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Assessment of Depression Prevalence and Its Relation With Interleukin 18 One Year After Renal Transplantation

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Renal transplantation is the treatment of choice for many patients with end-stage renal disease. Because there is little information about depression after kidney transplantation, we investigated frequency and determinant factors of depression and also its association with interleukin (IL)-18. Kidney transplant recipients were investigated between January 2011 and February 2013. Depression was assessed using the Beck Depression Inventory (BDI, BDI-II). We investigated the relationship between 1-year posttransplantation depression and all-cause mortality, acute kidney injury, and serum creatinine 1, 3, and 12 months after transplantation. Furthermore, the association of depression with IL-18 biomarker was recorded 1 year after transplantation. A total of 74 patients (age: 37.06 ± 16.2 years; 59.5% male) were enrolled in this study 1 year after transplantation. Nineteen (25.6%), 2 (2.7%), and 1 (1.3%) of them experienced mild, moderate, and severe depression, respectively. IL-18 biomarker (independent variable) was significantly associated with depression 1 year after transplantation. Our data suggested that IL-18 level increased significantly in renal transplant patients with depression.

Keywords: depression, interleukin 18, renal transplantation

INTRODUCTION

Renal transplantation is the treatment of choice in many patients with end-stage renal disease (ESRD). Successful transplantation improves survival and the quality of life in patients and reduces mortality risk. Also, it offers emotional and psychological benefits for patients. Nonetheless, new concerns such as feeling of losing new kidney exist after transplantation. Emotional distress and psychological disorders in kidney transplant patients correlate with a compromised quality of life.[1–3]

Kidney transplant recipients are at risk for developing psychological distress and depression.[4,5] The result of a study by Dobbels et al showed that the cumulative incidence of depression was 7%, 11%, and 13% 1, 2, and 3 years after transplantation, respectively.[6] Depression is more common in waiting patients compared with transplanted patients. However, posttransplantation depression seems to be a persistent problem.[4] The identification of risk factors associated with depression in transplant recipients will help to develop appropriate protocols for screening transplant candidates and improve patients' outcomes. Various risk factors associated with the presence of depression after transplantation have been identified by previous studies. In these studies, depression increases the risk of treatment noncompliance.[7,8] In another study, it has been shown that the adverse effects of depression on noncompliant patients may lead to worse health outcome.[9] Other studies have identified various risk factors for posttransplantation depression such as

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gender,[6,10] living alone,[11] number of comorbid disorders,[5] marital status,[4,5] and type of immunosuppressive therapy.[5,6] Depression is strongly associated with an inflammatory reaction and induction of cell-mediated immunity. Stressors may activate the proinflammatory cytokine network. The proinflammatory cytokine interleukin (IL)-18 is not well studied in depression. However, it is hypothesized that IL-18 stimulates production of tumor necrosis factor-alpha and impairs synthesis of anti-inflammatory cytokines such as IL-10.[12] In previous studies, increased tumor necrosis factor-alpha levels have been detected in patients with depression.[13,14] Other studies have demonstrated that IL-10 is a key cytokine in depression, and its expression is possibly associated with an increased risk of depression.[15,16] Based on various studies, higher IL-18 level is associated with an increased susceptibility of patients to depression.[17–19] A few studies are conducted on the prevalence of depression after renal transplantation. Limited data exist regarding the relationship between depression and long-term outcomes. Dobbels et al[6] showed that a 2-fold higher risk of graft failure and death is associated with depression. Zelleet et al[20] found that depression is associated with cardiovascular problems, all-cause mortality, and decreased graft survival in renal transplant patients. Despite the high incidence of depression after transplantation, transplant guidelines do not address the screening, evaluation, or treatment of psychiatric comorbidities in end-stage renal disease (ESRD) or postgraft patients.[21]

Therefore, one of the most important issues in renal transplantation is identifying the patients at risk for depression and also the clinical factors with negative effects on long-term outcomes of renal transplant recipients. This study for the first time investigated the correlation between depression and circulating proinflammatory cytokine IL-18 1 year after transplantation. Also, association of depression with recipients' characteristics and outcomes of patients 1, 3, and 12 months after transplantation was evaluated in a large center.

