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# The impact of calcineurin inhibitors and mammalian target of rapamycin inhibitors on anxiety and depression scores in kidney transplant patients

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**Background/aim:** Depression and anxiety are prevalent symptoms in kidney transplant patients. We aimed to evaluate the frequency and the severity of depression and anxiety symptoms in kidney transplant recipients using the Beck Depression Inventory (BDI) and Beck Anxiety Inventory (BAI). The data were compared between the patients on CNI-based and mTORi-based maintenance immunosuppressive regimens.

**Materials and methods:** A total of 94 kidney transplant patients were enrolled in the study after exclusion of the patients already taking neuropsychiatric medications or unwilling to participate in the study. Participants were asked to self-report the inventories.

**Results:** Analysis of data showed that 62 (66%) recipients had BDI scores that indicated depression. The patients on CNI-based regimens (n = 74) had increased total BDI scores compared those on mTORi-based regimens [18 (8.75–28) vs. 6 (5.25–14.25), respectively, $P < 0.001$]. Regarding BAI scores, 79 patients (84%) had prominent anxiety symptoms. The patients on CNI-based regimens had significantly increased total BAI scores compared to those on mTORi-based regimens [21 (13–30.50) vs. 10.50 (8.25–14.75), respectively, $P < 0.001$].

**Conclusion:** Our results identified fewer side effects of mTORi-based maintenance immunosuppressive regimens regarding depression and anxiety symptoms compared to CNI-based regimens in kidney transplant patients.

**Key words:** Anxiety, calcineurin inhibitors, depression, kidney transplantation, mammalian target of rapamycin inhibitors

## 1. Introduction

Kidney transplantation is the best treatment modality for patients having end-stage renal disease and enhances their quality of life (1). The recipients remain on life-long maintenance immunosuppressive therapies including frequently a corticosteroid, an antiproliferative agent, and either a calcineurin inhibitor (CNI) or a mammalian target of rapamycin inhibitor (mTORi) (2). The advance of CNIs in the early 1980s provided improvements in short-term allograft survival by reducing acute rejection rates. However, they exhibited serious adverse effects such as new-onset diabetes mellitus, chronic allograft nephropathy, and neurotoxicity in long-term follow -up (3,4). Hence, a relatively newer immunosuppressive group, mTORis, has been increasingly used as a part of CNI-withdrawal or CNI-avoidance regimens in kidney recipients (5).

During the transplantation process, physicians mainly focus on allograft functions as well as short- and long-term complications of immunotherapy. However, accumulated data show that this particular population also has considerably increased prevalence of psychiatric disorders including cognitive (6) and affective dysfunctions (7). In the medical literature, the neuropsychiatric adverse effects of corticosteroids have been well established (8). However, there has been a limited number of clinical studies exploring the impact of CNIs and mTORis on psychiatric symptoms in solid organ transplant recipients (6,9,10). In the present study, we aimed to evaluate the frequency and the severity of depression and anxiety symptoms in kidney transplant patients by using self-report inventories and to explore the associations of CNI-based and mTORi-based regimens with the results of inventories.

## 2. Materials and methods

This single-center observational study was performed at Dışkapı Yıldırım Beyazıt Education and Research Hospital, Ankara, Turkey. The study protocol was in accordance with the Helsinki Declaration and the local ethics committee approved it.

### 2.1. Study population

All living-donor or deceased-donor kidney transplant patients (between 18 and 65 years of age, transplanted at

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least 1 year ago) presenting to our outpatient nephrology clinic for follow-up treatment were invited to the study. The ones who were unwilling to participate in the study (n = 15) and/or the ones already taking psychiatric medications (n = 16) were excluded. Finally, 94 patients were enrolled in the study. They were on maintenance immunosuppression with either CNI-based (n = 74) or mTORi-based (n = 20) regimens. As a part of their maintenance immunosuppressive regimens, patients were also receiving prednisolone (5 mg per day) and an antiproliferative agent (mycophenolate at a dosage of 1000–2000 mg per day or azathioprine at a dosage of 50–100 mg per day). All the patients on mTORi-based regimens had been previously on CNI-based regimens, but their therapies were switched to mTORi as a CNI-avoidance strategy due to adverse effects such as nephrotoxicity, hirsutism, and gingival hypertrophy. All of these 20 patients were on mTORi-based regimens at least for 6 months. The dosages of CNI (either tacrolimus or cyclosporine (CsA)) and mTORi (either sirolimus or everolimus) were being adjusted according to blood concentrations.

