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Prevalence of depression and suicidal ideation increases proportionally with renal function decline, beginning from early stages of chronic kidney disease

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Abstract

Depression and suicidal ideation are prevalent mental health problems in patients with chronic kidney disease (CKD. However, the association between mental health problems and kidney disease has been investigated in severe cases only. Thus, this study evaluated the relationship between mental health problems and renal function in a community-based prospective cohort study comprising patients with mild to moderate kidney disease. A total of 44,938 participants who were participated in Korean National Health and Nutrition Examination Survey IV, V, and VI from 2007 to 2014 were enrolled. Estimated glomerular filtration rate (eGFR) was calculated using the CKD Epidemiology Collaboration equation. The study outcome was the prevalence of depression and suicidal ideations assessed by self-reporting surveys. Logistic regression analysis was performed to evaluate the relationship between renal function and outcomes. The mean age of the study subjects was 49.2 ± 16.6 years, and the mean eGFR was 94.0 mL/min/1.73 m^2. The prevalence of depression and suicidal ideation increased with decreasing eGFR. Multivariate logistic regression analysis showed that the risk of depression increased in subjects with eGFR <45 mL/min/1.73 m^2 [odds ratio (OR) 1.47; 95% confidence interval (CI) 1.09–1.98]. The risk of suicidal ideation gradually increased in groups with eGFR <90 mL/min/1.73 m^2 (OR, 1.11; 95% CI, 1.03–1.20), even after adjustments for confounding variables. In conclusion, depression and suicidal ideation are related closely with renal dysfunction. The risk of having depression and suicidal ideation increased even in patient with mild renal dysfunction. Therefore, evaluation and management strategies regarding mental health problems should be taken into account throughout all stages of CKD.

Abbreviations: BMI = body mass index, CI = confidence interval, CKD = chronic kidney disease, CKD-EPI = CKD Epidemiology Collaboration, DM = diabetes mellitus, eGFR = estimated glomerular filtration rate, HTN = hypertension, KNHANES = Korean National Health and Nutrition Examination Survey, OR = odds ratio.

Keywords: chronic kidney disease, depression, suicide

1. Introduction

The number of patients with chronic kidney disease (CKD) is increasing at a rapid rate worldwide.[1–3] This has become a global health problem because CKD leads to a reduced quality of life and increased mortality rate.[4–6] Among the factors that affect quality of life and survival in patients with CKD are mental health problems that often develop in patients with reduced renal function.[7,8]

Depression is a well-known independent risk factor for hospitalization or death in patients with impaired renal function.[9,10] The prevalence of depression in the general population ranges from 2% to 4%.[11,12] Depression is more common in patients with CKD and considerably affects the disease outcome.[9] In previous reports, depression was found in up to 20% of patients with severe CKD before dialysis initiation.[13,14] In addition, the prevalence of depression in patients undergoing dialysis are higher than in patients with CKD without dialysis (~20%–30% of that of patients on dialysis), with investigations reporting rates as high as 47%.[15–17] On the other hand, suicide, one of the gravest results of depression, has also been known to be more common in patients with CKD than in the general population. In a recent study, 22% of patients treated with hemodialysis were reported to have had suicidal ideations.[18,19]

Although the causes of this increased mental health problems in patients with CKD are uncertain, symptoms related to chronic comorbid conditions and the direct effect of uremic toxins have

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The authors declare no conflicts of interest. The epidemiologic data used in this study were obtained from the Korea National Health and Nutrition Examination Survey (KNHANES IV, V, and 'VI) from 2007 to 2014, Republic of Korea.

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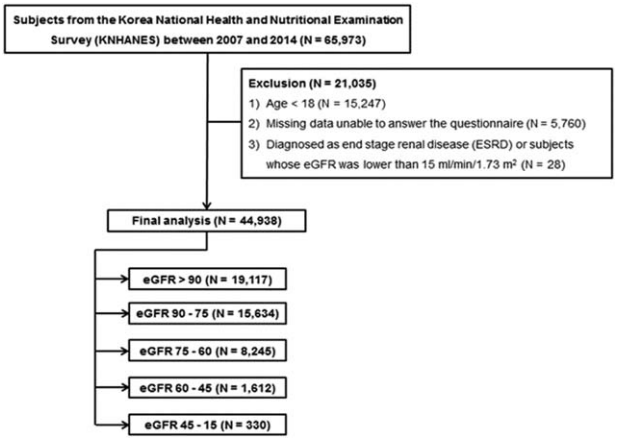

Figure 1. Flow diagram of the study cohort. Abbreviation: eGFR = estimated glomerular filtration rate.

been suspected as contributing factors.[20] Considering that several uremic toxins are already increased in the early stages of CKD, the prevalence of mental health problems may begin to increase even in patients with mild impairment in renal function. However, most of the previous reports only investigated patients with severe CKD or patients on dialysis, and the associations of mental health problems and renal function in patients with early CKD is not well known.

