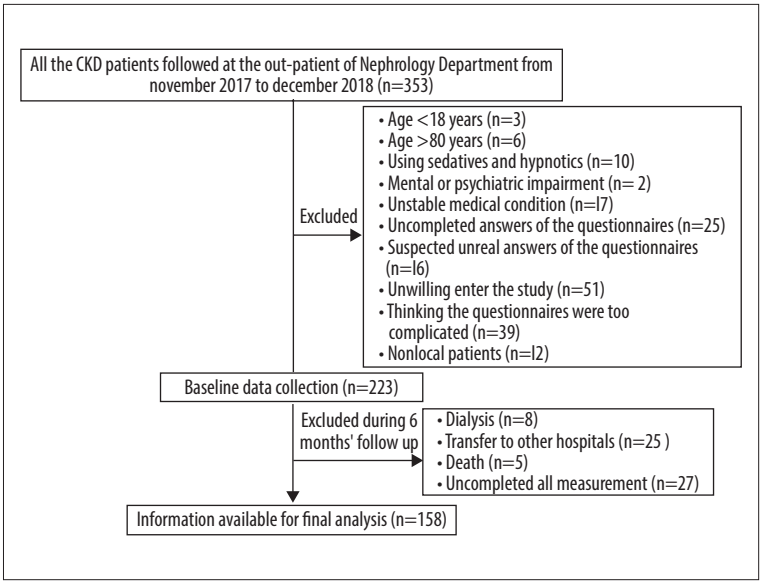

Figure 1. Flow diagram of participant recruitment.

SPSS version 22 (IBM, Japan) and STATA version 14 (StataCorp LP, College Station, Texas, United States). *P*<0.05 was considered statistically significant.

Results

Prevalence of depression at baseline and patient characteristics

The CKD cohort for this study included 223 patients. The flow diagram for participant recruitment is shown in Figure 1. The percentage of patients who were male was 68.2% (71/223). The mean age was 50.3±15.8 years, mean eGFR was 51.8±35.0 mL/min/1.73 m^2, and DM and a history of CVD were present in 13.5% and 11.7% of patients, respectively. The average BDI score was 4.0 [range, 2.0 to 7.0]. Seventeen patients (7.72%) were experiencing depression at baseline. Table 1 lists baseline clinical characteristics and laboratory data for patients who were and were not depressed. The patients with depression were predominantly female (64.7 *vs.* 29.1%, *P*=0.005), had higher PSQI scores (7.82±4.75 *vs.* 5.94±3.50, *P*=0.040), and had lower SUA levels (5.40±1.56 *vs.* 6.50±1.65 mg/dL, *P*=0.008). There were no significant differences for other parameters.

Independent predictors of depression

Table 2 shows the associated baseline clinical factors for depression by logistic regression analysis. In the univariate models, a higher PSQI score (OR 1.130, 95% CI 1.003 to 1.273, *P*=0.045), being female (OR 0.224, 95% CI 0.079 to 0.634, *P*=0.005), and lower SUA levels (OR 0.617, 95% CI 0.430 to 0.886, *P*=0.009) were associated with depression. These 3 parameters were then put into a multivariate model, which showed that being female (OR 0.319, 95% CI 0.108 to 0.944, *P*=0.039) and having lower SUA levels (OR 0.675, 95% CI 0.469 to 0.970, *P*=0.034) were independent risk factors for depression. SUA levels had the highest Wald value, indicating the strongest ability to predict depression among the associated clinical factors. The relationships between SUA levels and BDI scores are plotted in Figure 2.

Association of BDI score with SF-36

Patients who were depressed had lower SF-36 total scores compared with the patients who were not depressed, as shown in Table 3. With the exceptions of PF and BP, patients who were depressed scored significantly lower than patients who were not depressed on all 6 additional parameters. Linear regression revealed that BDI scores were inversely correlated with SF-36 total scores (β=–3.551, 95% CI –4.293 to –2.809, *P*<0.001). The relationship between BDI scores and SF-36 total scores is plotted in Figure 3.

ROC curve analysis

ROC curves for female gender and SUA levels in predicting depression are shown in Figure 4. The AUC was 0.678 for female gender and 0.694 for SUA levels. The combined AUC for female gender and SUA levels increased to 0.746. The SUA level cut-off value for indicating depression in patients with CKD was <5.38 mg/dL.