**2.2. Data collection tools**

Sociodemographic features of the patients including age, sex, and marital and employment status were noted based on patients' charts and interviews. The type and time on dialysis before transplantation, transplantation history including donor type, presence of acute rejection episode, time since transplantation, current immunosuppressive medications, and concentrations of serum creatinine at the last visit were recorded. Each patient was assessed by clinical interview and the Beck Anxiety Inventory (BAI) and Beck Depression Inventory (BDI).

**2.3. Beck Depression Inventory**

The BDI is a self-report inventory used to measure the severity of depression. The questionnaire includes 21 multiple-choice items that describe specific depressive symptoms over the past week. Each item is scored on a scale from 0 to 3 and the sum of these gives the total BDI score. Patients having <10 total BDI score are accepted as normal. A total BDI score of ≥10 indicates symptomatic patients, 10–18 indicates mild depression, 19–29 indicates moderate depression, and ≥30 indicates severe depression (11). The validity and reliability of the BDI in Turkish population were evaluated by Hisli (12).

**2.4. Beck Anxiety Inventory**

The BAI is a self-report inventory developed by Beck et al. (13) to determine the frequency of anxiety symptoms. It is composed of 21 items. Each item is scored on a scale from 0 to 3 and the sum of these gives the total BAI score. Scores of 0–7 were accepted as negative symptomatology for anxiety. Scores of 8–15 show mild, scores of 16–25 show moderate, and scores of 26–63 show severe anxiety (13). The reliability and validity of the BAI were established in Turkey (14).

**2.5. Statistical analysis**

Statistical analysis was conducted using SPSS 18 (SPSS Inc., Chicago, IL, USA). Normality of distribution was tested by the Kolmogorov–Smirnov test and histograms for continuous variables. Normally distributed variables were expressed as mean ± standard deviation and the others are presented as median and interquartile ranges (the range of values lying between the 25th and 75th percentiles). The Student t-test or Mann–Whitney U test was used for comparisons of two groups. Categorical variables were shown as frequency and percentages and were assessed by using the chi-square test or Fisher exact test as appropriate. All P-values were calculated as two-sided, and $P < 0.05$ was considered as significant.

## 3. Results

Demographic characteristics of the participants are presented in Table 1. The mean age of the patients was 42.84 ± 10.23 years. Of the patients, 74.5% were male, 56.4% were married, and 48.9% were employed.

There was no significant difference between group I (CNI-based regimen, n = 74 patients) and group II (mTORi-based regimen, n = 20) with regard to sex, age, marital status, employment status, dialysis history, or transplantation history. There was a trend toward higher serum creatinine values in group II patients (Table 1).

Analysis of the data obtained from the BDI showed that 62 patients (66%) had total scores of ≥10 and were rated as symptomatic for depression; 27 had mild, 21 had moderate, and 14 had severe levels of depression. The mean BDI score was found to be significantly higher in group I compared to group II ($P < 0.001$). Fifty-six patients (75.6%) had depression (total BDI score of ≥10) in group I (21 patients with mild, 21 with moderate, and 14 with severe depression scores); 6 patients (30%) had depression (total BDI score of ≥10) in group II (all with mild levels of depression scores) ($P < 0.001$) (Table 1). The prevalence of moderate and severe levels of depression was higher among CNI users ($P = 0.015$) (Table 1).

Analysis of the data collected with the BAI showed that 79 patients (84%) had prominent anxiety symptoms (total BAI score of >7); 31 patients had mild, 26 moderate, and 22 severe levels anxiety. The mean anxiety score was significantly higher in group I than in group II ($P < 0.001$). However, the prevalence of prominent anxiety symptoms was similar in the two groups ($P = 0.299$). Sixty-four patients (86.5%) had prominent anxiety (18 patients with mild, 24 with moderate, and 22 with severe anxiety scores) in group I; 15 patients (75.0%) had prominent anxiety (13 patients with mild and 2 with moderate anxiety scores) in group II (Table 1). The prevalence of moderate and severe

