Prevalence of Depression in Maintenance Hemodialysis Patients and Its Correlation With Adherence to Medications

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Introduction. This study was designed to evaluate the adherence of maintenance hemodialysis patients to medications and its correlation with quality of life and depressive symptoms.
Materials and Methods. A total of 150 maintenance hemodialysis patients with a mean age of 56.4 ± 16.4 years (52.7% women) were included. Medication adherence was evaluated via the Simplified Medication Adherence Questionnaire, based on which nonadherent patients were identified. Specifically, the Drug-Intake Percentage Questionnaire was used for evaluation of adherence to phosphate binders, quality of life was assessed with short Form-36 and depression by the Beck Depression Inventory (BDI).
Results. A BDI score of 15 and greater was documented in 40.7%, and nonadherence in 24.7% of the patients. Adherent patients were significantly older than nonadherent ones, had a lower mean parathyroid hormone level, and had lower BDI scores. The quality of life scores were not significantly different between adherent and nonadherent patients. Multivariable analysis demonstrated that BDI score was a significant predictor of nonadherence (odds ratio for each unit increase, 1.11; 95% confidence interval, 1.04 to 1.18; $P = .001$). Overall, 55.5% of patients were taking more than 66% of their prescribed dose of calcium carbonate, while 10.3% and 53.8% of patients were taking more than 66% of their prescribed dose of aluminum hydroxide and sevelamer, respectively.
Conclusions. Adherence to medication was mainly associated with hemodialysis patients' depressive symptom scores. Control of depression may significantly improve adherence to medications and patient management.

INTRODUCTION

End-stage renal disease (ESRD) is an irreversible loss of kidney function which requires lifelong maintenance renal replacement therapy.[1] As a chronic disabling disease, ESRD is associated with various psychological consequences. Particularly, hemodialysis, one of the main treatment modalities of ESRD, imposes a great psychosocial burden on the patients, which may cause many psychological impacts, the most frequent of which is depression.[2-4] Overall, depression has been reported in 20% to 30% of ESRD patients.[5-7] Nonetheless, the underdiagnosis of depression is a challenge in these patients, mainly due to the fact that many signs of depression such as anorexia, fatigue, irritability, decreased sexual drive and sleep pattern disturbance are similar to the signs of uremic state. Thus, the true epidemiology of depression in ESRD patients is quite unknown.[8]

Various studies have shown that depression is associated with higher morbidity and mortality in ESRD patients.[9-11] Kimmel and colleagues evaluated the relationship between depression and mortality in a group of hemodialysis patients and showed that patients with a Beck Depression Inventory (BDI) score higher than 10 had a greater mortality rate than those with lower scores.[9] One of the main links between depression and high mortality in chronic diseases is nonadherence to medications. Compared with patients without depressive symptoms, the odds of being nonadherent with medical treatment recommendations are 3 times greater in depressed patients.[12] Recent data show that many treatment adherence measurements, including both laboratory and behavioral adherence indexes, are associated with patient outcome.[13] On the other hand medication, dietary, fluid, and treatment adherence are essential components of the dialysis prescription, and nonadherence is associated with increased mortality.[6,13] Furthermore, transplant centers consider adherence to hemodialysis treatment as an important factor in evaluation of their candidates for kidney transplantation.[14]

The aim of the present study was to evaluate the adherence of a group of patients on maintenance hemodialysis to the prescribed medications and to evaluate its correlation with the patients' quality of life, depressive symptoms, and routine laboratory results.

METHOD AND MATERIALS
Participants

This study was designed as a cross-sectional study on maintenance hemodialysis patients of Hasheminejad Kidney Center in 2011. One-hundred and fifty of 180 patients on maintenance hemodialysis consented to participate in the study. Patients who were unwilling or unable to answer the questions due to advanced aged, advanced psychological problems other than depression (3 cases), or inability to communicate were excluded.

Medication Adherence

Medication adherence was evaluated via two methods: a Simplified Medication Adherence Questionnaire (SMAQ), assessing patients' general adherence with medication[15]; and the Drug Intake Percentage Questionnaire (DIPQ), for evaluation of adherence with prescribed phosphate binders.