Longitudinal changes in BDI scores and clinical parameters

Repeated measurements of BDI scores and clinical parameters after 6 months of follow-up were performed on 158 patients. During the 6-month follow-up, 65 patients were lost because

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Table 1. Baseline clinical characteristics and laboratory data for depressed and non-depressed patients (n=223).

Characteristic	Depressed (n=17)	Non-depressed (n=206)	*P* value*
Age, year	50.9±18.0	50.3±15.6	0.885
Gender, Male, *n* (%)	11 (64.7%)	60 (29.1%)	0.005
BDI score	17.0 [14.0, 20.5]	3.0 [1.0, 6.0]	<0.001
PSQI score	7.82±4.75	5.94±3.50	0.040
eGFR, mL/min/1.73 m^2	49.5±38.5	52.2±34.9	0.760
Charlson comorbidity score	1.0 [0.0–2.0]	2.0 [0.0–3.0]	0.428
DM, *n* (%)	3 (17.6%)	27 (13.1%)	0.709
CVD history, n (%)	1 (5.9%)	25 (12.1%)	0.700
Smoking history, n (%)	3 (17.6%)	68 (33.0%)	0.739
Drinking history, n (%)	2 (11.8%)	58 (28.2%)	0.347
Marital status			0.648
Married, *n* (%)	14 (82.4%)	184 (89.3%)	
Unmarried, *n* (%)	2 (11.8%)	16 (7.8%)	
Divorced, *n* (%)	0 (0.0%)	2 (1.0%)	
Widowed, *n* (%)	1 (5.9%)	4 (1.9%)	
Educational status			0.247
Elementary school and below, *n* (%)	3 (17.6%)	19 (9.2%)	
Junior high school, *n* (%)	7 (41.2%)	73 (35.4%)	
High school, *n* (%)	5 (29.4%)	44 (21.4%)	
College and above, *n* (%)	2 (11.8%)	70 (34.0%)	
Original disease			0.511
Glomerulonephritis, *n* (%)	13 (76.5%)	125 (60.7%)	
Diabetic nephropathy, *n* (%)	2 (11.8%)	24 (11.7%)	
Hypertensive nephrosclerosis, *n* (%)	2 (11.8%)	48 (23.3%)	
Others, *n* (%)	0 (0%)	9 (4.4%)	
SBP, mmHg	131.5±11.1	136.2±17.0	0.266
BMI, kg/m^2	23.2±2.9	25.1±4.3	0.067
Blood parameters			
Hb, g/dL	12.2±2.1	12.9±2.2	0.213
Na, mEq/L	139.4±4.2	140.7±2.4	0.065
K, mEq/L	4.68±0.92	4.49±0.66	0.294
Cl, mEq/L	103.4±4.6	102.9±7.7	0.800
Ca, mmol/L	2.23±0.17	2.26±0.22	0.573
P, mmol/L	1.30±0.25	1.18±0.23	0.101
Mg, mmol/L	0.91±0.13	0.86±0.11	0.212

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Table 1 continued. Baseline clinical characteristics and laboratory data for depressed and non-depressed patients (n=223).

Characteristic	Depressed (n=17)	Non-depressed (n=206)	*P* value*
BUN, mmol/L	11.7±8.6	9.9±5.9	0.259
Cr, mg/dL	2.29±1.73	2.12±1.49	0.658
UA, mg/dL	5.40±1.56	6.50±1.65	0.008
Alb, g/dL	3.98±0.49	4.10±0.62	0.488
TC, mmol/L	5.16±1.40	5.21±1.60	0.913
TG, mmol/L	2.20±1.79	1.81±1.11	0.248
CO_2, mEq/L	25.2±3.3	25.4±3.2	0.867
UB score of spot urine	1.0 [0.0–3.0]	0.0 [0.0–2.0]	0.309
24-hour urine protein, g/day	0.66 [0.44–2.90]	0.84 [0.30–2.69]	0.751
Treatment			
RASi, *n* (%)	5 (29.4%)	76 (36.9%)	0.610
CCB, *n* (%)	7 (41.2%)	99 (48.1%)	0.623
β-blocker, *n* (%)	2 (11.8%)	53 (25.7%)	0.253
Diuretic, *n* (%)	0 (0.0%)	17 (8.3%)	0.246

* Independent Sample *t* test or Mann-Whitney U test (BDI score, Charlson score, UB score of spot urine and 24-hour urine protein) as appropriate. Alb – albumin; β-blocker – β receptor blocker; BDI – Beck Depression Inventory; BMI – body mass index; BUN – blood urea nitrogen; Ca – calcium; CCB – calcium channel blocker; Cl – chlorine; CO_2 – venous carbon dioxide; Cr – creatinine; CVD – cardiovascular disease; DM – diabetes mellitus; eGFR – estimated glomerular filtration rate; Hb – hemoglobin; K – potassium; Mg – magnesium; Na – sodium; P – phosphorus; PSQI – Pittsburgh Sleep Quality Index; RASi – RAS inhibitor; SBP – systolic blood pressure; TC – total cholesterol; TG – triglyceride; UA – uric acid; UB – urine blood.