Therefore, in this study, the relationship between renal function and mental health problems, including depression and suicidal ideations, was investigated in a community-based cohort comprising patients with early CKD.

2. Materials and methods

2.1. Study subjects

This study was performed by using data from the Korean National Health and Nutrition Examination Survey (KNHANES IV, V, and VI 2007 to 2014). KNHANES has been conducted periodically to assess the health and nutritional status of the Korean civilian noninstitutionalized population. The sampling frame was developed on the basis of the 2005 population and housing census in Korea. Household units were selected by using a stratified multistage probability sampling design for the South Korean population. KNHANES IV, V, and VI were cross-sectional, nationally representative surveys conducted by the Division of Chronic Disease Surveillance, Korea Centers for Disease Control and Prevention, among ~260,000 primary sampling units, each of which included ~60 households. A total of 65,973 subjects were screened. Patients younger than 18 years, with a diagnosis of end-stage renal disease, with estimated glomerular filtration rate (eGFR) $<15\,mL/min/1.73\,m^2$, and with missing data were excluded. A total of 44,938 subjects were included in the final analysis (Fig. 1). This study was conducted in accordance with the Declaration of Helsinki and was approved by the institutional review board of the Yonsei University Health System Clinical Trial Center (4-2016-0882).

2.2. Anthropometric and laboratory data

Anthropometric measurements were obtained by trained experts following standardized protocols. Body mass index (BMI) was calculated as weight (kg) divided by the square of height (m^2). Diabetes mellitus (DM) was defined as serum fasting blood glucose level ≥126 mg/dL, use of antidiabetic medication, or previous diagnosis by a physician. Hypertension (HTN) was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or use of antihypertensive medications. Indicators of socioeconomic status, such as education (high school or lower/university or higher) and occupation (currently employed or not), were surveyed. Economic status was assessed as the total household income, and marital status was categorized as currently married or single. Health behaviors such as sleep duration, alcohol consumption, and smoking status were evaluated with questionnaires. According to smoking status, subjects were classified as current or past smokers versus nonsmokers. Sleeping hours were assessed with the question "How much time do you usually sleep per day?" Stress level was reported as none, mild, moderate, and severe during routine daily life.

Blood samples were collected after an at least 8 hours fast, and transported to a central laboratory within 24 hours. Serum creatinine was measured by using the colorimetric method. ADVIA 1650 (Siemens, Tarrytown, New York) was used for KNHANES 2007, and the Automatic Analyzer 7600 (Hitachi, Tokyo, Japan) was used for KNHANES 2008 to 2014. Blood hemoglobin levels were measured by using the impedance method for KNHANES 2007 and the sodium lauryl sulfate hemoglobin method for KNHANES 2008 to 2013. Proteinuria was defined as values ≥1+ determined by using the dipstick urine test.

2.3. Renal function estimation

Renal function was estimated by using the CKD Epidemiology Collaboration (CKD-EPI) equation, with serum creatinine levels calibrated to an isotope-dilution mass spectrometry traceable standard for KNHANES 2008 to 2014.[21] As measurements were not standardized for creatinine levels of KNHANES 2007, creatinine levels that were reduced by a calibration factor of 5% were used to calculate eGFR.[22] The accuracy of the CKD-EPI equation in estimating the glomerular filtration rate has previously been validated.[23] Patients were categorized into 6 groups according to eGFR. Patients with eGFR 45 to 30 mL/min/$1.73\,m^2$ and those with eGFR 30 to 15 mL/min/$1.73\,m^2$ were grouped together owing to the small number of patients allocated to these categories (Fig. 1).

2.4. Mental health measures

Data on mental health were obtained from a self-reported questionnaire administered under the supervision of an investigator. Depressive symptoms were assessed with the question "Have you felt sadness or despair affecting your daily life for more than 2 weeks over the past year?" In addition, the question "are you currently diagnosed with depression?" was also asked. The participants answered these questions with a "yes" or "no" response. Subjects were defined as having depression when they reported having depressive symptoms or were currently diagnosed as having depression. Suicidal ideation was assessed by a positive answer to the question "in the last 12 months, did you think about committing suicide?" A "yes" or "no" response was also used to determine whether they had suicidal ideations. This indicator has been previously documented as a predictor of suicide in other surveys.[24]

Table 1

Baseline characteristics according to eGFR categories.

