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Impact of Depression on Long-Term Outcome After Renal Transplantation: A Prospective Cohort Study

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Background. Renal transplantation is the treatment of choice for end stage renal disease. Although there is more depression in wait-listed versus transplant patients, depression persists after transplantation. We investigated the determinants of depression in renal transplantation recipients (RTRs) and the association with cardiovascular (CV) and all-cause-mortality and graft failure.

Methods. RTR were investigated between 2001 and 2003. Depression was assessed using the Depression Subscale of the Symptom Checklist (SCL-90). Mortality and graft failure were recorded until May 2009.

Results. A total of 527 RTR (age, 51±12 years; 55% men) were studied; 31% of the RTR were indicated with depression. Independent variables associated with depression were medically unfit for work, proteinuria, lower physical activity level, and longer dialysis duration. During follow-up for 7.0 (6.2–7.5) years, 114 RTR (59 CV) died. In Cox regression analyses, depression was strongly associated with increased risk for CV (HR=2.12 [1.27–3.53], P=0.004) and all-cause mortality (HR=1.96 [1.36–2.84], P<0.001). Adjustments for confounders did not materially change these associations. The association with graft failure (HR=1.77 [1.01–3.10]. P=0.047) disappeared after adjustment for kidney function (P=0.6).

Conclusions. Although our study has several limitations, including the lack of pretransplant depression status, we identified medically unfit for work, proteinuria, lower physical activity level, and longer dialysis duration as independent variables associated with depression. We furthermore found that depression is associated with CV and all-cause mortality in RTR.

Keywords: Depression, All-cause mortality, Cardiovascular mortality, Graft failure.

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Transplantation is the preferred treatment in end-stage renal disease (ESRD). Compared with maintenance dialysis, it offers significant survival advantage and brings emotional and psychological benefits to patients. On the other hand, it also introduces new concerns such as fear of losing the new kidney and complications that may lead to emotional distress (*1–3*). Although there is more depression in wait-listed versus transplant patients, depression seems to be a persistent problem after transplantation (*4*).

Research among individuals with chronic medical conditions, such as type 2 diabetes and coronary artery disease, shows that depressed patients have increased mortality compared with their nondepressed counterparts (*5–9*). Various studies have shown that depression is common among patients on dialysis, with a prevalence of depression ranging from 5 to as high as 71% (*10*), depending on the study population and method of diagnosis. We also know that depression has been associated with increased morbidity and mortality in ESRD (*11, 12*).

There is only limited data about the prevalence of depression after renal transplantation, and few studies were done on the relation of depression with long-term outcome. Dobbels et al. (*13*) show that depression is associated with a twofold greater risk of graft failure and death. Novak et al. (*14*) show that mortality in patients with depression after kidney transplantation was higher than in patients without depression. No data are available about the risk of cardiovascular mortality in RTR in relation to depression. Early

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TABLE 1. Baseline characteristics according to groups of depression score

	Depression score (SCL-90)		
	No-depression: score <25 (n=366)	**Possible depression: score >25 (n=161)**	***P***
General characteristics			
Age (yr)	51.16±11.85	51.38±12.03	0.84
Sex (male), n (%)	209 (57)	81 (50)	0.15
Living alone, n (%)	56 (15)	32 (20)	0.21
Employment status			
Paid employment	139 (39)	126 (21)	<0.001
Medically unfit for work, n (%)	80 (22)	68 (42)	<0.001
Unemployed, n (%)	70 (20)	23 (14)	0.16
Retired, n (%)	30 (8)	15 (9)	0.7
Unspecified, n (%)	34 (9)	16 (10)	0.85
Lifestyle			
Metabolic Syndrome, n (%)	242 (66)	101 (63)	0.45
Physical activity (METS)	147.82 (37.08–345.17)	90.15 (8.36–227.30)	<0.001
Smoking			
- In the past, n (%)	152 (42)	74 (46)	0.34
- Currently, n (%)	79 (22)	41 (26)	0.33
Alcohol consumption			
- Abstainers, n (%)	170 (46)	75 (47)	0.96
- <10 g/d, n (%)	140 (38)	64 (40)	0.80
- 10–30 g/d, n (%)	51 (14)	18 (11)	0.37
- >30 g/d, n (%)	2 (1)	4 (3)	0.06
Body composition			
Body mass index (kg/m^2)	26.23±4.29	25.81±4.40	0.31
Waist circumference (cm) women	94.23±14.21	93.35±15.68	0.67
Waist circumference (cm) men	100.49±12.74	98.92±12.20	0.34
Urinary creatinine excretion (mmol/24 hr)	11.85 (9.73–14.58)	11.70 (8.85–13.95)	0.05
History of cardiovascular disease			
Myocardial infarction, n (%)	27 (7)	12 (8)	0.22
CVD event, n (%)	54 (15)	28 (17)	0.44
Antidepressant use			
Selective serotonin re-uptake inhibitors n (%)	7 (2)	12 (7)	0.002
Tricyclic antidepressants n (%)	3 (1)	1 (1)	0.8
Benzodiazepines n (%)	14 (4)	25 (16)	<0.001
Vitamin D status			
25(OH)D (nmol/L)	51.4 (37.5–68.9)	47.4 (35.4–67.2)	0.21
Hemoglobin level			
Hemoglobin (mmol/L)	8.7 (8.1–9.3)	8.4 (7.7–9.2)	0.03
Blood pressure			
Systolic blood pressure (mmHg)	152.75±22.52	154.70±23.62	0.36
Diastolic blood pressure (mmHg)	90.14±9.81	89.94±9.81	0.84
Antihypertensive medication, n (%)	339 (93)	149 (93)	0.98
Use of ACE inhibitor, n (%)	139 (38)	46 (29)	0.04
Use of β-blocker, n (%)	230 (63)	99 (62)	0.77
Lipids and inflammation			
Total cholesterol (mmol/L)	5.64±1.14	5.61±1.04	0.76
HDL-cholesterol (mmol/L)	1.09±0.33	1.11±0.31	0.55
Low-density lipoprotein cholesterol (mmol/L)	3.57±1.07	3.56±0.88	0.91
Triglycerides (mmol/L)	1.92 (1.42–2.61)	1.89 (1.39–2.64)	0.59
hsCRP (mg/L)	2.13 (0.93–4.60)	2.64 (0.77–7.46)	0.30