Table 2. Associated baseline clinical factors for depression (BDI Score ≥14) (n=223).

Parameter	Univariate				Multivariate			
	Wald	OR	95% CI	*P* value	Wald	OR	95% CI	*P* value
Gender, Female	7.955	0.224	0.079–0.634	0.005	4.257	0.319	0.108–0.944	0.039
PSQI score	4.026	1.130	1.003–1.273	0.045	3.104	1.122	0.987–1.275	0.078
SUA, mg/dL	6.822	0.617	0.430–0.886	0.009	4.512	0.675	0.469–0.970	0.034

PSQI – Pittsburgh Sleep Quality Index; SUA – serum uric acid.

of entering dialysis, transferring to other hospitals, death and uncompleted all measurement, including 6 who were depressed and 59 who were not depressed. One hundred fifty-eight patients were divided into a BDI decline group (n=72) and a BDI non-decline group (n=86), based on their BDI score changes after 6 months. In the BDI decline group, the mean change in PSQI score was significantly lower than that in the BDI non-decline group (–1.44±3.62 *vs.* 0.02±2.82, *P*=0.005). The mean SUA levels slightly increased in the BDI decline group, while in the BDI non-decline group, the SUA levels decreased (0.45±1.69 *vs.* –0.53±1.96, *P*=0.002). Comparisons of longitudinal changes for clinical parameters between the BDI decline and BDI non-decline groups are shown in Table 4.

Associated longitudinal clinical factors for BDI decline

Both univariate and multivariate logistic regression results are shown in Table 5. A decrease in PSQI score (OR 0.873, 95% CI 0.777 to 0.981, *P*=0.022) and an increase in SUA levels (OR 1.383, 95% CI 1.115 to 1.715, *P*=0.003) were both independent factors for BDI decline. A change in SUA levels had the highest Wald value.

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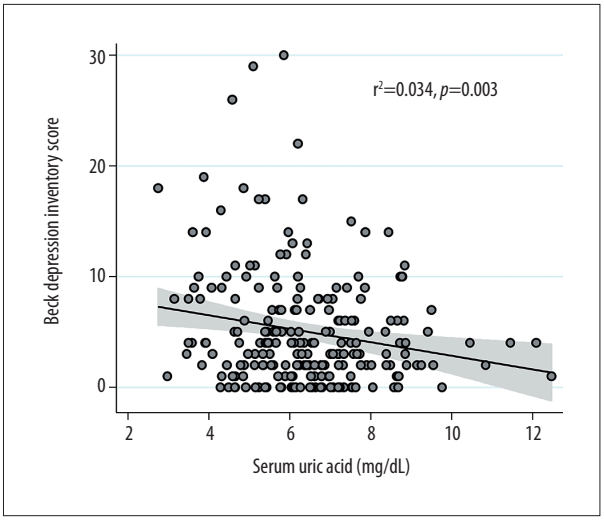

Figure 2. Correlation between baseline Serum Uric Acid (SUA) level and Beck Depression Inventory (BDI) score. Baseline SUA showed a negative correlation with BDI score in non-dialysis CKD patients with r^2=0.034, P=0.003.

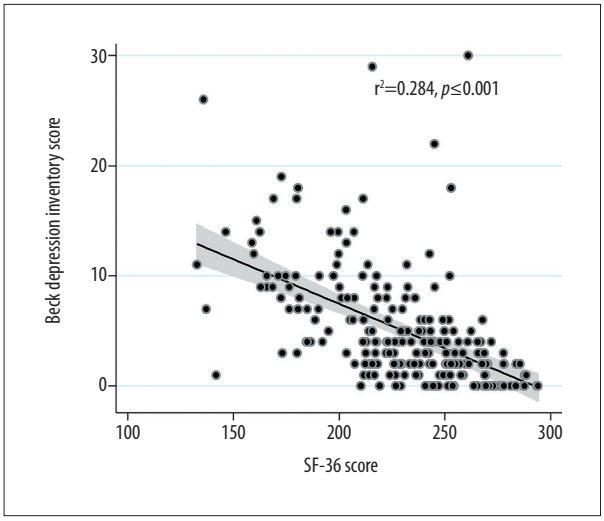

Figure 3. Correlation Between Beck Depression Inventory (BDI) Score and SF-36 Score. The BDI score showed a negative correlation with SF-36 score in non-dialysis CKD patients with r^2=0.284, P<0.001.