	eGFR Categories (mL/min/1.73 m^2)					
	>90 (n = 19,117)	90–75 (n = 15,634)	75–60 (n = 8245)	60–45 (n = 1612)	45–15 (n = 330)	*P*
Age, y	41.8 (13.7)	57.3 (14.1)	65.1 (11.5)	72.1 (8.7)	72.6 (9.9)	<.001
Female	16,715 (61.1)	5,757 (50.0)	2,255 (50.4)	666 (52.6)	166 (51.2)	<.001
BMI, kg/m^2	23.4 (3.5)	23.9 (3.1)	24.4 (3.1)	24.5 (3.3)	24.2 (3.6)	<.001
HTN	2,961 (10.8)	3,144 (27.3)	1,855 (41.5)	807 (63.8)	218 (67.3)	<.001
DM	1,197 (4.4)	1,072 (9.3)	671 (15.0)	338 (26.7)	130 (40.1)	<.001
Depression	3,886 (14.0)	2,710 (15.9)	238 (18.0)	65 (18.0)	13 (23.1)	<.001
Suicidal ideation	3,099 (11.3)	2,299 (13.6)	256 (16.3)	61 (20.2)	18 (24.4)	<.001
Smoking status, ever	9,900 (36.2)	5,026 (43.7)	2,006 (44.9)	564 (44.6)	160 (49.4)	<.001
Alcohol status, ever	24,062 (87.9)	9,236 (80.3)	3,384 (75.7)	880 (69.6)	221 (68.2)	<.001
Socioeconomic status						
Marital status, current	21,133 (77.2)	10,908 (94.8)	4377 (97.9)	1246 (98.5)	320 (98.8)	<.001
Currently employed	17,715 (64.7)	6946 (60.4)	2041 (45.7)	414 (32.7)	92 (28.4)	<.001
Economic status						<.001
Low	6,758 (25.0)	2,664 (23.6)	1,018 (23.4)	297 (24.3)	82 (25.9)	
Moderate	13,700 (50.7)	5,661 (50.2)	2,135 (49.1)	594 (48.6)	152 (47.9)	
High	6,569 (24.3)	2,959 (26.2)	1,194 (27.5)	332 (27.1)	83 (26.2)	
Education status						<.001
≤Elementary	3,902 (14.7)	4,057 (36.4)	2,104 (48.7)	737 (61.3)	189 (62.6)	
Middle–high school	13,549 (51.0)	4,472 (40.1)	1,542 (35.7)	366 (30.4)	91 (30.1)	
≥College	9,110 (34.3)	2,628 (23.6)	670 (15.5)	100 (8.3)	22 (7.3)	
Sleeping hours, h/day	7.8 (0.1)	8.1 (0.1)	8.0 (0.2)	9.1 (0.4)	9.1 (0.8)	<.001
Level of stress						<.001
None	3,924 (14.3)	2,565 (22.3)	1,331 (29.8)	471 (37.2)	127 (39.2)	
Mild to moderate	22,157 (80.9)	8,459 (73.5)	2,947 (65.9)	757 (59.8)	183 (56.5)	
Severe	1,292 (4.7)	482 (4.2)	192 (4.3)	37 (2.9)	14 (4.3)	
Laboratory data						
eGFR, mL/min/1.73 m^2	105.1 (10.5)	83.4 (4.3)	68.9 (4.1)	54.3 (4.1)	36.3 (7.1)	<.001
Proteinuria	1,286 (6.7)	1,194 (7.6)	765 (9.3)	252 (15.6)	101 (30.5)	<.001
Hemoglobin, g/dL	13.9 (1.6)	14.1 (1.5)	14.0 (1.5)	13.4 (1.7)	12.5 (1.9)	<.001
HbA1c, %	5.8 (0.9)	6.0 (0.9)	6.3 (1.1)	6.5 (1.2)	6.9 (1.6)	<.001
Total cholesterol, mg/dL	185.2 (35.4)	192.7 (35.9)	193.7 (37.8)	188.7 (40.1)	181.8 (41.7)	<.001

Data are presented as mean (standard deviation) or number (%).

BMI = body mass index, DM = diabetes mellitus, eGFR = estimated glomerular filtration rate, HTN = hypertension.

2.5. Statistical analysis

All statistical analyses were performed by using SPSS for Windows version 21.0 (SPSS Inc., Chicago, IL). Continuous variables are expressed as mean ± standard deviation, and categorical variables as absolute numbers with percentages. Each variable was tested for normality before statistical analysis. Comparisons between the groups were made by using analysis of variance or Student *t* test for continuous variables and the χ^2 test or Fisher exact test for categorical variables. The Kolmogorov–Smirnov test was performed to determine the normality of the distribution of parameters. If the resulting data did not show a normal distribution, geometric mean ± standard deviation was reported; the Mann–Whitney *U* test or Kruskal–Wallis test was used for multiple comparisons. Logistic regression analysis was conducted to evaluate the associations of depression and suicidal ideation with eGFR. Odds ratios (ORs) for depression and suicidal ideation were compared among groups of eGFR categories. Multivariable models were also constructed for logistic regression. Variables that showed statistical significance ($P < .05$) in the univariate analysis were included in the multivariable models. Variables that did not meet the statistical criteria were included if they were considered to have clinical significance. Colinearity was assessed by using Pearson correlation coefficients. $P < .05$ were considered statistically significant.