Participants were classified as adherent and nonadherent based on SMAQ results.[15] Medications evaluated using the DIPQ were phosphate binders including calcium carbonate, aluminum hydroxide, and sevelamer hydrochloride. The questionnaire was separately filled out for each phosphate binder. The DIPQ was designed as a simple quantitative classification, based on interview with the patients by an experienced hemodialysis nurse, regarding the actual intake of daily medications and comparison with the prescribed medications during routine visits at the dialysis unit. Based on the DIPQ results, participants were classified into group 1, taking more than 66% of the prescribed phosphate binder dose; group 2, taking 33% to 66% of the prescribed phosphate binder dose; and group 3, taking less than 33% of the prescribed phosphate binder dose.

Depressive Symptoms

Depression was assessed using the BDI questionnaire.[16] The BDI consists of 21 questions, which is used for screening and evaluation of the severity of depressive symptoms with scores ranging from zero to 63. For the general population, scores higher than 10 and for hemodialysis patients scores equal to higher than 15 are defined as indication of clinical depression.[10,17-20] Severity of depressive symptoms was graded as mild (15 to 20), moderate (21 to 30), severe (31 to 40), and very severe (41 to 63).

Quality of Life

Socioeconomic status was assessed by a simplified economic questionnaire, classifying those who could afford their family food, housing, and education, as middle class, those who could not afford each of the above as low class, and those who could afford more than all of the above and have extra savings, as high class. Health-related quality of life was assessed using the Short Form-36 (SF-36) questionnaire.[21] This questionnaire includes 36 phrases that evaluate 8 different aspects of health including vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and mental health. Validity and reliability of the Persian version of SF-36 has been previously confirmed.[22] For patients who were not able to read, the questionnaire was filled in by a study collaborator.

Clinical and Laboratory Data

Serum levels of phosphorus, potassium, intact parathyroid hormone (PTH), and protein as well as interdialytic weight gain were collected from the medical charts and their mean values during the past 6 months were recorded.

Statistical Analyses

Continuous data were demonstrated as mean ± standard deviation. Comparisons between the groups were done using the *t* test and the chi-square test, as appropriate. The correlations were tested using the Pearson correlation coefficient. A logistic regression model was built to assess factors predicting nonadherence and age, sex, education, marital status, diabetes mellitus, hypertension, BDI score, and SF-36 score were included in the model. All statistical analyses were done using the SPSS software (Statistical Package for the Social Sciences, version 17.0, SPSS Inc, Chicago, Ill, USA). A *P* value less than .05 was considered significant.

RESULTS

Of 150 patients, 79 were women (52.7%). The mean age was 56.4 ± 16.4 years (range, 15 to 86 years). The mean hemodialysis vintage was 4.7 ± 5.2 years. The most common cause of ESRD was diabetes mellitus (35.3%), followed by hypertension (25.3%), polycystic kidney disease (4%), reflux nephropathy (4%), glomerulonephritis (2.7%), urolithiasis (2.7%), lupus nephritis (1.3%), urinary tract infection (0.7%), and urinary tuberculosis (0.7%), while in 23.3% the cause was unknown. The frequency of depressive symptoms indicating clinical depression according to the BDI scores was 42.7% (Figure). The mean SF-36 score was 51.5 ± 16.7. There was a negative correlation between BDI and SF36 scores (Pearson r = -0.48, *P* < .001), and the mean SF-36 score was significantly lower in patients with depressive symptoms versus those with negative BDI results (42.9 ± 14.7 versus 57.2 ± 15.6, *P* < .001).

The SMAQ results showed that 113 (75.3%) patients were adherent to medications. Adherent patients were significantly older than nonadherent ones (59.2 ± 15.6 years versus 48.0 ± 16.1 years, *P* < .001); had lower PTH levels (297.2 ± 256.8 pg/mL versus 399.4 ± 277.5 pg/mL; *P* = .04); and had lower BDI scores (12.6 ± 7.8 versus 19.7 ± 11.3, *P* < .001; Table 1). Nonadherence was more frequent
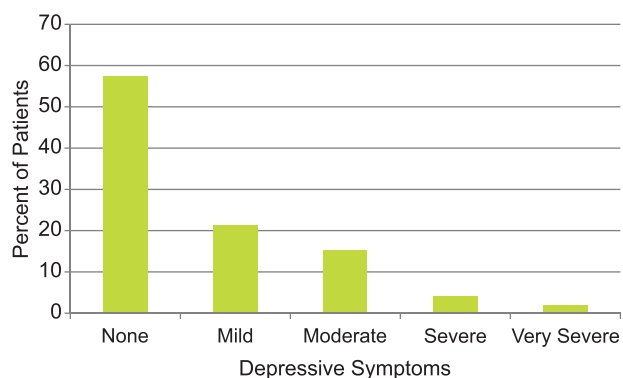
Prevalence of different levels of depressive symptoms according to the Beck Depression Inventory scores in hemodialysis patients.