**Table 1.** Demographic features of study population.

| | Total group (n = 94) | Patients on CNI-based regimens (n = 74) | Patients on mTORi-based regimens (n = 20) | P |
|---|---|---|---|---|
| Sex (male, n,%) | 70 (74.5%) | 56 (75.7%) | 14 (70%) | 0.606 |
| Age (years) | 42.84 ± 10.23 | 42.70 ± 10.72 | 43.35 ± 8.43 | 0.803 |
| Marital status (married, n,%) | 53 (56.4%) | 42 (56.8%) | 11 (55%) | 0.888 |
| Employment status (employed, n,%) | 46 (48.9%) | 34 (45.9%) | 12 (60%) | 0.265 |
| Dialysis history before transplantation | | | | |
| Dialysis type (n,%) | | | | |
| Hemodialysis | 61 (64.9%) | 49 (66.2%) | 12 (60%) | 0.605 |
| Peritoneal dialysis | 33 (35.1%) | 25 (33.8%) | 8 (40%) | |
| Time on dialysis (months) | 21.5 (9–36) | 20 (8–36) | 30 (12.5–47.0) | 0.062 |
| Transplantation history | | | | |
| Living donor (n,%) | 50 (53.2%) | 39 (52.7%) | 11 (55.0%) | 0.855 |
| Rejection episode (n,%) | 21 (22.3%) | 19 (25.7%) | 2 (10%) | 0.225 |
| Time since transplantation (months) | 72 (41–97) | 66 (36–102) | 72 (60–93) | 0.539 |
| Serum creatinine (mg/dL) | 1.5 (1.2–2.0) | 1.5 (1.13–2.0) | 1.65 (1.5–2.0) | 0.055 |
| BDI results | | | | |
| Total BDI scores | 15 (7–26) | 18 (8.75–28) | 6 (5.25–14.25) | <0.001 |
| Total BDI scores ≥10 (n, %) | 62 (66%) | 56 (75.6%) | 6 (30%) | <0.001 |
| Total BDI scores 10–18 (n ,%) | 27 (43.5%) | 21 (37.5%) | 6 (100%) | 0.015* |
| Total BDI scores 19–29 (n, %) | 21 (33.9%) | 21 (37.5%) | - | |
| Total BDI scores ≥30 (n, %) | 14 (22.6%) | 14 (25.0%) | - | |
| BAI results | | | | |
| Total BAI scores | 18 (10.75–25) | 21 (13–30.50) | 10.50 (8.25–14.75) | <0.001 |
| Total BAI scores >7 (n, %) | 79 (84%) | 64 (86.5%) | 15 (75.0%) | 0.299 |
| Total BAI scores 8–15 (n, %) | 31 (39.2%) | 18 (28.1%) | 13 (86.7%) | <0.001* |
| Total BAI scores 16–25 (n, %) | 26 (32.9%) | 24 (37.5%) | 2 (13.3%) | |
| Total BAI scores 23–63 (n, %) | 22 (27.8%) | 22 (34.4%) | - | |

CNI, Calcineurin inhibitors; mTORi, mammalian target of rapamycin inhibitor; BDI, Beck Depression Inventory; BAI, Beck Anxiety Inventory.
*P-value belongs to chi-square testing that compares the frequencies of three levels of depression/anxiety between patients on CNI-based and mTORi-based regimens.

anxiety levels was higher among CNI users (P < 0.001) (Table 1).

When the patients on CNI-based regimens were divided into two groups as those on tacrolimus (n = 41) and those on CsA (n = 33), the groups were similar in regard to total BDI and BAI scores, and the prevalence of depression (total BDI score ≥10 ) and anxiety (total BAI score >7). However, the patients on tacrolimus had moderate and severe levels of depression and anxiety symptoms (P < 0.05 for both) (Table 2).