(Continued on next page)

TABLE 1. *(Continued)*

	Depression score (SCL-90)		
	No-depression: score <25 (n=366)	**Possible depression: score >25 (n=161)**	***P***
Glucose homeostasis			
Glucose (mmol/L)	4.88±1.38	4.83±1.42	0.71
Insulin (μmol/L)	11.4 (4.80–16.33)	10.9 (7.90–14.75)	0.61
Diabetes mellitus, n (%)	66 (18)	28 (17)	0.86
Renal function			
Serum creatinine (μmol/L)	132 (111.75–167.00)	137 (114–169.5)	0.24
Creatinine clearance (mL/min)	62 (49–79)	57 (42–75)	<0.01
Urinary protein excretion (g/24 h)	0.2 (0.00–0.50)	0.3 (0.00–0.60)	0.11
Proteinuria ≥0.5 g/24 h, n (%)	92 (25)	60 (37)	0.01
Transplantation and history			
Dialysis duration (mo)	25 (12–45.25)	31 (17–56)	<0.01
Living donor, n (%)	61 (17)	14 (9)	0.02
Time since transplantation (yr)	5.81 (2.51–11.10)	6.52 (2.82–12.20)	0.53
Number of previous transplants			
- 0, n (%)	331 (90)	137 (85)	0.07
- 1 or more, n (%)	35 (10)	24 (15)	
Acute rejection, n (%)	163 (45)	74 (46)	0.76
Immunosuppression			
Prednisolone dose, mg/d	9.17±1.33	9.29±1.21	0.59
Calcineurine inhibitor, n (%)	287 (78)	125 (78)	0.84
Proliferation inhibitor, n (%)	270 (74)	121 (75)	0.74
Tacrolimus (trough level, ug/L)	8.64±2.76	8.64±5.31	0.99
Cyclosporine (trough level, ug/L)	114.10±47.98	112.99±46.42	0.85

Data are represented as mean±SD, or median (95% CI). Differences were tested by *t* test or Kruskal-Wallis test for continuous variables and with chi-square for categorical variables.

identification of patients at risk is hampered by the lack of knowledge about the determinants of depression in RTR. Therefore, recipient-related factors, such as proteinuria, blood pressure, and lifestyle factors, need to be explored for their potential association with depression (*12–14*).

We hypothesize, first, that there is a high prevalence of depression in RTR and, second, that symptoms of depression may lead to a worse survival and graft failure, the former possibly attributable to cardiovascular disease. To study these hypotheses, we investigated several recipient-related factors for their association with depression in RTR in a large single-center cohort. We furthermore aimed to investigate whether symptoms of depression are associated with cardiovascular and all-cause mortality and graft survival.

RESULTS

A total 527 RTRs (mean age, 51±12 years; 55% male subjects) participated at median time of 6.0 (2.6–11.4) years posttransplant. The median SCL-90 score on depression in the RTR was 21 [25th–75th percentile; 18–26]; 31% (n=161) of the RTR scored above the cutoff score of 25 and were categorized as depressed (median SCL-90 score 30 [27–39]). Baseline characteristics of the RTR according to the two groups of depression score are shown in Table 1. Depressed RTR had significantly lower physical activity level, urinary creatinine excretion, hemoglobin levels, ACE inhibitor intake, and creatinine clearance; had less often paid employment; and had less often a living donor. Depressed patients also were more often medically unfit for work, had more often proteinuria, had a longer history of dialysis, and used more often antidepressant medication. Use of SSRIs or TCAs in the total population was 4%.

Independent variables associated with depression in RTR are shown in Table 2. Medically unfit for work, proteinuria, low physical activity level, and longer previous dialysis duration were the most important independent determinants of depression in a logistic regression analysis.