3. Results

3.1. Baseline characteristics according to eGFR categories

The baseline characteristics of the study population are described in Table 1. The mean age of the subjects was 49.2 ± 16.6 years, and 43.1% were men. The mean eGFR of the subjects was 94.0 mL/min/1.73 m^2. A total of 6781 (15.1%) of subjects had depression, and suicidal ideation was reported in 5733 (12.8%) subjects.

When comparisons were made among the eGFR category groups, subjects in the lower eGFR category groups tended to be older and were more likely to have a diagnosis of HTN or DM. The percentage of smokers increased in the lower eGFR category groups, whereas the proportion of drinkers decreased. Concerning socioeconomic status, subjects in the lower eGFR category groups were less educated and less likely to be employed. Laboratory data assessment revealed that the proportion of subjects with proteinuria increased, whereas blood hemoglobin levels decreased in category groups with lower eGFR.

3.2. Mental health problems

Experience of depression during the past year was reported in 14.0% of subjects in the eGFR > 90 mL/min/1.73 m^2 group. The

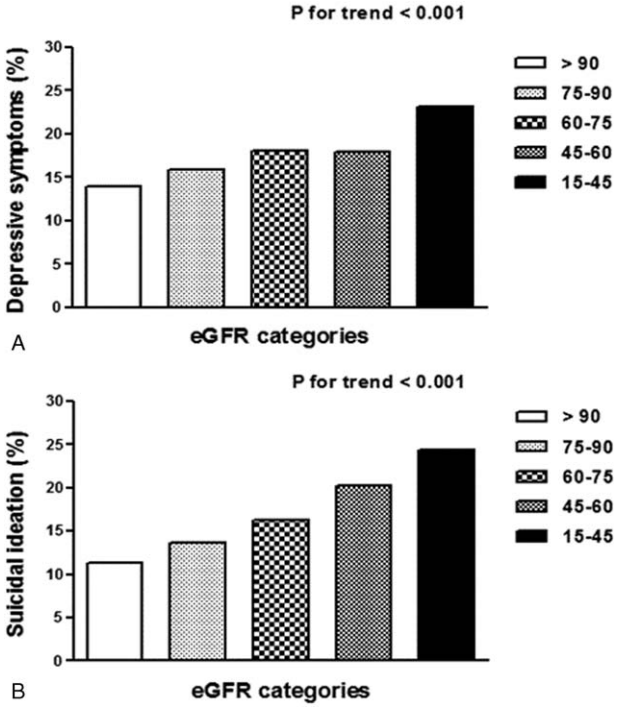

Figure 2. Prevalence of depression (A) and suicidal ideations (B) among the eGFR category groups. Abbreviation: eGFR = estimated glomerular filtration rate.

proportion of subjects with depression gradually increased in category groups with lower eGFR, resulting in a rate of 23.1% in the eGFR 45 to 15 mL/min/1.73 m^2 category group ($P < .001$). A similar trend was found for suicidal ideation. The proportion of subjects with suicidal ideation gradually increased from 11.3% in the eGFR > 90 mL/min/1.73 m^2 category group to 24.4% in the eGFR 45 to 15 mL/min/1.73 m^2 category group ($P < .001$, Fig. 2).

3.3. Factors associated with depression and suicidal ideations

Logistic regression analysis revealed that older age, female sex, comorbidities including HTN and DM, and severe level of stress were significantly related with depression and suicidal ideation. On the other hand, current employment, having a higher household income, being college educated, and having longer sleeping hours were factors found to be protective against depression or suicidal ideations (Table 2).

3.4. Relationship of eGFR with depression and suicidal ideations

When the association between eGFR and depression was evaluated by using multivariate regression analysis, the ORs for depression was found to gradually increase as eGFR decreased in each category group. The OR for depression was significantly increased in the eGFR 15 to 45 mL/min/1.73 m^2 category group [OR, 1.47; 95% confidence interval (CI) 1.09–1.98; $P = .01$], after adjustments for confounding factors (Table 3).

The association between eGFR and suicidal ideations showed a similar trend. The OR for having suicidal ideation gradually increased as eGFR decreased in each category group. The OR for having suicidal ideations was significantly increased from the eGFR 75 to 90 mL/min/1.73 m^2 category group (OR, 1.11; 95% CI, 1.03–1.20; $P = .01$) through the eGFR 15 to 45 mL/min/1.73 m^2 category group (OR, 1.79; 95% CI, 1.35–2.39; $P < .001$), after adjustment for confounding factors (Table 4).

Moreover, when the associations of depression and suicidal ideations with eGFR as a continuous variable were assessed, the risks of depression (OR, 0.98; 95% CI, 0.97–0.99; $P = .02$) and

Table 2

Factors associated with depression and suicidal ideation.