**Table 2.** Comparison of the BDI and BAI results between patients on tacrolimus and cyclosporine regimens.

| | Patients on CNI-based regimens | | |
|---|---|---|---|
| | Patients on tacrolimus (n = 41) | Patients on cyclosporine (n = 33) | P |
| BDI results | | | |
| Total BDI score | 24 (10–35) | 15 (8–24.5) | 0.073 |
| Total BDI scores ≥10 (n, %) | 31 (75.6%) | 25 (75.8%) | 0.988 |
| Total BDI scores 10–18 (n, %) | 9 (29.0%) | 12 (48.0%) | 0.002* |
| Total BDI scores 19–29 (n, %) | 8 (25.8%) | 13 (52.0%) | |
| Total BDI scores ≥30 (n, %) | 14 (45.2%) | - | |
| BAI results | | | |
| Total BAI score | 22 (12.5–40) | 20 (13–23.50) | 0.129 |
| Total BAI scores >7 (n, %) | 34 (82.9%) | 30 (90.9%) | 0.496 |
| Total BAI scores 8–15 (n, %) | 7 (20.6%) | 11 (36.7%) | 0.004* |
| Total BAI scores 16–25 (n, %) | 9 (26.5%) | 15 (50.0%) | |
| Total BAI scores 23–63 (n, %) | 18 (52.9%) | 4 (13.3%) | |

CNI, Calcineurin inhibitors; BDI, Beck Depression Inventory; BAI, Beck Anxiety Inventory.
*P-value belongs to chi-square testing that compares the frequencies of three levels of depression/anxiety between patients on CNI-based and mTORi-based regimens.

When the patients with total BDI score of ≥10 (n = 62) were compared with those with total BDI scores of <10 (n = 32), the age (41.95 ± 9.60 vs. 44.56 ± 11.33, respectively, P = 0.243), male sex [46 (74.2%) vs. 24 (75.0%), respectively, P = 0.932], rate of marriage [31 (50%) vs. 22 (68.7%), respectively, P = 0.082], time since transplantation [57 (36–96.5) vs. 74 (58.5–99), respectively, P = 0.140], and rate of employment [36 (58.1%) vs. 12 (37.5%), respectively, P = 0.059] were similar. However, patients with BDI scores indicating depression (total BDI score ≥10) had more commonly performed hemodialysis as a dialysis modality before transplantation [45 (72.6%) vs. 16 (50.0%), respectively, P = 0.03] and had a longer time on dialysis before transplantation [27 (17.5–38) vs. 9.5 (5–17.25), respectively, P < 0.001], a higher rate of cadaveric donors [39 (62.9%) vs. 5(15.6%), respectively, P < 0.001], and an increased number of acute rejection episodes [20 (32.3%) vs. 1 (3.1%), respectively, P = 0.001].

When the patients with prominent anxiety (n = 79) (total BAI score >7) symptoms were compared with those with total BAI scores of <7 (n = 15), the age (43.18 ± 9.93 vs. 41.07 ± 11.94, respectively, P = 0.467), sex [58 (73.4%) vs. 12 (80%), respectively, P = 0.753], dialysis type as hemodialysis [53 (67.1%) vs. 8 (53.3%), respectively, P = 0.306], and time since transplantation [60 (40–96) vs. 84 (48–110), respectively, P = 0.285] were similar. However, patients with prominent anxiety symptoms (total BAI score of >7) had a lower rate of marriage [39 (49.4) vs. 14 (93.3%), respectively, P = 0.002], a lower rate of employment [34 (43.0%) vs. 12 (80%), respectively, P = 0.009], a longer time on dialysis before transplantation [24 (10–36) vs. 5 (2–18), respectively, P < 0.001], a higher rate of cadaveric donors [43 (54.4%) vs. 1 (6.7%), respectively, P = 0.001], and an increased number of acute rejection episodes [21 (26.6%) vs. zero, respectively, P = 0.020].

## 4. Discussion

In the present study, we observed that the total depression and anxiety scores as well as the severity levels of the diseases were increased in patients on CNI-based regimens compared to those of the patients on mTORi-based regimens. To the best of our knowledge, this is the first study comparing the impacts of CNI-based and mTORi-based regimens on depression and anxiety scores and disease severity levels determined by using the BDI and BAI. We found that 66% of our patients had total BDI scores of ≥10 and 84% of them had total BAI scores of >7. These were relatively higher scores compared to the other studies that reported distinctive values for depression ranging from 20% to 75% and for anxiety ranging from 27% to 50% in kidney transplant patients (15–18). The types of diagnostic tools, the special characteristics of the study populations

(socioeconomic situations, extremely low deceased donor rates, and subsequently longer duration of dialysis treatments in Turkey) could have affected the results.