During median follow-up for 7.0 [6.2–7.5] years, 114 recipients died, with 59 deaths being cardiovascular (CV)

TABLE 2. Independent determinants of depression

Multivariable	**Exp(B) (95% CI)**	***P***
Medically unfit for work	2.48 (1.52–4.04)	<0.001
Proteinuria (≥0.5 g/24 hr)	2.18 (1.34–3.53)	0.002
Physical activity (200 METS)	0.65 (0.44–0.98)	0.039
Dialysis duration (yr)	1.08 (1.01–1.15)	0.028

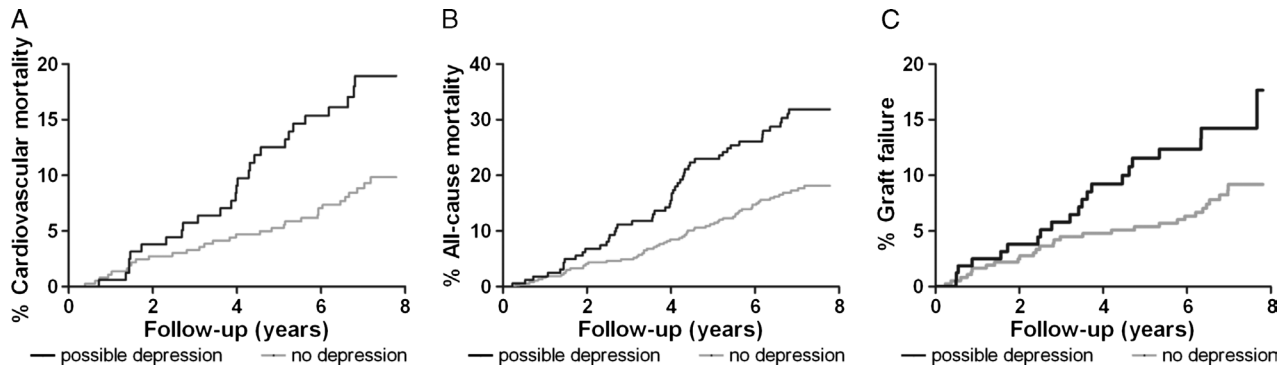

FIGURE 1. A, Kaplan-Meier curve of cardiovascular mortality according to depression score groups tested with Log-rank test ($P<0.001$).B, Kaplan-Meier curve of all-cause mortality according to depression score groups tested with Log-rank test ($P=0.004$). C, Kaplan-Meier curve of graft failure according to depression score groups tested with Log-rank test ($P=0.04$).

in origin. PTA was performed twice (3%), PTCA was performed once (2%), and CABG was performed in 3 (5%) RTR. Cardiovascular mortality was significantly increased in the depression group as compared with the no-depression group (27 [17%] vs 32 [9%], respectively $P=0.004$; Fig. 1A). The same was found for all-cause mortality, with respective numbers of 64 (18%) and 50 (31%) ($P<0.001$, Fig. 1B).

Results of the Cox regression analyses for the association of depression with cardiovascular (CV) and all-cause mortality are shown in Table 3. Depression was strongly associated with increased risk for CV mortality and all-cause mortality (model 1). These associations were independent of age and gender (model 2). Adjustment for dialysis duration (model 3), creatinine clearance and proteinuria (model 4), hemoglobin levels (model 5), physical activity level (model 6), and medically unfit for work (model 7) did not materially change the association.

During median follow-up for 7.0 (6.2–7.5) years, a total of 50 (9%) RTR experienced graft failure necessitating return to dialysis. In the no-depression group, 29 (8%) of the RTR experienced graft failure compared with 21 (13%) in the possible depression group ($P=0.04$, Fig. 1C). Results of Cox regression for depression and graft failure are shown in Table 4. Depression was associated with a higher risk for graft failure. After adjustments for proteinuria and creatinine clearance, the relationship disappeared.

DISCUSSION

In this study, we showed that the prevalence of depression after transplantation is high. Important independent variables associated with depression were medically unfit for work, proteinuria, low physical activity, and longer dialysis duration. Furthermore, we showed that depression was associated with CV, all-cause mortality, and graft failure in RTR.

In our study, 31% RTR were categorized as depressed based on the depression cutoff score of the SCL-90 questionnaire. This number of occurrence is higher than that in the general population (15.9%) (*15*) but comparable with other studies, which were also based on self-reported depressive symptoms (*14, 16, 17*). The large study by Dobbels et al. (*13*) in patients from the United States Renal Data System reported a much lower prevalence of 9% to 13%,

TABLE 3. Depression is associated with cardiovascular and all-cause mortality

	Cardiovascular mortality ($n=59$)			All-cause mortality ($n=134$)		
Model	No depression Reference	Possible depression HR (95% CI)	*P*	No depression Reference	Possible depression HR (95% CI)	*P*
1	1.0	2.12 (1.27–3.53)	0.004	1.0	1.96 (1.36–2.84)	<0.001
2	1.0	2.06 (1.23–3.45)	0.006	1.0	1.92 (1.33–2.79)	0.001
3	1.0	1.94 (1.16–3.26)	0.012	1.0	1.89 (1.30–2.74)	0.001
4	1.0	1.84 (1.09–3.11)	0.022	1.0	1.74 (1.19–2.55)	0.004
5	1.0	1.85 (1.09–3.12)	0.022	1.0	1.74 (1.19–2.54)	0.005
6	1.0	1.82 (1.07–3.09)	0.026	1.0	1.73 (1.18–2.54)	0.005
7	1.0	1.73 (1.01–2.94)	0.045	1.0	1.61 (1.09–2.37)	0.016

Model 1: crude model. Model 2: model 1 + adjustment for age and gender. Model 3: model 2 + adjustment for dialysis duration (months) Model 4: model 3 creatinine clearance and for proteinuria (≥0.5 g/24 hr) Model 5: Model 4 + adjustment for hemoglobin. Model 6: model 4 + adjustment for physical activity. Model 7: model 4 + adjustment for medically unfit for work.