METHODS

This cross-sectional study was conducted on Iranian renal transplant patients between January 2011 and February 2013. Ninety patients with ESRD who were supposed to undergo renal transplantation were enrolled in the study. The immunosuppressive regimen was similar in all patients, consisting of preoperative cyclosporine (CSA) and mycophenolate mofetil that were continued postoperatively along with prednisolone.

Inclusion and exclusion criteria

Inclusion criteria included age 18 years and older with kidney transplant from living donors. Exclusion criteria were any condition that may interfere with measuring IL-18 such as active inflammatory diseases, active infectious diseases, sepsis, sickle cell anemia, meningitis, pregnancy, cardiorenal syndrome, Cushing syndrome, multiple sclerosis, recent acute pancreatitis, hyperoxaluria, and mood disorders or schizophrenia.[22–30] Patients were excluded if they were receiving antidepressant agents. Patients who did not sign the consent form or had some problems with the interview were not included in the study.

Of 90 patients who enrolled in this study, 74 patients completed the questionnaire. The study was approved by the Ethics Committee of Shahid Beheshti University of medical sciences.

Data collection

During hospitalization

Baseline data, demographic characteristics (age, gender, and body mass index), clinical data, duration and type of dialysis before transplantation, the cause of renal failure, and delayed graft function were collected during hospitalization. Diabetes mellitus, hypertension, and glomerulonephritis were considered the leading causes of renal failure. Delayed graft function was defined as the need for dialysis in the first week after transplantation.

1 and 3 months after transplantation

The patients were followed over 1- and 3-month period after transplantation either by direct phone call or a visit in nephrology clinic. The serum creatinine levels and occurrence of acute kidney injury (AKI), graft failure or rejection, infections, adverse drug reactions (especially cyclosporine toxicity), and mortality were assessed on days 30 and 90 after transplantation.

AKI was evaluated by RIFLE criteria[31] (Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease) and renal biopsy. Graft failure or rejection was defined as a return to dialysis or retransplantation. Cyclosporine toxicity was defined as an elevated serum level >300 ng/mL for the first 3 months after transplantation. Patients with good condition did not have any of mentioned complications.

1 year after transplantation

One year after transplantation, Beck Depression Inventory (BDI) questionnaire was used to assess depression status in patients. Patients were asked to fill the questionnaire in a nephrology clinic.

The BDI is a 21-item questionnaire that measures characteristic symptoms of depression. Each item is scored between 0 and 3, and the possible total BDI score ranges from 0 to 63. The BDI was originally developed to provide a quantitative assessment of the intensity of depression. It is most commonly used by psychologists for clinical and research purpose. Validation of the BDI in Iranian population has been done by Ghassemzadeh et al.[32] We used the following cutoffs for indication of possible depression: 0–9, 10–18, 19–29, and 30–63 were considered as no, mild to moderate, moderate to severe, and severe depression, respectively.[33]

Ten-milliliter urine samples were taken for analysis. All urine samples were centrifuged at 5000 rpm for 5 minutes to remove particulate matter and cell debris, and finally stored at −70°C. Elisa kits were used for measuring urine IL-18 (Medical and Biological Laboratories, Nagoya, Japan).

Primary endpoints

Assessing the prevalence of depression 1 year after transplantation and also its association with proinflammatory cytokine IL-18 urine level.

Secondary endpoints

Clinical 30-day, 90-day, and 1-year follow-up (mortality, AKI, serum creatinine, graft failure, or rejection) was performed by an investigator through a visit in a nephrology clinic or a telephone call. Also, the correlation of depression with these clinical outcomes was evaluated.