Table 3. SF-36 scores for depressed and non-depressed patients.

Characteristic	Depressed (n=17)	Non-depressed (n=206)	*P* value
PF	65.0±25.4	74.2±19.3	0.067
RP	25.0±36.4	57.8±64.0	0.038
BP	74.6±15.8	81.4±17.0	0.112
GH	32.8±16.1	49.6±20.8	0.001
VT	45.3±20.4	69.9±18.8	<0.001
SF	69.1±31.0	92.3±18.2	<0.001
RE	39.2±41.2	61.9±38.4	0.021
MH	45.9±12.8	71.6±17.6	<0.001
PCS	101.3±17.6	112.7±21.2	0.026
MCS	92.7±23.7	120.4±23.9	<0.001
SF-36	194.1±36.1	233.1±32.8	<0.001

BP – bodily pain; GH – general health; MCS – Mental Component Summary; MH – mental health; PCS – Physical Component Summary; PF – physical functioning; RE – role emotional; RP – role physical; SF – social functioning; VT – vitality.

Discussion

In the present study, we found a relatively low prevalence of depression (7.72%) in our non-dialysis CKD cohort, compared with previous studies. One possible reason is that we excluded patients who were using sedatives and hypnotics. If we added them to the cohort, the prevalence of depression would slightly increase to 11.6% (27/233). Another reason may be that the present study was cross-sectional and most patients received CKD education in our center for a period of time, thus their depression may have been alleviated to a certain extent. The depressed patients were predominantly female and had higher PSQI scores and lower SUA levels. Lower SUA levels and being female were independent risk factors for depression. The results showed that a lower SUA level in depressed patients was consistent with the findings of previous studies [18–20]. BDI score was inversely associated with QoL in non-dialysis CKD patients. A decrease in PSQI score and elevated SUA levels were independently associated with BDI score decline at the 6-month follow-up exam. This study did not take into account any drugs that could affect SUA levels.

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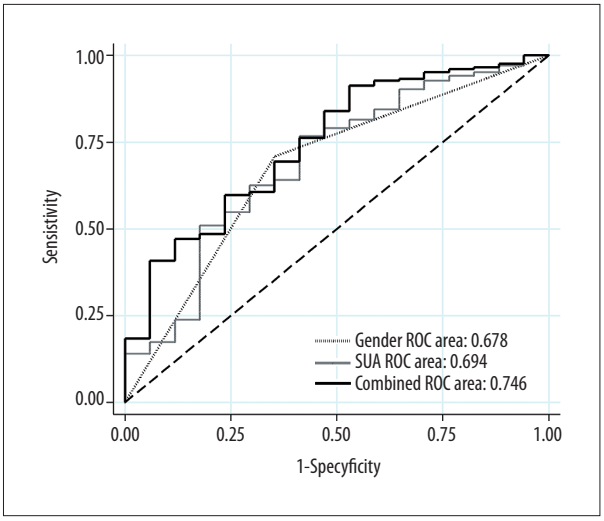

Figure 4. ROC curves for baseline SUA and gender predicting depression status in non-dialysis CKD patients.

Depression is one of the main psychological disorders in CKD patients, and it is also a major component of psychological pain [21]. In psychonephrology concepts, the pain experienced in patients with CKD is physical, psychological, social, and spiritual. Physical pain includes general fatigue, itchy skin, and shortness of breath. Social pain includes time constraints, being labeled as a "person with a disability," and barriers to promotion, and discord within the family. Spiritual pain includes isolation, loneliness, a fear of death, and feeling dependent on dialysis. Psychological pain includes sleep disorders, anxiety about having complications, denial of dialysis, and depression. Psychologically, although many patients with CKD can accept that they have abnormal kidney function to some extent, the continued decrease in eGFR can still stimulate various psychological reactions, including depression.