TABLE 4. Association between depression and graft failure disappears after adjustment for kidney function

		Graft failure (n=50)	
Model	No depression Reference	Possible depression HR (95% CI)	*P*
1	1.0	1.77 (1.01–3.10)	0.047
2	1.0	1.82 (1.04–3.20)	0.037
3	1.0	1.93 (1.09–3.41)	0.024
4	1.0	1.19 (0.66–2.11)	0.6

Model 1: crude model. Model 2: model 1 + adjustment for age and gender. Model 3: model 2 + adjustment for dialysis duration (months). Model 4: model 3 + adjustment for proteinuria (≥0.5 g/24 hr) and creatinine clearance.

3 years after transplantation. In that study, diagnoses of depression were based on Medicare claims, which, as the authors say, probably underestimate the real prevalence of depression after renal transplantation (*13*).

We identified several important independent variables associated with depression after renal transplantation. In our study, medically unfit for work is the strongest independent variable associated with depression. Medically unfit for work can be the consequence of a bad physical health, leading to more depressive symptoms. The other way around, depression can lead to a bad physical health, which can lead to being unable to work. Proteinuria was the second strongest independent variable associated with depression. The burden of disease in these patients is higher, which gives more psychological distress and a higher risk for depression. Twenty-four hours of protein excretion was only retained in the final model of determinants of depression if it was included as a dichotomized variable with proteinuria defined as 0.5 g/24 h or greater, indicating that risk is particularly present in the high end of the distribution of 24 h protein excretion. Physical activity is also strongly associated with depression. Depression can negatively influence lifestyle behaviors like physical activity, which would add to risk consequences of low physical activity that is already present in RTR (*18*). We found that longer dialysis duration is a factor that is related to possible depression. Renal transplantation recipients with a longer duration of dialysis have a longer history of chronic kidney disease, increasing the risk for comorbidity and mortality (*19*). These findings are in line with the notion that depression can be caused by psychological distress from a higher burden of disease.

Besides these important variables described above, we know from the literature that immunosuppressive medication could also influence depression (*20*). In the general population, use of corticosteroids is associated with depression (*20*). Brown et al. (*21*) show that the risk for depression seems to increase with higher corticosteroid doses. It is, however, difficult to determine whether depression is caused by steroidal treatment or by a higher burden of disease. In our study, however, we did not find a relationship between corticosteroids and depression. This may be the consequence of low variation in steroid doses in the population we investigated, which did not allow for us finding such a relationship. Tryptophan metabolism may provide a link between renal function and depression. Rosso et al. (*22*) hypothesized about the role of tryptophan in psychopathology and somatic states. Even mild degrees of renal insufficiency as often encountered in RTR are associated with chronic low-grade inflammation. Chronic inflammation in turn leads to a high activity of indoleamine 2,3-dioxygenase (IDO), resulting in low tryptophan levels, with insufficient amounts for the formation of serotonin, resulting in depression (*23*). In line with this, Pawlak et al. (*24*) showed that dialyzed patients have significantly lower tryptophan than controls. Further research is needed to explore whether this mechanism plays a role in RTR.

The association of depression with mortality and graft failure could have been confounded by comorbidity or a complex recovery after transplantation. Several chronic illnesses are associated with psychiatric comorbidity. Noohi et al. (*25*) found an increased morbidity among depressed RTR, compared with nondepressed RTR. Renal transplantation recipients with proteinuria are at higher risk for graft failure, comorbidity, and mortality (*26*). Patients with low GFR may have an increased physical symptom burden (*27*). In our Cox regression analyses for CV and all-cause mortality, we therefore adjusted for creatinine clearance and for proteinuria. Upon these analysis, hazard ratio for all-cause mortality decreased from 1.89 (1.30–2.74) to 1.74 (1.19–2.55), remaining significant. Showing that creatinine clearance and proteinuria only explain a very small part of the association. The relationship between depression and graft failure was confounded by a deterioration of kidney function. Another potential confounder of the association of depression with mortality in RTR could be dialysis duration. Longer dialysis duration means that patients are longer exposed to the chronic effects of end-stage renal failure and dialysis treatment. Dialysis treatment is associated with altered inflammatory state, altered immunologic function and acceleration of atherosclerosis (*28–30*). Previous studies showed that dialysis duration was associated with risk for mortality and graft failure in RTR (*19, 31*). In our study, dialysis duration was strongly associated with symptoms of depression. This is in line with the study of Dobbels et al. (*13*), in which patients with high depressive symptoms had significant longer dialysis duration, compared with patients with moderate or low depressive symptoms. Although we found that dialysis duration was related to depression, it was not significant in the Cox regression analysis. As hemoglobin level is an important risk factor for outcome in RTR, we additionally adjusted for hemoglobin levels (*32*); this adjustment did not change the results. We previously showed that low physical activity is a risk factor for mortality in RTR (*18, 33*); therefore, we adjusted for physical activity in our analysis. Upon this analysis, physical activity level did explain a small part of the association. Unfit for work refers to the status that RTR are physically or mentally unfit for work, which can be a result of a long history of chronic kidney disease and transplantation with possible complications, together representing a substantial overall burden of disease. Adjustment for this confounder showed that part of the association was explained by medically unfit for work. Although we adjusted for all potential confounders, residual confounding could not be ruled out.