	Depression			Suicidal ideation		
	OR	95% CI	P	OR	95% CI	P
eGFR categories, mL/min/1.73 m^2						
>90		Reference			Reference	
75–90	1.16	1.09–1.23	<.001	1.24	1.16–1.32	<.001
60–75	1.34	1.24–1.46	<.001	1.53	1.40–1.67	<.001
45–60	1.34	1.15–1.55	<.001	1.99	1.72–2.29	<.001
15–45	1.84	1.42–2.39	<.001	2.53	1.95–3.26	<.001
eGFR, per 5 mL/min/1.73 m^2	0.96	0.95–0.97	<.001	0.95	0.94–0.96	<.001
Age, per 1 year	1.01	1.01–1.02	<.001	1.02	1.01–1.02	<.001
Sex, female	2.22	2.09–2.35	<.001	2.01	1.89–2.13	<.001
BMI, per 1 kg/m^2	1.00	0.99–1.01	.56	1.00	0.99–1.01	.49
Smoking status (ever)	0.77	0.73–0.81	<.001	0.91	0.86–0.96	.01
Alcohol status (ever)	0.83	0.78–0.89	<.001	0.87	0.81–0.93	<.001
HTN (yes)	1.50	1.41–1.59	<.001	1.50	1.41–1.60	<.001
DM (yes)	1.42	1.30–1.55	<.001	1.56	1.43–1.71	<.001
Marital status (current)	1.32	1.22–1.43	<.001	1.12	1.04–1.21	.004
Currently employed (yes)	0.57	0.55–0.61	<.001	0.59	0.56–0.62	<.001
Economic status (high vs other)	0.76	0.72–0.81	<.001	0.63	0.58–0.67	<.001
Education status (college vs other)	0.51	0.48–0.55	<.001	0.49	0.46–0.53	<.001
Sleeping hours per day (per 1 h)	0.99	0.98–0.99	<.001	0.98	0.98–0.99	<.001
Level of stress (severe vs other)	6.85	6.25–7.51	<.001	5.72	5.22–6.28	<.001

BMI = body mass index, CI = confidence interval, DM = diabetes mellitus, eGFR = estimated glomerular filtration rate, HTN = hypertension, OR = odds ratio.

Table 3

Multivariate logistic regression analysis for depression according to eGFR categories.

	Crude*		Model 1†		Model 2‡	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
eGFR categories, mL/min/1.73 m^2						
>90	Reference		Reference		Reference	
75–90	1.16 (1.09–1.23)	<.001	1.02 (0.96–1.10)	.49	1.05 (0.97–1.13)	.20
60–75	1.34 (1.24–1.46)	<.001	1.08 (0.98–1.19)	.13	1.10 (0.99–1.22)	.07
45–60	1.34 (1.15–1.55)	<.001	1.00 (0.82–1.13)	.67	1.05 (0.88–1.24)	.60
15–45	1.84 (1.42–2.39)	<.001	1.34 (1.03–1.76)	.02	1.47 (1.09–1.98)	.01
eGFR, per 5 mL/min/1.73 m^2	0.96 (0.95–0.97)	<.001	0.99 (0.98–0.99)	.01	0.98 (0.97–0.99)	.02

* Unadjusted model.

† adjusted model for age and sex.

‡ adjusted model for model 1 + HTN, DM, smoking, alcohol intake, marital status, education status, economic status, level of stress, and sleeping.

CI = confidence interval, eGFR = estimated glomerular filtration rate, OR = odds ratio.

Table 4

Multivariate logistic regression analysis for suicidal ideation according to eGFR categories.

	Crude*		Model 1†		Model 2‡	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
eGFR categories, mL/min/1.73 m^2						
>90	Reference		Reference		Reference	
75–90	1.24 (1.16–1.32)	<.001	1.09 (1.02–1.18)	.02	1.11 (1.03–1.20)	.01
60–75	1.53 (1.40–1.67)	<.001	1.23 (1.11–1.36)	<.001	1.21 (1.09–1.35)	.01
45–60	1.99 (1.72–2.29)	<.001	1.45 (1.24–1.70)	<.001	1.47 (1.25–1.74)	<.001
15–45	2.53 (1.95–3.26)	<.001	1.86 (1.43–2.44)	<.001	1.79 (1.35–2.39)	<.001
eGFR, per 5 mL/min/1.73 m^2	0.95 (0.94–0.96)	<.001	0.98 (0.97–0.99)	.01	0.98 (0.96–0.99)	<.001

* Unadjusted model.

† adjusted model for age and sex.

‡ adjusted model for model 1 + HTN, DM, smoking, alcohol intake, marital status, education status, economic status, level of stress, and sleeping hours.

CI = confidence interval, eGFR = estimated glomerular filtration rate, OR = odds ratio.

having suicidal ideations (OR, 0.98; 95% CI, 0.96–0.99; $P < .001$) decreased significantly as eGFR increased (Tables 3 and 4).

4. Discussion

In this study, we evaluated a community-based cohort comprising subjects with normal to moderately declined renal function. The prevalence of depression and suicidal ideations were found to increase with the decrease of eGFR. In addition, the association between mental health problems and renal function was found to be significant even in the relatively early stages of CKD.