In the medical literature, there have been limited and conflicting results concerning the psychiatric effects of immunosuppressive agents in patients with solid organ transplantation. A small-sized study including nine heart-transplanted cases showed improved mood, memory, and quality of life after switching from CNI-based regimens to everolimus (10). On the other hand, the psychiatric effects of immunosuppressive agents in kidney recipients were investigated in a single study that yielded impaired attention and memory in sirolimus and tacrolimus users, while cyclosporine users had similar outcomes compared to healthy volunteers (6). In our study, CNI users had significantly increased total BDI and BAI scores as compared to mTORi users. The understanding of the physiological actions of calcineurin and/or mTORi molecules could help in the interpretation of these results. Calcineurin regulates the neurotransmission, neuronal excitability, and plasticity in the amygdala and provides normal mood reactions in human bodies. Some researchers have suggested that it is involved in the regulation of depressive behaviors (19), and antidepressive agents develop their effects via calcineurin activation (20). Experimental studies have shown that calcineurin blockage increases depressive-like symptoms (21) and the prevalence of depression and anxiety (22). Experimental studies showed that mTORi signaling is needed for hippocampus-dependent fear, long-term memory (23), and the synthesis of brain-derived-neurotrophic factor (BDNF), which is a growth factor secreted from the hippocampus (24,25). Recently published data showed alterations of BDNF synthesis in patients with depression (26) and BDNF polymorphism in patients with anxiety (27). An mTORi, CCI-779, resulted in euphoria followed by melancholia (similar to a temporary bipolar disorder) in one-fifth of patients with malignancy after administration of a single dose (28). As a consequence, not only calcineurin inhibition but also mTORi inhibition seems to be related with depression and anxiety. The alterations in BDNF and related growth factors in CNI and mTORi users might be subject of further studies.

As general knowledge, tacrolimus more frequently causes psychiatric and neurological symptoms than cyclosporine (29). However, some authors showed similar results for tacrolimus and cyclosporine (9), whereas some others showed deteriorated results with tacrolimus (7). In our study, although the frequency and total scores were similar for the BDI and BAI, tacrolimus users were prone to having more severe levels of symptoms.

We observed that marital status was similar between the patients with BDI scores of ≥10 or <10, whereas patients with prominent anxiety symptoms had lower rates of marriage. Sayın et al. noted that marital status did not affect the psychological status of transplanted patients (30). However, Akman et al. reported a higher incidence of depression in single patients (31). We thought that family support is important for the mood of the patients. There was a trend towards increased unemployment in patients with BDI scores of ≥10 and a higher rate of unemployment was observed in those with BAI scores of <7. In support of this, a prior study showed that employment affects the prevalence of depression, which appears more frequently in people of low socioeconomic status (32). These data suggest that unemployment may trigger either depression or anxiety. In our study, the time on dialysis before transplantation was longer in patients with depression and anxiety, in line with the observations of other researchers (33). The renal replacement modality was hemodialysis in our patients with BDI scores of ≥10, whereas other authors reported no difference in this regard (34). Similar to Parsei et al. (35), we showed higher rates of deceased donors in patients with depression and anxiety symptoms. Acute rejection history was significantly higher in patients with depression and anxiety. These findings suggest that fear of rejection may be associated with depressive and anxiety symptoms. One of our patients was retransplanted and had severe levels of depression and anxiety symptoms. A previous study showed a higher incidence of mental disorders in retransplanted patients than in those with a single liver transplantation (36). Further studies with larger samples are needed to confirm our findings.

Studies have shown that patients who are depressed are less likely to adhere to their medications (37,38). A metaanalysis showed that depressed patients were 3-fold more likely to be noncompliant to their medical regimen than patients without depression (37). The results of another study also suggested that psychological distress such as anxiety and anger may lead to nonadherence to drugs in adolescent renal transplant recipients (38). Since decreased medication adherence causes organ rejections in transplant recipients, it is very important to diagnose and treat depression in a timely manner. Hence, we suppose that renal transplant recipients should be screened for depression and anxiety regularly and treated appropriately to enhance their quality of life and treatment adherence and to decrease morbidity.

Our study has some limitations. The cross-sectional study design prevents us from establishing an exact cause-and-consequence relation between drug groups and depression and anxiety symptoms. The relatively small number of patients on mTORi-based regimens was a result of the primary choice of CNI-based regimens in maintenance immunotherapy in kidney transplant patients in our center.