There are several pathways that could explain the relationship between symptoms of depression and mortality. Depression could be a result of a long history of chronic kidney disease and transplantation with possible complications, together representing a substantial overall burden of disease. We will distinguish between biological, lifestyle, and psychosocial factors to describe the possible mechanisms that could explain the relationship between depression and outcome after renal transplantation. Results from a large systematic review showed that there is a link between depression and increased risk for cardiovascular disease (*34*). This is in line with our study, were cardiovascular mortality is strongly associated with depression. Research into possible mechanisms of depression in cardiovascular disease shows that much of the association remains unclear because of the complexity of the network of systems involved (*35*). Lifestyle factors are important factors in the association between depression and mortality. In our study, depressive symptoms were associated with an unhealthy lifestyle. Renal transplantation recipients with more depressive symptoms had significantly lower physical activity levels and were more likely to consume more than three alcoholic drinks per day. These unhealthy lifestyle behaviors may directly or indirectly lead to mortality. We previously showed that low physical activity was a strong independent predictor for CV and all-cause mortality in RTR (*18*). Whereas moderate alcohol consumption is protective in RTR, alcohol dependence before transplantation is related to mortality and graft failure (*36*). Lifestyle factors are modifiable, which offers an opportunity for intervention toward a healthier lifestyle in RTR.

Psychosocial factors might modulate the relationship between depressive symptoms and mortality. A potential cause of death in patients with high depressive symptoms relates to compliance with therapy. DiMatteo et al. (*37*) showed that depressed patients had a threefold greater risk of nonadherence behavior. Depressive symptoms like feelings of hopelessness and difficulties with memory may result in behaviors that include forgetting to take pills or missing regular follow-up appointments (*37*). In kidney and pancreas transplantation patients and patients with coronary artery disease, noncompliance with therapy adversely affects the recovery and subsequent life (*38–40*). In our study, however, we did not find any differences in trough levels of tacrolimus and cyclosporine.

In most clinics, there is no active screening program for depression after transplantation. Based on the low antidepressant use in our study (4 %), depression after renal transplantation is presumably under diagnosed and under treated. Screening for depression in RTR could therefore be useful in this high-risk population. Further research is needed to develop and evaluate these screening programs and consequently apply existing interventions studies targeting depression. Perceived control could be an important target for intervention in managing the high stress levels in the recovery after transplantation. Cukor et al. (*41*) found that transplantation recipients who had better perceived control over their outcome had decreased levels of depression, compared with patients who attributed their health outcome to chance. In this respect, self-management is important. Self-management strategies should be stimulated and guided by the health-care professionals and can be incorporated in the health-care treatment plan. Self-management strategies can be used to target behaviors like: exercise, diet, smoking, and adherence to medication.

A strength of our study is its prospective design. Renal transplantation recipients in this study were closely monitored by regular check-up in our clinic, which allows for extensive information gathering on patients status.

We furthermore assessed depression using the Depression Subscales of SCL-90. This subscale measures only psychological depressive symptoms and no somatic symptoms of depression. This makes the depression subscale more suitable for measuring depression in RTR. Some depression questionnaires do not distinguish between depressive and somatic symptoms, which can lead to unreliable results in patients with chronic disease.

Some methodological topics warrant consideration. First, we used a self-report questionnaire for measuring depression, which is informative but does not replace diagnosis of depression by psychiatric clinical assessment according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition,* criteria for major or minor depression. Nevertheless, questionnaires are valuable screening instruments for depressive symptoms in large epidemiological studies, and the questionnaire was validated against the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition,* criteria for major or minor depression, in stroke patients (*42*). It remains unclear, however, whether the validation of the cutoff values in stroke patients, 1 month after they experienced their first-ever ischemic stroke, may be of influence on the classification of depression in RTR (*42*). In a sensitivity analysis (data not published), the use of the depression score as a continuous variable were comparable to the findings of depression assessed with cutoff values. Next, this study is based on a single measurement design; it is possible that depressive symptoms could have changed over time. Pretransplant information on depression is not available in this study. Multiple measurements of depression and pretransplant information on depressive symptoms would have strengthened our results. Information on psychotherapy was unavailable in this study. Moreover, this study is observational in design, and thus, conclusions on causality cannot be drawn. Multiple measurements of depression would have strengthened our results. Also, no information was available on the use of antidepressant agents.