Table 1. Characteristic of Hemodialysis Patients With and Without Adherence to Medication

Parameter	All Participants	Adherent Patients (n = 113)	Nonadherent Patients (n = 37)	P
Age, y	46.5 ± 16.4	59.2 ± 15.6	48.0 ± 16.1	< .001
Sex				
Male	71	50	21	
Female	79	63	16	.18
Married	108	81	27	.87
Hemodialysis vintage, y	4.6 ± 5.1	4.8 ± 5.3	4.1 ± 4.5	.44
Mean hemoglobin, g/dL	10.8 ± 1.5	10.9 ± 1.4	10.4 ± 1.7	.13
Mean KT/V	1.2 ± 0.2	1.2 ± 0.1	1.2 ± 0.3	.43
Mean phosphorus, mg/dL	5.2 ± 1.2	5.1 ± 1.2	5.3 ± 1.0	.50
Mean parathyroid hormone, pg/mL	322.4 ± 264.8	297.2 ± 256.8	399.4 ± 277.5	.04
Mean plasma protein, g/L	7.5 ± 0.5	7.5 ± 0.5	7.6 ± 0.6	.30
Mean potassium, mEq/L	5.1 ± 0.6	5.2 ± 0.6	5.1 ± 0.5	.68
Mean interdialytic weight gain, kg	2.8 ± 0.9	2.8 ± 1.0	2.7 ± 0.7	.80
Mean depression score	14.3 ± 9.3	12.6 ± 7.8	19.7 ± 11.3	< .001
Mean Short Form-36 score	51.4 ± 16.7	52.4 ± 17.3	48.4 ± 14.4	.20

in patients with depressive symptoms (BDI ≥ 15) compared to those with low BDI score (38.3% versus 15.5%; P = .002). However, the mean SF-36 score was not significantly different between adherent and nonadherent patients (52.5 ± 17.4 versus 48.4 ± 14.5; P = .16; Table 1). Adherence status was not different between various socioeconomic classes (P = .25) and educational levels (P = .16). The mean interdialytic weight gain and plasma levels of protein, phosphorus, and potassium were not significantly different between adherent and nonadherent patients. Multivariable analysis of predictors of nonadherence demonstrated that BDI score was a significant factor (odds ratio for each unit increase, 1.11; 95% confidence interval, 1.04 to 1.18; P = .001). Older age was associated with adherence, while male sex was linked with nonadherence. Other factors in the model, including SF-36 score were not a significant predictor of nonadherence (Table 2).

The DIPQ showed that 55.5% of patients were taking more than 66% of their prescribed dose of calcium carbonate (DIPQ group1), while 10.3% and 53.8% of patients were taking more than 66% of their prescribed dose of aluminum hydroxide and sevelamer, respectively (Table 3). The mean phosphorus level was significantly lower in the DIPQ group1 for calcium carbonate intake compared to other groups (P < .001; Table 4). However, the difference was not significant between different aluminum hydroxide and sevelamer DIPQ groups (P = .25 and P = .83, respectively). The mean PTH level was significantly lower in the DIPQ group1 for calcium carbonate intake compared to other groups (P = .02; Table 4). The difference was not

Table 2. Multivariable Analysis of Factors Associated With Nonadherence

Parameter	Odds ratio (95% Confidence Interval)	P
Age	0.94 (0.91 to 0.97)	< .001
Male sex	3.92 (1.41 to 10.87)	.009
Married	2.07 (0.63 to 6.82)	.23
Education level		
High school	0.42 (0.10 to 1.82)	.18
Undergraduate degree	0.46 (0.09 to 2.42)	.41
Postgraduate degree	1.03 (0.18 to 6.08)	.38
Diabetes mellitus	0.94 (0.33 to 2.70)	.91
Hypertension	0.43 (0.12 to 1.48)	.18
Beck Depression Inventory score	1.11 (1.04 to 1.18)	.001
Short Form-36 score	0.99 (0.95 to 1.02)	.39

significant between different aluminum hydroxide and sevelamer DIPQ groups (P = .97 and P = .83, respectively).