Data analysis

Data were analyzed using SPSS for windows version 19 (SPSS Inc., Chicago, IL). A 3-stage analysis was designed to build the final model of predictors related to depression. In the first stage, normally distributed variables are expressed as mean ± SD, whereas skewed distributed variables are given as median (25th–75th percentile); percentages were used to summarize categorical variables. Log transformation was used for variables with a skewed distribution. Recipients' characteristics were separately analyzed for depression scores (0–9, 10–18, 19–29, and 30–63 for no, mild to moderate, moderate to severe, and severe depression, respectively). Differences between groups were tested for statistical significance using one-way analysis of variance for normally distributed variables, Kruskal–Wallis H test for skewed distributed variables and χ^2 test for categorical variables. In the second stage, all covariates from last stage with $P < 0.1$ were evaluated in an ordinal logistic analysis. Any collinearity between variables selected in the first stage was assessed and significant interactions were considered to be included in the analysis. At the end stage, selected risk factors and their significant interactions were entered into an ordinal logistic regression for the final model building to indentify explanatory factors of depression. A P value <0.05 was considered statistically significant.

RESULTS

We investigated a total of 90 renal transplant recipients with mean age of 36.75 ± 16.59 years (55.6% male and 44.4% female). There are no data for depressed patients who died after 1 year, patients who we did not have access for completing the questionnaire and those who were taking antidepressant agents (16 of 90 patients) 1 year after transplantation. Finally, 74 patients were analyzed for depression. The median depression score in renal transplant recipients was 7 (25th–75th percentile; 4–10). According to BDI definitions, 52 (70.2%) patients did not have depression and 19 (25.6%), 2 (2.7%), and 1 (1.3%) patients had mild, moderate, and severe depression, respectively. Among recipients, 59 (79.7%) patients were using CSA, 74 (100%) patients were taking prednisolone, 71 (95.9%) patients were using mycophenolate mofetil, 12 (16.2%) patients were taking tacrolimus, and 3 patients (4%) were using sirolimus in last follow-up. Baseline characteristics of patients according to 4 groups of depression scores are shown in Table 1. The correlations between patients' depression scores and demographic and clinical variables are shown in Table 1. During follow-up period (1, 3, and 12 months after transplantation), 0, 0, and 4 (4.4%) recipients died, respectively. We found a significant positive correlation between depression and urine IL-18 level, 1 year after transplantation. Independent variables associated with depression are shown in Table 2. When we performed analysis, the BDI score was not significantly correlated with patients' demographic and clinical variables. Also, there was not statistically significant association between depression and clinical follow-up.

DISCUSSION

In this study, we showed that the prevalence of depression after renal transplantation is 29.7%. Similar to our finding, in previous studies, 22%–39% of kidney transplant recipients reported depressive symptoms according to the BDI.[4] In comparison with our study, in a study by Dobbels et al[6] on 47,899 patients, much lower rate of depression was reported (9%–13%)

Table 1. Baseline characteristics according to groups of depression score.