In summary, depression is a condition that is very common among RTR. Independent risk factors for depression were medically unfit for work, proteinuria, lower physical activity level, and longer dialysis duration. Our data show that depression after kidney transplantation is a serious condition associated with reduced patient and graft survival. Based on the association between symptoms of depression and mortality, it is tempting to speculate that reduction of depressive symptoms could contribute to improved survival in RTR. Additional studies on detection and treatment of depression after renal transplantation are needed.

MATERIALS AND METHODS

Design and Subjects

Study design and inclusion/exclusion criteria have been described previously (*18*). In brief, for this prospective cohort study, all adult allograft

recipients between August 2001 and July 2003 who survived with a functioning allograft beyond the first year after transplantation were eligible to participate at their next visit to the outpatient clinic. A total of 606 RTR signed written informed consent, from an eligible 847. Data on depression were available in 527 RTR. Baseline data were collected between August 2001 and July 2003, and RTR were followed for several years. The institutional review board approved the study protocol.

End Points of the Study

The primary end points of this study were recipient mortality and graft failure. Graft failure was defined as a return to dialysis or retransplantation. The continuous surveillance system of the outpatient program ensures up-to-date information on patient status and cause of death. We contacted general practitioners or referring nephrologists if the status of a patient was unknown. For this study, we used follow-up data for mortality and graft loss, recorded until May 2009.

We also collected follow-up data on percutaneous transluminal angioplasty (PTA), percutaneous transluminal coronary angioplasty (PTCA) and coronary artery bypass grafting (CABG). Cause of death was obtained by linking the number of the death certificate to the primary cause of death as coded by a physician from the Central Bureau of Statistics. Causes of death were coded according to the International Classification of Diseases, 9th revision (ICD-9) (*43*).

Renal Transplant Characteristics

The Groningen Renal Transplant Database contains information on all renal transplantations performed at our center since 1968. Relevant transplant characteristics such as age, gender, and date of transplantation were extracted from this database. Current medication was taken from the medical record. Standard immunosuppressive treatment was described previously (*44*). Information on employment status, living situation, smoking and alcohol consumption, and cardiovascular history were obtained by self-report questionnaire.

Depression

Quantitative information on depression was obtained by the Depression Subscales of the Symptom Checklist (SCL-90). The SCL-90 is the screening instrument most commonly used by psychologists in clinical practice as well as in research settings in the Netherlands (*45*). The SCL-90 is widely used as an outcome measure in intervention studies and as a screening instrument in both psychiatric and medical patients for clinical and research purposes (*46–48*). SCL-90 is designed to measure a broad range of psychological problems and symptoms of psychopathology and has shown to have good psychometric properties (*49, 50*). The SCL-90 depression subscale measures the typical symptoms of depression; dysphoric mood, signs of withdrawal of life interest, lack of motivation, and loss of vital energy. Feelings of hopelessness and thoughts of suicide are also included in the depression subscale. The SCL-90 depression subscale was administered once in all RTR between August 2001 and July 2003. In the depression subscale, patients are asked to indicate on a five-point scale how much hindrance they experienced from psychiatric complaints in the last week. The depression subscale measures only psychological depressive symptoms and no somatic symptoms of depression. The depression subscale was validated in patients who experienced their first-ever ischemic stroke. The C-statistic of the SCL-90 depression subscale was 0.81 (*42*). For the indication of possible depression, we used a cutoff score of 25 on the depression subscale. Sensitivity and specificity of this threshold were 88.5 and 60.7, respectively (*42*).

Measurements and Definitions

Physical activity was assessed using validated questionnaires (*18*). Single imputation was used to obtain more complete data on physical activity. Body mass index, waist circumference, and blood pressure were measured as described previously (*18*).

Blood was drawn after an overnight fasting period, which included no intake of medication. Total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, serum triglycerides, glucose, insulin, 24-hour creatinine excretion as a measure for muscle mass (*51*), serum and urine creatinine concentration were measured as described previously (*18*); 25-hydroxyvitamin D3 levels were determined using isotope dilution–online solid phase extraction liquid chromatography–tandem mass spectrometry. Proteinuria was defined as urinary protein excretion of 0.5 g/24 h or higher. Metabolic syndrome (MS) and diabetes were defined according to the guidelines as described previously (*43*). Medically unfit for work applies to both the physical and mental status of a patient.

Statistical Analyses

Data were analyzed with SPSS version 19.0 (SPSS Inc., Chicago, IL) and GraphPad Prism version 5.01 (GraphPad Software, San Diego, CA). Normally distributed variables were 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. Hazard ratios are reported with 95% confidence interval.

Recipient-related characteristics were analyzed separately for the group below the cutoff score of 25 and the group above this score. Differences between groups were tested for statistical significance with Student *t* test for normally distributed variables, Mann-Whitney test for skewed distributed variables, and chi-squared test for categorical variables. Forward logistic regression analysis was performed including all variables with a $P<0.1$ to determine independent determinants of depression. All covariates from Table 1 with a $P<0.2$ were used in the logistic regression. To analyze whether symptoms of depression are associated with cardiovascular and all-cause mortality, and graft failure, we performed Kaplan-Meier analysis with log rank test to assess significance of difference between groups. Cox regression analyses were performed to study whether depression was independently associated with cardiovascular and all-cause mortality and graft failure. In these analyses, we considered several potential covariates known to be associated with mortality and graft failure in RTR as well as covariates that were independently associated with depression (*18, 19, 26, 32, 33*).