DISCUSSION

Depression is frequently seen in ESRD patients both as a reaction to the diagnosis of a potentially irreversible disease and the long-term losses experienced in terms of health, life style, and financial status. Different figures have been reported for the prevalence of depression in ESRD patients, as assessed by various methods.[23] Smith and coworkers evaluated 60 ESRD patients for existence of depression via 3 methods.[24] They classified 47%, 17%, and 5% of patients as depressed, according to the evaluations by the BDI, Multiple Affect Adjective Check List, and Diagnostic and Statistical Manual of Mental Disorders revised 3rd edition criteria, respectively.[24] In the study by

Table 3. Level of Adherence to Phosphate Binders Based on Drug Intake Percentage Questionnaire (DIPQ)

DIPQ	Group I (> 66%)	Group II (33% to 66%)	Group III (< 33%)
Calcium carbonate (n = 136)	70 (51.5)	46 (33.8)	20 (14.7)
Aluminum hydroxide (n = 29)	3 (10.3)	8 (27.6)	18 (62.1)
Sevelamer (n = 26)	14 (53.8)	9 (34.6)	2 (7.7)
Erythropoietin (n = 143)	121 (84.6)	17 (11.9)	5 (3.5)
Intravenous iron (n = 96)	71 (74.7)	13 (13.7)	11 (11.6)
Antihypertensives (n = 34)*	25 (73.5)	7 (20.6)	2 (5.9)

*Calcium blockers, beta blockers, antgiotensin-converting enzyme inhibitors, angiotensin receptor blockers, alpha blockers, minoxidil, and any combination of these.

Table 4. Phosphorus and Parathyroid Hormone Levels for Drug Intake Percentage Questionnaire Groups for Calcium Carbonate

Parameter	Group I (> 66%)	Group II (33% to 66%)	Group III (< 33%)	P
Mean phosphorus, mg/dL	4.6 ± 0.9	5.3 ± 1.0	5.5 ± 1.1	< .001
Mean parathyroid hormone, pg/mL	273.6 ± 230.0	291.0 ± 217.5	444.7 ± 317.6	.02

Einwohner and colleagues, the Zung Self-Rating Depression Scale showed a depression prevalence of 32%, among 66 maintenance peritoneal dialysis patients.[25] In our study, prevalence of depression, using the BDI, was 42.7%, which, considering the differences in methodologies, is almost similar to other studies. It is noteworthy that in the general population, the point prevalence of depression has been reported to be 5% to 9% in women and 2% to 3% in men,[25] and life time prevalence of depression in the general population is 21.3% among women and 12.7% among men.[26]

Depression has been associated with increased morbidity and mortality in patients with ESRD.[9,11,25] One of the major mediators of the link between depression and morbidity and mortality may be nonadherence to medications, diet, and fluid restriction in depressed patients, which is a serious problem in ESRD patients.[12,13] Depression and other psychological problems could impact patient adherence, perception of quality of life, morbidity, and mortality through several pathways.[13] Patients with ESRD may manifest suicidal behavior in a manner different from non-medically ill populations by refusing dialysis, lack of adherence with dietary prescriptions, or even manipulation of their vascular access.[13]