General characteristics	Depression score				*P*
	Normal	Mild depression	Moderate depression	Severe depression	
Age (yrs), mean ± SD	35.82 ± 17.43	35.73 ± 10.85	50.5 ± 2.12	56	0.36
Sex (male), n (%)	33 (44.6)	9 (12.2)	2 (2.7)	0	0.14
BMI (kg/m^2), mean ± SD	23.53 ± 4.37	25.26 ± 4.66	25.74 ± 3.67	29.29	0.29
Dialysis duration before transplantation, mo	13.28 ± 16.08	6.42 ± 4.43	9.5 ± 7.77	7	0.32
Dialysis type, n (%)					
No	13 (17.6)	1 (1.4)	1 (1.4)	1 (1.4)	
HD	37 (50.0)	16 (21.6)	1 (1.4)	0	
PD	2 (2.7)	2 (2.7)	0	0	0.17
Familial relation, No (%)	47 (63.5)	19 (25.7)	2 (2.7)	1 (1.4)	0.98
Familial relation, Yes (%)	5 (6.8)	0	0	0	
Serum creatinine at baseline (mean ± SD)	9.8 (7.3–12.6)	9.7 (8.2–14)	12.53	—	0.25
Serum creatinine (1 mo)	1 (1.3–1.5)	1.4 (1.2–1.6)	1.75	—	0.10
Serum creatinine (3 mo)	1.3 (1–1.4)	1.3 (1.15–1.6)	1.45	—	0.84
Serum creatinine (2 yrs)	1.2 ± 0.289	1.194 ± 0.229	1.25 ± 0.07	—	0.72
Residual diuresis (UO), n (%)					0.32
<50	12 (16.9)	5 (7)	1 (1.4)	0	
50–500	7 (9.9)	6 (8.5)	1 (1.4)	0	
500–1000	15 (21.1)	2 (2.8)	0	0	
>1000	16 (22.5)	5 (7)	0	1 (1.4)	
No. previous transplants					
First transplant (%)	49 (66.2)	17 (23.0)	2 (2.7)	1 (1.4)	0.83
Retransplant (%)	3 (4.1)	2 (2.7)	0	0	
Underlying disease, n (%)					0.84
HTN	22 (29.7)	8 (10.8)	1 (1.4)	1 (1.4)	
DM	9 (12.2)	2 (2.7)	0	0	
GN	8 (10.8)	4 (5.4)	0	0	
Others	13 (17.6)	5 (6.8)	1 (1.4)	0	
DGF (yes)	9 (12.2)	3 (4.1)	0	0	0.77
First follow-up event, n (%)					
Good	29 (41.4)	9 (12.9)	1 (1.4)	1 (1.4)	0.81
Cyclosporine toxicity	9 (12.9)	1 (1.4)	0	0	
CMV	4 (5.7)	3 (4.3)	0	0	
VZV	0	1 (1.4)	0	0	
Rejection	3 (4.3)	2 (2.9)	1 (1.4)	0	
CMV + rejection	2 (2.9)	2 (2.9)	0	0	
VZV + rejection	2 (2.9)	0	0	0	
Second follow-up event, n (%)					0.97
Good	32 (46.4)	12 (17.4)	1 (1.4)	1 (1.4)	
Cyclosporine toxicity	4 (5.8)	1 (1.4)	1 (1.4)	0	
CMV	6 (8.7)	3 (4.3)	0	0	
VZV	1 (1.4)	0	0	0	

(*Continued on next page*)

Table 1. (*Continued*) Baseline characteristics according to groups of depression score.

General characteristics	Depression score				*P*
	Normal	Mild depression	Moderate depression	Severe depression	
Rejection	2 (2.9)	1 (1.4)	0	0	
CMV + rejection	3 (4.3)	1 (1.4)	0	0	
2-yr follow-up event, n (%)					0.99
Good	34 (45.9)	14 (18.9)	2 (2.7)	1 (1.4)	
Cyclosporine toxicity	1 (1.4)	1 (1.4)	0	0	
CMV	15 (20.3)	4 (5.4)	0	0	
Retransplant	1 (1.4)	0	0	0	
Thrombosis	1 (1.4)	0	0	0	
IL-18	13.79 (11.26–22.11)	16.51 (11.46–18.84)	14.96 (14.18–14.96)	—	0.07

BMI, body mass index; cyclosporine toxicity was defined as an elevated serum level >300 ng/mL for the first 3 months after transplantation; CMV, Cytomegalovirus infection; DGF, delayed graft function; DM, diabetes mellitus; GN, glomerulonephritis; HTN, hypertension; PD, peritoneal dialysis; R/D, recipient/donor; rejection, rejection or graft failure was defined as a return to dialysis or retransplantation; VZV, Varicella zoster virus; normal data, mean ± SD; no normal data: median (25%–75%).