Previous studies reported that the estimated prevalence of depression in non-dialysis CKD patients was 21% to 27% [4]. In an observational cross-sectional study that included 272 patients with stages 2 to 5 non-dialysis CKD, the prevalence of a major depressive episode was reported as 21% and it did not vary significantly by CKD stage [22]. In another study, the prevalence of depressive symptoms and major depression were 54.8% and 21.6% in patients with severe CKD whose eGFR was less than 30 mL/min/1.73 m^2, and 32.8% and 13.0% in patients with non-severe CKD, respectively [23]. A similar result was reported in a Taiwan study of 428 patients with CKD: 37% participants had depressive symptoms [24]. The prevalence of depression is significant higher in patients with CKD compared with the general population as well as with other patients with chronic disease [2,3]. For example, in a study of patients with cancer, the prevalence of depression was only 10.8% [25]. In the present study, the prevalence of depression in our CKD cohort was relatively lower than in previous studies' results, perhaps because we excluded patients who were using sedatives and hypnotics. There may be 2 additional explanations: First, our study recruited stage 1 to 5 non-dialysis CKD patients with mean eGFR of 51.8±35.0 mL/min/1.73 m^2. Most previous studies included patients with who had more advanced disease. Second, in our study, the majority of participants had recognized their disease and accepted CKD management for some time. Further research is needed on whether integrated management strategies such as diet education, exercise guidance, or assistance quitting smoking can have an impact on psychological disorders for patients with CKD.

In patients with CKD, depression was associated with death, hospitalization, and rapid decline in renal function [5]. In a meta-analysis of 22 studies of 83 381 adults with CKD that comprised 12 063 cases of depression, the mean prevalence of depression was 27.4% [5]. These results showed that patients with CKD who were depressed had a 1.59-fold increased risk for all-cause death compared with patients with CKD who were not depressed. Similarly, a prospective observational cohort study of 568 non-dialysis CKD patients found that having significant depressive symptoms resulted in a more rapid GFR decrease (eGFR slopes of –2.3 *vs.* –1.2 mL/min/1.73 m^2 per year) and increased risk of first hospitalization [24]. Another prospective study involving 267 veterans with CKD stages 2 to 5 reported that the presence of a current major depressive episode was associated with higher risk of death, dialysis initiation, or hospitalization [26]. Similar results showing an association between depression and mortality risk in non-dialysis CKD patients have also been identified in other studies [23,27,28], suggesting that there is an urgent need to identify the risk factors for depression and to introduce effective interventions.

A relationship between inflammation, malnutrition, and depression has been previously proposed [9–13]. However, our study did not identify any impact of BMI, serum Alb, Hb, TC, or TG on depression. In addition, we did not test the concentrations of inflammatory factors in this study. Our results showed that having lower SUA levels and being female were associated with depression presentation, and that relatively elevated SUA levels were independently associated with BDI score decline after 6 months of follow-up. Previous studies found lower SUA levels in subjects who were depressed, which showed a possible role for the purinergic system in those individuals and associated with other affective disorders [18–20]. UA is the end product of purine metabolism. Higher concentrations of SUA have been shown to induce endothelial dysfunction, mediate pro-oxidative effects on vascular cells, and stimulate the production of a variety of inflammatory mediators [29,30]. Hyperuricemia is also known to be associated with hypertension, CKD, DM, and cardiovascular and cerebrovascular diseases [31–36]. However, UA has multifaceted effects on the

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Table 4. Longitudinal changes in clinical parameters in patients with and without BDI decline (n=158).

Characteristic	With BDI decline (n=72)	Without BDI decline (n=86)	*P* value*
BDI score change	–3.00 [–5.00, –1.00]	1.00 [0.00, 2.00]	<0.001
PSQI score change	–1.44±3.62	0.02±2.82	0.005
eGFR change, mL/min/1.73 m^2	0.15±1.05	–1.39±7.51	0.272
SBP change, mmHg	–0.74±14.97	–1.55±14.20	0.744
BMI change, kg/m^2	–0.32±1.33	–0.06±0.93	0.175
Blood parameters			
Hb change, g/dL	–2.54±12.52	0.90±1.89	0.093
Na change, mEq/L	1.22±2.69	0.48±2.88	0.135
K change, mEq/L	–0.005±0.682	–0.061±0.604	0.622
Cl change, mEq/L	0.93±3.37	–1.12±12.32	0.204
Ca change, mmol/L	–0.02±0.18	–0.01±0.14	0.752
P change, mmol/L	0.09±0.24	0.06±0.21	0.469
Mg change, mmol/L	0.02±0.10	–0.03±0.09	0.114
BUN change, mmol/L	0.41±4.37	3.37±2.63	0.302
Cr change, mg/dL	2.03±1.85	2.00±1.53	0.902
UA change, mg/dL	0.45±1.69	–0.53±1.96	0.002
Alb change, g/dL	3.91±0.44	3.80±0.59	0.223
TC change, mmol/L	–0.35±0.89	–0.32±1.31	0.910
TG change, mmol/L	–0.05±0.83	–0.32±0.95	0.337
CO_2 change, mEq/L	–0.20±2.39	0.31±3.18	0.407
UB score of spot urine change	0.00 [–1.00, 0.00]	0.00 [0.00, 0.00]	0.341
24-hour urine protein change, g/day	0.00 [–1.00, 1.00]	0.00 [–1.00, 0.00]	0.272