Depression and suicidal ideations have been considered as problems affecting patients with advanced stages of CKD. Previous reports have described the prevalence of depression in patients with moderate to severe CKD to be from 15% to 50%. In patients with advanced CKD with eGFR <30 mL/min/1.73 m^2, the point prevalence of depression screened by using the Beck depression inventory was demonstrated to be as high as 54.8%.[13,25,26] A recent meta-analysis of 55,982 patients showed that 39.3% of patients undergoing dialysis had depression assessed with self-reported rating scales.[19] These reported prevalence of depression in predialysis patients with CKD and patients undergoing dialysis are much higher than the prevalence of depression in the general population, which is approximately 2% to 4%.[2,27] Similar to depression, suicidal ideations, and suicidal attempts are more frequent in patients with CKD. A recent investigation of a health insurance-based database revealed that the risk of committing suicide was 25% higher in patients with CKD and >30% higher in patients receiving dialysis than in those without CKD.[19] Although previous studies have repeatedly shown that depression and suicidal ideations are common problems in patients with CKD, the risk of developing these mental health problems in the early stages of CKD and the relationship with the degree of renal function decline have seldom been investigated. Compared with previous reports, the present study investigated nonhospitalized patients with CKD recruited through a community-based cohort, which enabled the evaluation of the full range of renal function.

The prevalence of depression was significantly increased in subjects with moderately decreased renal function. Moreover, the risk of having suicidal ideations clearly increased even in asymptomatic subjects with mild renal dysfunction. Interestingly, the prevalence of suicidal ideations increased as renal function further deteriorated. Mental health problems, especially depression and suicidal ideations, are more prevalent not only in patients with CKD but also among patients with other chronic medical conditions such as chronic obstructive pulmonary disease, coronary artery disease, DM, and cerebrovascular accidents.[28–32] This is believed to be caused by the decrease in the quality of life owing to symptoms resulting from the chronic diseases. However, considering that symptoms of uremia only begin to manifest in patients with severe renal dysfunction, the results of the present study suggest that factors other than impaired quality of life play a role in the development of these mental health problems.

Recent studies have found that systemic inflammation and oxidative stress may have direct effects on the central nervous system, resulting in a close relationship with depression and suicide.[33,34] Systemic inflammation and oxidative stress is known to be aggravated with mild reductions of renal function.[35] In addition, several uremic products are known to be elevated in patients with early CKD. Furthermore, the amino acid neurotransmitter milieu has been shown to be altered in uremic rats, suggesting that uremic toxins may act centrally and influence mental health and behavior.[36] Therefore, these factors may have a role in affecting mental health even in asymptomatic subjects whose renal function is only mildly decreased. Further investigations linking uremia-induced factors and mental health would be needed to confirm this hypothesis.

Comorbid conditions that precede renal function decline, such as DM and HTN, could also play a role in increasing the risk of depression and suicidal ideations. In this study, subjects in the lower eGFR group were more likely to be older, have HTN, or have been treated for DM, all of which are known factors that increase the risk for developing mental health problems such as depression and suicide.[37–40] Therefore, these factors may have increased the prevalence of depression and suicidal ideations among the subjects regardless of eGFR. However, eGFR was an independent risk factor for depression and suicidal ideations even after adjustments for confounding medical illnesses and behavior factors known to influence mental health. This implies that the decrease in eGFR itself may have influenced the development of depression and suicidal ideations.

Suicide is a growing medical and social problem in developing and developed countries. In Korea, the suicide rate has increased rapidly and steadily during recent years. The average rate of suicide was 9.8 per 100,000 persons in 1990, which increased to an average of 28.1 per 100,000 persons in 2012.[41,40] Along with socioeconomic factors, chronic diseases such as DM,[42] cardiovascular disease,[43] cancer,[44] and chronic obstructive pulmonary diseases are known to be risk factors for suicide.[45] Suicide is also well established as a prevalent mental health problem in patients on hemodialysis.[46,47] Sudden transition of lifestyle and deterioration of the quality of life have been implicated as factors responsible for this increased prevalence. However, little is known about the risk of suicidal ideation in patients with early CKD. Although the effect of proper management on improving the rate of suicide in patients with early CKD needs to be further investigated, the findings of this study suggest that evaluation and intervention for suicide would be needed beginning from the early stages of CKD.

This study has several limitations. First, mental health problems were assessed by using a single question, opening the possibility for misclassifications. However, single-question methods have been used as a rapid and reasonable alternative to more lengthy questionnaires in surveys involving large samples. In addition, the accuracy of detecting depression through a single-question method has been verified in a recent analysis of patients with cerebrovascular accidents.[48] Nevertheless, further investigations with more cognitive measures delineating depression in patients with CKD would be needed. Second, this study was composed of an Asian population of a developing country. The prevalence of depression and suicide has been reported to be largely dependent on ethnicity and socioeconomic environment.[49] Therefore, the findings may not be applicable to other communities. Despite these weak points, the data used in this study were obtained from a nationwide community-based cohort with a high response rate and therefore may provide information representative of the whole population. Moreover, the extensive data on potential confounders and large number of participants enabled statistical adjustments for multiple confounding factors, further strengthening the observed relationship between renal function and mental health problems.