3 years after transplantation. The authors of this study claimed that the real prevalence of post transplantation depression has been probably underestimated.[6] Urine IL-18 level was an important independent variable positively associated with depression, 1 year after transplantation. So in this study, higher urine IL-18 levels are associated with depression in post-transplanted patients. IL-18 is a proinflammatory cytokine and a new member of the IL-1 family that has been found elevated in depressed patients[18,19] and also in depression after stroke.[34] In a study by Prossin et al,[35] IL-18 elevation was observed in depressed patients. This finding is consistent with previous studies showing proinflammatory cytokine elevation in depressed patients.[36] Russo et al[37] hypothesized that tryptophan plays a role in psychopathology states. In line with this, results from another study showed that even mild degrees of renal insufficiencies are related to chronic low-grade inflammation. Chronic inflammation might lead to a higher activity of indoleamine 2,3-dioxygenase (IDO), resulting in insufficient tryptophan level, necessary for serotonin formation. All of them are involved in depression.[38] A markedly elevated IL-18 level has been observed in patients with ESRD,[39] which could predict outcomes in hemodialysis (HD) patients.[40] Elevated serum concentrations of inflammatory cytokines are common in patients undergoing HD. However, the mechanisms underlying this phenomenon remain controversial.[41] Also, in a study by Merendino et al,[18] IL-18 level in moderate–severe depressed patients were significantly higher than healthy subjects. Elevation of IL-18 level was also found in other psychiatric disorders such as schizophrenia and panic disorder.[19] In a study in 2012, researchers found that stress-related high IL-18 production may contribute to depression. A genetic disposition to a high IL-18 production may increase the susceptibility of patients to depression.[17] IL-18 may be classified as a general psychological stress-associated marker. Here, we found for the first time that higher urinary IL-18 concentration was related to depression in transplanted subjects. This is consistent with previous studies that suggested a correlation between IL-18 with depression in some population. Mechanisms underlying the relationship between depression and poor clinical outcomes are unclear. In a study by Dobbles et al,[6] depression was suggested to be one of the causes of poor outcomes or acute rejection and poor graft function in transplanted patients. Several theoretical reasons may explain why depression could cause poor outcomes after kidney transplantation. Cardiovascular disease (CVD) is the leading cause of death after transplantation. Also, depression is associated with systemic inflammation that may contribute to CVD.[42–44] Depression is also associated with cigarette smoking and a more sedentary lifestyle, both of which are risk factors for CVD.

Table 2. Independent determinants of depression.

	EXP (B) (95% CI)	*P*
IL-18 biomarker after transplantation	0.331 (0.024–0.638)	0.035

CI, confidence interval.

Furthermore, depression may increase platelet adhesion that may lead to both CVD and kidney allograft failure.[44] Also, the results of a large systematic review showed that there is a relationship between depression and increased risk for CVD.[45] In most clinics, an active screening program for depression after transplantation has not been used yet. Therefore, diagnosis of depression by clinical criteria or related biomarkers even earlier than clinical symptoms can be an important point in reducing morbidity and improving therapeutic outcomes in transplanted patients. Posttransplantation depression is likely underdiagnosed and undertreated. Consequently, screening programs for depression among kidney transplanted patients could be beneficial in this high-risk population.

However, our study has some limitations. First, this study is based on a single measurement design. It is possible that depressive symptoms could have changed over time. Next, pretransplant information on depression is not available in this study. Also, multiple assessments of depression and pretransplant information on depressive symptoms would have strengthened our results. Despite these limitations, our study has important implications for clinical practice.

In conclusion we identified IL-18 as an independent predictor of depressive symptoms in kidney transplant recipients. Furthermore, based on these finding, identification of this factor may reduce prevalence of depression in renal transplanted patients. Since improving depressive symptoms could contribute to improved survival in these patients, additional studies on detection of inflammatory cytokines after renal transplantation are needed.

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