In conclusion, we demonstrated increased scores for depression and anxiety by using self-reported inventories in kidney transplant patients, particularly in those on CNI-based regimens. In clinical practice, physicians should also consider the potential adverse effects of CNIs and mTORis on depression and anxiety, besides their more well-known adverse effects. Further studies are warranted to confirm our results and to elucidate the possible underlying mechanisms.

## References


1. Hunsicker LG. A survival advantage for renal transplantation. N Engl J Med. 1999; 341: 1762-1763.
2. Halloran PF. Immunosuppressive drugs for kidney transplantation. N Engl J Med 2004; 351: 2715-2729.
3. Nankivell B, Borrow R, Fung Cl, O'Connell PJ, Chapman JR, Allen RD. Calcineurin inhibitor nephrotoxicity: Longitudinal assessment by protocol histology. Transplantation 2004; 78: 557-565.
4. Bechstein WO. Neurotoxicity of calcineurin inhibitors: impact and clinical management. Transplant Int 2000; 13: 313-326.
5. Cardinal H, Froidure A, Dandavino R, Daloze P, Hébert MJ, Colette S, Boucher A. Conversion from calcineurin inhibitors to sirolimus in kidney transplant recipients: a retrospective cohort study. Transplant Proc 2009; 41: 3308-3310.
6. Martínez-Sanchis S, Bernal MC, Montagud JV, Candela G, Crespo J, Sancho A, Pallardó LM. Effects of immunosuppressive drugs on the cognitive functioning of renal transplant recipients: a pilot study. J Clin Exp Neuropsychol 2011; 33: 1016-1024.
7. Abbott KC, Agodoa LY, O'Malley PG. Hospitalised psychoses after renal transplantation in the United States: incidence, risk factors, and prognosis. J Am Soc Nephrol 2003; 14: 1628-1635.
8. Wada K, Yamada N, Sato T, Suzuki H, Miki M, Lee Y, Akiyama K, Kuroda S. Corticosteroid-induced psychotic and mood disorders: diagnosis defined by DSM-IV and clinical pictures. Psychosomatics 2001; 42: 461-466.
9. Griva K, Hansraj S, Thompson D, Jayasena D, Davenport A, Harrison M, Newman SP. Neuropsychological performance after kidney transplantation: a comparison between transplant types and in relation to dialysis and normative data. Nephrol Dial Transplant 2004; 19: 1866-1874.
10. Lang UE, Heger J, Willbring M, Domula M, Matschke K, Tugtekin SM. Immunosuppression using the mammalian target of rapamycin (mTOR) inhibitor everolimus: pilot study shows significant cognitive and affective improvement. Transplant Proc 2009; 41: 4285-4288.
11. Beck AT, Waed CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry 1961; 4: 561-571.
12. Hisli N. Beck depression inventory of university students on the validity and reliability. J Psychol 1989; 7: 3-13.
13. Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety: Psychometric properties. J Consult Clin Psychol 1988; 56: 893-897.
14. Eren I, Sahin M, Tunc SE, Cure E, Civi II. Psychiatric symptoms and quality of life in patients with Behçet's disease. Neurol Psychiatr Brain Res 2006; 13: 169-174.
15. Novac M, Molnar MZ, Szeifert L, Kovacs AZ, Vamos EP, Zoller R, Keszei A, Mucsi I. Depressive symptoms and mortality in patients after kidney transplantation: a prospective prevalent cohort study. Psychosom Med 2010; 72: 527-534.
16. Arapaslan B, Soykan A, Soykan C, Kumbasar H. Cross-sectional assessment of psychiatric disorders in renal transplantation patients in Turkey: a preliminary study. Transplant Proc 2004; 36: 1419-1421.
17. Noohi S, Khaghani-Zadeh M, Javadipour M, Assari S, Najafi M, Ebrahiminia M, Pourfarziani V. Anxiety and depression are correlated with higher morbidity after kidney transplantation. Transplant Proc 2007; 39: 1074-1078.
18. Anvar-Abnavi M, Bazargani Z. Prevalence of anxiety and depression in Iranian kidney transplant recipients. Neurosciences (Riyadh) 2010; 15: 254-257.
19. Zhu WL, Shi HS, Wang SJ, Wu P, Ding ZB, Lu L. Hippocampal CA3 calcineurin activity participates in depressive-like behavior in rats. J Neurochem 2011; 117: 1075-1086.
20. Crozatier C, Farley S, Mansuy IM, Dumas S, Giros B, Tzavara ET. Calcineurin (protein phosphatase 2B) is involved in the mechanisms of action of antidepressants. Neuroscience 2007; 144: 1470-1476.
21. Bahi A, Mineur YS, Picciotto MR. Blockade of protein phosphatase 2B activity in the amygdala increases anxiety and depression-like behaviors in mice. Biol Psychiatry 2009; 66: 1139-1146.
22. Mineur YS, Taylor SR, Picciotto MR. Calcineurin downregulation in the amygdala is is sufficient to induce anxiety-like and depression-like behaviors in C57BL/6 male mice. Biol Psychiatry 2014; 75: 991-998.
23. Bekinschtein P, Katche C, Slipczuk LN, Igaz LM, Cammarota M, Izquierdo I, Medina JH. mTOR signaling in the hippocampus is necessary for memory formation. Neurobiol Learn Mem 2007; 87: 303-307.
24. Botterill JJ, Brymer KJ, Caruncho HJ, Kalynchuk LE. Aberrant hippocampal neurogenesis after limbic kindling: relationship to BDNF and hippocampal-dependent memory. Epilepsy Behav 2015; 47: 83-92.
25. Grados M, Sung HM, Kim S, Srivastava S. Genetic findings in obsessive-compulsive disorder connect to brain-derived neutrophic factor and mammalian target of rapamycin pathways: implications for drug development. Drug Dev Res 2014; 75: 372-383.