* Independent Sample T test or Mann-Whitney U test (BDI score change, UB score of spot urine change and 24-hour urine protein change) as appropriate. Alb – albumin; BDI – Beck Depression Inventory; BMI – body mass index; BUN – blood urea nitrogen; Ca – calcium; Cl – chlorine; CO_2 – venous carbon dioxide; Cr – creatinine; eGFR – estimated glomerular filtration rate; Hb – hemoglobin; K – potassium; Mg – magnesium; Na – sodium; P – phosphorus; PSQI – Pittsburgh Sleep Quality Index; SBP – systolic blood pressure; TC – total cholesterol; TG – triglyceride; UA – uric acid; UB – urine blood.

Table 5. Longitudinal clinical factors associated with BDI decline (n=158).

Parameter	Univariate				Multivariate			
	Wald	OR	95% CI	*P* value	Wald	OR	95% CI	*P* value
PSQI score change	7.314	0.863	0.776–0.960	0.007	5.227	0.873	0.777–0.981	0.022
SUA change, mg/dL	8.207	1.368	1.104–1.696	0.004	8.704	1.383	1.115–1.715	0.003

CI – confidence interval; OR – odds ratio; PSQI – Pittsburgh Sleep Quality Index; SUA – serum uric acid.

physiology and pathology of the human body. For example, extracellular UA (or SUA) can have antioxidant effects. In an experimental study, UA was shown to be able to bind peroxynitrite produced by lipopolysaccharide-stimulated mouse monocyte line cells, and acted as a strong peroxynitrite scavenger [37]. Previous studies have also found that UA shows neuroprotective effects in many neuropsychic diseases, such as Parkinson's disease [38], multiple sclerosis [39], and cognitive impairment [40]. In patients with current major depressive disorder and/or anxiety disorder, plasma UA levels were lower than in

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patients with whose disorders were in remission and in control patients [41]. Another study that included 96 989 individuals reported that high SUA levels were associated with lower risk of hospitalization with depression and antidepressant medication use [42]. It is assumed that SUA's antioxidant capacity may account for these effects, as depression has been shown to be associated with increased oxidative stress [43].

Apart from the antioxidant effects of SUA, a study of patients with major depressive disorder that examined brain structural characteristics by magnetic resonance imaging found that cases presented with lower fractional anisotropy and higher radial diffusivity values. In addition, SUA levels were significantly associated with altered white matter connectivity, potentially through demyelination [44].

The present study has limitations. First, it was performed in a single center with relatively small samples. Multicenter studies with larger sample sizes should be performed to verity the results from the present study. Moreover, although the participants were closely followed up within our CKD center, 65 patients were lost because they entered dialysis, transferred to other hospitals, died, or did not complete all measurement. Finally, the longitudinal study period was relatively short and a longer-term trial needs to be carried out to estimate the effect on CKD progression of prophylaxis and treatment for depression and intervening associated clinical factors.

Conclusions

In conclusion, this is the first study to demonstrate an association between longitudinal SUA levels and depression in non-dialysis CKD patients. Further studies will be needed to verify the multiple roles of SUA in CKD progression and CKD-related psychological disorders. The QoL of non-dialysis CKD patients deserves attention. Excessively low SUA levels should be avoided in CKD patients, as they can increase risk of depression, particularly in female patients. Improved sleep quality and relatively elevated SUA levels can relieve depression.

Ethics statement

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee (document no.: 2015008S) of Tianjin First Center Hospital, which permitted the studies on our CKD cohort to explore factors that influence CKD progression.

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Conflict of interest

None.

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