REFERENCES

1. Baines LS, Joseph JT, Jindal RM. Prospective randomized study of individual and group psychotherapy versus controls in recipients of renal transplants. *Kidney Int* 2004; 65: 1937.
2. Cameron JI, Whiteside C, Katz J, et al. Differences in quality of life across renal replacement therapies: a meta-analytic comparison. *Am J Kidney Dis* 2000; 35: 629.
3. Rocha G, Poli de Figueiredo CE, d'Avila D, et al. Depressive symptoms and kidney transplant outcome. *Transplant Proc* 2001; 33: 3424.
4. Akman B, Ozdemir FN, Sezer S, et al. Depression levels before and after renal transplantation. *Transplant Proc* 2004; 36: 111.
5. Herrmann C, Brand-Driehorst S, Buss U, et al. Effects of anxiety and depression on 5-year mortality in 5,057 patients referred for exercise testing. *J Psychosom Res* 2000; 48: 455.
6. Barefoot JC, Brummett BH, Helms MJ, et al. Depressive symptoms and survival of patients with coronary artery disease. *Psychosom Med* 2000; 62: 790.
7. Bush DE, Ziegelstein RC, Tayback M, et al. Even minimal symptoms of depression increase mortality risk after acute myocardial infarction. *Am J Cardiol* 2001; 88: 337.
8. Bruce DG, Davis WA, Starkstein SE, et al. A prospective study of depression and mortality in patients with type 2 diabetes: the Fremantle Diabetes Study. *Diabetologia* 2005; 48: 2532.
9. Whooley MA, de JP, Vittinghoff E, et al. Depressive symptoms, health behaviors, and risk of cardiovascular events in patients with coronary heart disease. *JAMA* 2008; 300: 2379.
10. Chilcot J, Wellsted D, Da Silva-Gane M, et al. Depression on dialysis. *Nephron Clin Pract* 2008; 108: c256.
11. 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.
12. Cukor D, Rosenthal DS, Jindal RM, et al. Depression is an important contributor to low medication adherence in hemodialyzed patients and transplant recipients. *Kidney Int* 2009; 75: 1223.
13. Dobbels F, Skeans MA, Snyder JJ, et al. Depressive disorder in renal transplantation: an analysis of Medicare claims. *Am J Kidney Dis* 2008; 51: 819.