26. Lang UE, Hellweg R, Gallinat J. BDNF serum concentrations in healthy volunteers are associated with depression-related personality traits. Neuropsychopharmacology 2004; 29: 795-798.

27. Lang UE, Hellweg R, Kalus P, Bajbouj M, Lenzen KP, Sander T, Kunz D, Gallinat J. Association of a functional BDNF polymorphism and anxiety-related personality traits. Psychopharmacology (Berl) 2005; 180: 95-99.

28. Raymond E, Alexandre J, Faivre S, Vera K, Materman E, Boni J, Leister C, Korth-Bradley J, Hanauske A, Armand JP. Safety and pharmacokinetics of escalated doses of weekly intravenous infusion of CCI-779, a novel mTOR inhibitor, in patients with cancer. J Clin Oncol 2004; 22: 2336-2347.

29. Eidelman BH, Abu-Elmagd K, Wilson J, Fung JJ, Alessiani M, Jain A, Takaya S, Todo SN, Tzakis A, Van Thiel D. Neurologic complications of FK-506. Transplant Proc 1991; 23: 3175-3178.

30. Sayin A, Mutluay R, Sindel S. Quality of life in hemodialysis, peritoneal dialysis, and transplantation patients. Transplant Proc 2007; 39: 3047-3053.

31. Akman B, Ozdemir FN, Sezer S, Miçozkadioglu H, Haberal M. Depression levels before and after renal transplantation. Transplant Proc 2004; 36: 111-113.

32. Lorant V, Deliège D, Eaton W, Robert A, Philippot P, Ansseau M. Socioeconomic inequalities in depression: a meta-analysis. Am J Epidemiol 2003; 157: 98-112.

33. Feroze U, Martin D, Reina-Patton A, Kalantar-Zadeh K, Kopple JD. Mental health, depression, and anxiety in patients on maintenance dialysis. Iran J Kidney Dis 2010; 4: 173-180.

34. Stasiak CE, Bazan KS, Kuss RS, Schuinski AF, Baroni G. Prevalence of anxiety and depression and its comorbidities in patients with chronic kidney disease on hemodialysis and peritoneal dialysis. J Bras Nefrol 2014; 36: 325-331.

35. Parsaei Mehr Z, Hami M, Moshtagh Eshgh Z. Anxiety and depression: a comparison between living and cadaveric renal transplant recipients. Int J Organ Transplant Med 2011; 2: 178-183.

36. Nickel R, Wunsch A, Egle UT, Lohse AW, Otto G. The relevance of anxiety, depression, and coping in patients after liver transplantation. Liver Transplant 2002; 8: 63-71.

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: 2101-2107.

38. Penkower L, Dew MA, Ellis D, Sereika SM, Kitutu JM, Shapiro R. Psychological distress and adherence to the medical regimen among adolescent renal transplant recipients. Am J Transplant 2003; 3: 1418-1425.