5. Conclusions

In conclusion, decreased eGFR was significantly associated with depression and suicidal ideation. Furthermore, the prevalence of these mental health problems increased at a relatively early stage of CKD. Evaluation and management strategies for mental health issues should be provided throughout all stages of CKD.

References

[1] Coresh J, Byrd-Holt D, Astor BC, et al. Chronic kidney disease awareness, prevalence, and trends among U.S. adults, 1999 to 2000. J Am Soc Nephrol 2005;16:180–8.

[2] Chen J, Wildman RP, Gu D, et al. Prevalence of decreased kidney function in Chinese adults aged 35 to 74 years. Kidney Int 2005;68: 2837–45.

[3] Chadban SJ, Briganti EM, Kerr PG, et al. Prevalence of kidney damage in Australian adults: the AusDiab kidney study. J Am Soc Nephrol 2003;14: S131–138.

[4] Levey AS, Atkins R, Coresh J, et al. Chronic kidney disease as a global public health problem: approaches and initiatives—a position statement from Kidney Disease Improving Global Outcomes. Kidney Int 2007;72: 247–59.

[5] Go AS, Chertow GM, Fan D, et al. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med 2004;351:1296–305.

[6] Perlman RL, Finkelstein FO, Liu L, et al. Quality of life in chronic kidney disease (CKD): a cross-sectional analysis in the Renal Research Institute-CKD study. Am J Kidney Dis 2005;45:658–66.

[7] Kimmel PL, Peterson RA, Weihs KL, et al. Multiple measurements of depression predict mortality in a longitudinal study of chronic hemodialysis outpatients. Kidney Int 2000;57:2093–8.

[8] Lopes AA, Bragg J, Young E, et al. Depression as a predictor of mortality and hospitalization among hemodialysis patients in the United States and Europe. Kidney Int 2002;62:199–207.

[9] Kop WJ, Seliger SL, Fink JC, et al. Longitudinal association of depressive symptoms with rapid kidney function decline and adverse clinical renal disease outcomes. Clin J Am Soc Nephrol 2011;6:834–44.

[10] Hedayati SS, Jiang W, O'Connor CM, et al. The association between depression and chronic kidney disease and mortality among patients hospitalized with congestive heart failure. Am J Kidney Dis 2004;44: 207–15.

[11] Kessler RC, Berglund P, Demler O, et al. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry 2005;62:593–602.

[12] Weissman MM, Bland RC, Canino GJ, et al. Cross-national epidemiology of major depression and bipolar disorder. JAMA 1996;276:293–9.

[13] Hedayati SS, Minhajuddin AT, Toto RD, et al. Prevalence of major depressive episode in CKD. Am J Kidney Dis 2009;54:424–32.

[14] Hedayati SS, Minhajuddin AT, Afshar M, et al. Association between major depressive episodes in patients with chronic kidney disease and initiation of dialysis, hospitalization, or death. JAMA 2010;303:1946–53.

[15] Hedayati SS, Bosworth HB, Kuchibhatla M, et al. The predictive value of self-report scales compared with physician diagnosis of depression in hemodialysis patients. Kidney Int 2006;69:1662–8.

[16] Agganis BT, Weiner DE, Giang LM, et al. Depression and cognitive function in maintenance hemodialysis patients. Am J Kidney Dis 2010;56:704–12.

[17] Cukor D, Coplan J, Brown C, et al. Depression and anxiety in urban hemodialysis patients. Clin J Am Soc Nephrol 2007;2:484–90.

[18] Pompili M, Venturini P, Montebovi F, et al. Suicide risk in dialysis: review of current literature. Int J Psychiatry Med 2013;46:85–108.

[19] Liu CH, Yeh MK, Weng SC, et al. Suicide and chronic kidney disease: a case-control study. Nephrol Dial Transplant 2016;[Epub ahead of print].

[20] Hsu HJ, Yen CH, Chen CK, et al. Association between uremic toxins and depression in patients with chronic kidney disease undergoing maintenance hemodialysis. Gen Hosp Psychiatry 2013;35:23–7.