14. Novak M, Molnar MZ, Szeifert L, et al. Depressive symptoms and mortality in patients after kidney transplantation: a prospective prevalent cohort study. *Psychosom Med* 2010; 72: 527.
15. Moons P, De GS, Versteven K, et al. Psychometric properties of the ''Modified Transplant Symptom Occurrence and Symptom Distress Scale''. *J Nurs Meas* 2001; 9: 115.
16. Moons P, Vanrenterghem Y, Van Hooff JP, et al. Health-related quality of life and symptom experience in tacrolimus-based regimens after renal transplantation: a multicentre study. *Transpl Int* 2003; 16: 653.
17. Pascazio L, Nardone IB, Clarici A, et al. Anxiety, depression and emotional profile in renal transplant recipients and healthy subjects: a comparative study. *Transplant Proc* 2010; 42: 3586.
18. Zelle DM, Corpeleijn E, Stolk RP, et al. Low physical activity and risk of cardiovascular and all-cause mortality in renal transplant recipients. *Clin J Am Soc Nephrol* 2011; 6: 898.
19. Remport A, Keszei A, Vamos EP, et al. Association of pre-transplant dialysis duration with outcome in kidney transplant recipients: a prevalent cohort study. *Int Urol Nephrol* 2011; 43: 215.
20. Patten SB. Exogenous corticosteroids and major depression in the general population. *J Psychosom Res* 2000; 49: 447.
21. Brown ES, Khan DA, Nejtek VA. The psychiatric side effects of corticosteroids. *Ann Allergy Asthma Immunol* 1999; 83: 495.
22. Russo S, Kema IP, Fokkema MR, et al. Tryptophan as a link between psychopathology and somatic states. *Psychosom Med* 2003; 65: 665.
23. Christmas DM, Potokar J, Davies SJ. A biological pathway linking inflammation and depression: activation of indoleamine 2,3-dioxygenase. *Neuropsychiatr Dis Treat* 2011; 7: 431.
24. Pawlak K, Mysliwiec M, Pawlak D. Haemostatic system, biochemical profiles, kynurenines and the prevalence of cardiovascular disease in peritoneally dialyzed patients. *Thromb Res* 2010; 125: e40.
25. Noohi S, Khaghani-Zadeh M, Javadipour M, et al. Anxiety and depression are correlated with higher morbidity after kidney transplantation. *Transplant Proc* 2007; 39: 1074.
26. van Ree RM, Oterdoom LH, de Vries AP, et al. Circulating markers of endothelial dysfunction interact with proteinuria in predicting mortality in renal transplant recipients. *Transplantation* 2008; 86: 1713.
27. Murphy EL, Murtagh FE, Carey I, et al. Understanding symptoms in patients with advanced chronic kidney disease managed without dialysis: use of a short patient-completed assessment tool. *Nephron Clin Pract* 2009; 111: c74.
28. Zimmermann J, Herrlinger S, Pruy A, et al. Inflammation enhances cardiovascular risk and mortality in hemodialysis patients. *Kidney Int* 1999; 55: 648.
29. Descamps-Latscha B, Herbelin A, Nguyen AT, et al. Dysregulation of the immune system in chronic uremic and hemodialysed patients. *Presse Med* 1995; 24: 405.
30. Gris JC, Branger B, Vecina F, et al. Increased cardiovascular risk factors and features of endothelial activation and dysfunction in dialyzed uremic patients. *Kidney Int* 1994; 46: 807.
31. Meier-Kriesche HU, Port FK, Ojo AO, et al. Effect of waiting time on renal transplant outcome. *Kidney Int* 2000; 58: 1311.
32. Jones H, Talwar M, Nogueira JM, et al. Anemia after kidney transplantation; its prevalence, risk factors, and independent association with graft and patient survival: a time-varying analysis. *Transplantation* 2012; 93: 923.
33. Agarwal PK, Hellemons ME, Zelle DM, et al. Smoking is a risk factor for graft failure and mortality after renal transplantation. *Am J Nephrol* 2011; 34: 26.
34. Pan A, Sun Q, Okereke OI, et al. Depression and risk of stroke morbidity and mortality: a meta-analysis and systematic review. *JAMA* 2011; 306: 1241.
35. de JP, Rosmalen JG, Kema IP, et al. Psychophysiological biomarkers explaining the association between depression and prognosis in coronary artery patients: a critical review of the literature. *Neurosci Biobehav Rev* 2010; 35: 84.
36. Zelle DM, Agarwal PK, Ramirez JL, et al. Alcohol consumption, new onset of diabetes after transplantation, and all-cause mortality in renal transplant recipients. *Transplantation* 2011; 92: 203.
37. DiMatteo MR, Lepper HS, Croghan TW. Depression is a risk factor for noncompliance with medical treatment: meta-analysis of the effects of anxiety and depression on patient adherence. *Arch Intern Med* 2000; 160: 2101.
38. Carney RM, Freedland KE, Eisen SA, et al. Major depression and medication adherence in elderly patients with coronary artery disease. *Health Psychol* 1995; 14: 88.
39. Frazier PA, Davis-Ali SH, Dahl KE. Correlates of noncompliance among renal transplant recipients. *Clin Transplant* 1994; 8: 550.
40. Joseph JT, Baines LS, Morris MC, et al. Quality of life after kidney and pancreas transplantation: a review. *Am J Kidney Dis* 2003; 42: 431.
41. Cukor D, Newville H, Jindal R. Depression and immunosuppressive medication adherence in kidney transplant patients. *Gen Hosp Psychiatry* 2008; 30: 386.
42. Aben I, Verhey F, Lousberg R, et al. Validity of the beck depression inventory, hospital anxiety and depression scale, SCL-90, and hamilton depression rating scale as screening instruments for depression in stroke patients. *Psychosomatics* 2002; 43: 386.
43. Zelle DM, Corpeleijn E, van Ree RM, et al. Markers of the hepatic component of the metabolic syndrome as predictors of mortality in renal transplant recipients. *Am J Transplant* 2010; 10: 106.
44. Sinkeler SJ, Zelle DM, Homan van der Heide JJ, et al. Endogenous plasma erythropoietin, cardiovascular mortality and all-cause mortality in renal transplant recipients. *Am J Transplant* 2011; 12: 485.
45. Beljouw IMJvan, Verhaak PFM, NIVEL. Geschikte uitkomstmaten voor routinematige registratie door eerstelijns psychologen. 2010.
46. Stant AD, Ten Vergert EM, den Boer PC, et al. Cost-effectiveness of cognitive self-therapy in patients with depression and anxiety disorders. *Acta Psychiatr Scand* 2008; 117: 57.
47. Bruce DS, Newell KA, Josephson MA, et al. Long-term outcome of kidney-pancreas transplant recipients with good graft function at one year. *Transplantation* 1996; 62: 451.
48. Bernstein IH, Wendt B, Nasr SJ, et al. Screening for major depression in private practice. *J Psychiatr Pract* 2009; 15: 87.
49. Koeter MW. Validity of the GHQ and SCL anxiety and depression scales: a comparative study. *J Affect Disord* 1992; 24: 271.
50. Arrindell WA, Ettema JHM. Dimensional structure, reliability and validity of the Dutch version of the Symptom Checklist (SCL-90): Data based on a phobic and a ''normal'' population. *Ned Tijdschr Psychol* 1981; 36: 77.
51. Oterdoom LH, Gansevoort RT, Schouten JP, et al. Urinary creatinine excretion, an indirect measure of muscle mass, is an independent predictor of cardiovascular disease and mortality in the general population. *Atherosclerosis* 2009; 207: 534.