[21] Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150:604–12.
[22] Levey AS, Coresh J, Greene T, et al. Expressing the Modification of Diet in Renal Disease Study equation for estimating glomerular filtration rate with standardized serum creatinine values. Clin Chem 2007;53:766–72.
[23] Matsushita K, Mahmoodi BK, Woodward M, et al. Comparison of risk prediction using the CKD-EPI equation and the MDRD study equation for estimated glomerular filtration rate. JAMA 2012;307:1941–51.
[24] Gaynes BN, West SL, Ford CA, et al. Screening for suicide risk in adults: a summary of the evidence for the U.S. Preventive Services Task Force. Ann Intern Med 2004;140:822–35.
[25] Fischer MJ, Xie D, Jordan N, et al. Factors associated with depressive symptoms and use of antidepressant medications among participants in the Chronic Renal Insufficiency Cohort (CRIC) and Hispanic-CRIC Studies. Am J Kidney Dis 2012;60:27–38.
[26] Fischer MJ, Kimmel PL, Greene T, et al. Sociodemographic factors contribute to the depressive affect among African Americans with chronic kidney disease. Kidney Int 2010;77:1010–9.
[27] Palmer S, Vecchio M, Craig JC, et al. Prevalence of depression in chronic kidney disease: systematic review and meta-analysis of observational studies. Kidney Int 2013;84:179–91.
[28] Bonnet F, Irving K, Terra JL, et al. Anxiety and depression are associated with unhealthy lifestyle in patients at risk of cardiovascular disease. Atherosclerosis 2005;178:339–44.
[29] Empana JP, Sykes DH, Luc G, et al. Contributions of depressive mood and circulating inflammatory markers to coronary heart disease in healthy European men: the Prospective Epidemiological Study of Myocardial Infarction (PRIME). Circulation 2005;111:2299–305.
[30] Tisminetzky M, Gurwitz J, McManus DD, et al. Multiple chronic conditions and psychosocial limitations in patients hospitalized with an acute coronary syndrome. Am J Med 2016;129:608–14.
[31] Shi S, Liu T, Liang J, et al. Depression and risk of sudden cardiac death and arrhythmias: a meta-analysis. Psychosom Med 2017;79:153–61.
[32] Wu Q, Kling JM. Depression and the risk of myocardial infarction and coronary death: a meta-analysis of prospective cohort studies. Medicine (Baltimore) 2016;95:e2815.
[33] Black CN, Bot M, Scheffer PG, et al. Is depression associated with increased oxidative stress? A systematic review and meta-analysis. Psychoneuroendocrinology 2015;51:164–75.
[34] Andreazza AC, Kauer-Sant'anna M, Frey BN, et al. Oxidative stress markers in bipolar disorder: a meta-analysis. J Affect Disord 2008;111: 135–44.
[35] Himmelfarb J. Uremic toxicity, oxidative stress, and hemodialysis as renal replacement therapy. Semin Dial 2009;22:636–43.
[36] Schaefer F, Vogel M, Kerkhoff G, et al. Experimental uremia affects hypothalamic amino acid neurotransmitter milieu. J Am Soc Nephrol 2001;12:1218–27.
[37] Ganzini L, Smith DM, Fenn DS, et al. Depression and mortality in medically ill older adults. J Am Geriatr Soc 1997;45:307–12.
[38] Rodin G, Voshart K. Depression in the medically ill: an overview. Am J Psychiatry 1986;143:696–705.
[39] von Ammon Cavanaugh S. Depression in the medically ill. Critical issues in diagnostic assessment. Psychosomatics 1995;36:48–59.
[40] Chang JC, Yen AM, Lee CS, et al. Metabolic syndrome and the risk of suicide: a community-based integrated screening samples cohort study. Psychosom Med 2013;75:807–14.
[41] Yuan W, Pan W, Kong J, et al. 1,25-dihydroxyvitamin D3 suppresses renin gene transcription by blocking the activity of the cyclic AMP response element in the renin gene promoter. J Biol Chem 2007;282:29821–30.
[42] Batty GD, Kivimaki M, Park IS, et al. Diabetes and raised blood glucose as risk factors for future suicide: cohort study of 1 234 927 Korean men and women. J Epidemiol Community Health 2012;66:650–2.
[43] Khang YH, Kim HR, Cho SJ. Relationships of suicide ideation with cause-specific mortality in a longitudinal study of South Koreans. Suicide Life Threat Behav 2010;40:465–75.
[44] Ahn E, Shin DW, Cho SI, et al. Suicide rates and risk factors among Korean cancer patients, 1993–2005. Cancer Epidemiol Biomarkers Prev 2010;19:2097–105.
[45] Chung JH, Han CH, Park SC, et al. Suicidal ideation and suicide attempts in chronic obstructive pulmonary disease: the Korea National Health and Nutrition Examination Survey (KNHANES IV, V) from 2007–2012. NPJ Prim Care Respir Med 2014;24:14094.
[46] Chen CK, Tsai YC, Hsu HJ, et al. Depression and suicide risk in hemodialysis patients with chronic renal failure. Psychosomatics 2010;51:528–1528.e526.
[47] Keskin G, Engin E. The evaluation of depression, suicidal ideation and coping strategies in haemodialysis patients with renal failure. J Clin Nurs 2011;20:2721–32.
[48] Watkins C, Daniels L, Jack C, et al. Accuracy of a single question in screening for depression in a cohort of patients after stroke: comparative study. BMJ 2001;323:1159.
[49] Oquendo MA, Ellis SP, Greenwald S, et al. Ethnic and sex differences in suicide rates relative to major depression in the United States. Am J Psychiatry 2001;158:1652–8.