In a systematic review of 19 studies by Schmid and colleagues, nonadherence to the oral medication among dialysis patients ranged from 3% to 80% and more than half of the studies reported nonadherence rates of 50% and higher (mean 67%).[27] Phosphate binding therapy was the main surveyed oral medication, and self-reports, structured interviews, and predialysis serum phosphate levels were the most frequent adherence assessment tools. In our study, over 75% of patients were adherent to medications, as assessed by the SMAQ. Predialysis serum phosphate has been commonly used as an adherence indicator for patients taking the oral prescribed phosphate binding medication and microelectronic monitoring devices has also been used to monitor patient's adherence.[27] Marked differences in rates of nonadherence as measured by the microelectronic monitoring devices versus self-reports were observed; being 70% as repeatedly nonadherent for phosphate binder medication by microelectronic monitoring devices, versus 8% by self-reports.[28,29] Although the overall adherence was high in our cohort according to the SMAQ, the rate of nonadherence was higher when different phosphate binders were studied separately through the DIPQ. More than 50% of patients had high adherence to calcium carbonate and sevelamer (ie, taking more than 66% of the prescribed medication dose); however, only 10% were adherent to aluminum hydroxide at this level. Nonadherence to the latter medication may be due to the nonpalatability of aluminum hydroxide, both in syrup and tablet forms and the fear from aluminum intoxication, widely acknowledged by the patients. We followed strict rules to use this medication in cases of severe hyperphosphatemia (serum phosphorus $\geq$ 7 mg/dL and calcium-phosphorus product $\geq$ 70 mg^2/dL^2) when the patient could not afford to buy sevelamer (which would not be covered by most insurance companies at the time of the study). We also restricted its prescription for a total period of 6 to 8 weeks per year. It seems that further explanations about the indications, toxicity, and limitations of this medication and production of more palatable forms may help the patients to adhere to the prescription course when it is really needed. On the other hand if we assume that patients with phosphate levels greater than 7 mg/dL are inherently nonadherent patients, the assignment of these patients for receiving aluminum hydroxide may have caused a selection bias, actually targeting for nonadherent patients. These patients (those with medium or low adherence to aluminum hydroxide), which can be arbitrarily called, the very nonadherent group, include 26 out of 150 patients which are about 17% of our patient population.

Previous studies have examined the correlation between depression and adherence to medications. Cukor and coworkers found a significant negative correlation between BDI score and self-reported medication adherence in 65 hemodialysis patients (r = -0.47, P < .001).[6] In multivariable analysis, depression was the only significant predictor of medication adherence in addition to mode of treatment (P < .001). DiMatteo and colleagues examined the correlation between anxiety and adherence to medication in 13 studies and the relationship between depression and adherence in 12 studies associated with chronic medical diseases including ESRD.[12] They could not find a consistent correlation between anxiety and medical adherence, but the odds of nonadherence with

medical treatment was 3 times greater in depressed compared to nondepressed patients. In our study, we also showed a significantly lower BDI score in nonadherent patients.

Among the most frequently assessed demographic predictors of oral medication adherence, age seems to be a strong predictor of nonadherence in patients undergoing hemodialysis. Some studies reported that older age, particularly older than 65 years, was associated with higher levels of medication adherence.[30-33] Some recent observations report an emerging cognitive impairment and dementia in the aging dialysis population, which may affect adherence to prescribed medications.[34,35] In our study, older patients were significantly more adherent to prescribed medications . While this may be culturally explained by a stronger appreciation and attachment to life in the elderly, the exclusion criteria of this study and nonparticipations might also be associated with age and high overall adherence of the participants, which would limit our study's results in terms of adherent groups.

Quality of life is generally lower in patients with chronic diseases all over the world,[36] and hemodialysis patients have a lower compared to general population and kidney transplant patients.[37,38] Depression closely relates to quality of life and the relationship is very significant when determining measures to maintain a high level of quality of life.[39] It has been shown that the psychiatric burden experienced by ESRD patients could have profound effects on their quality of life.[40] Drayer and coworkers studied 62 hemodialysis patients who had a 28% prevalence of major or minor depression.[41] Depressed patients were younger and had a lower health-related quality of life than did nondepressed patients, together with a higher hazard ratio of mortality. In the present study, we also showed a significant negative correlation between quality of life and depression. We also examined the relationship between quality of life and adherence, as we had hypothesized that patients with better adherence to medications should have a better quality of life both physically, considering the positive bodily effects of the medication, and mentally, considering the relationship between quality of life and depression. There are not many studies examining the relationship between quality of life and adherence to medication in the literature. Chiu and colleagues showed a lower quality of life

in physical aspects in hemodialysis patients with higher pill burden, which could have been due to higher morbidity and the need for more medications in those patients.[42] Akman and colleagues studied the relationship between clinical nonadherence, depression, and quality of life in 86 patients on kidney transplant waiting list.[43] Clinical adherence was defined as skipping or shortening dialysis sessions, interdialytic weight gain greater than 5.7% body weight, a predialysis potassium level greater than 6 mEq/L, and a predialysis phosphate level greater than 7.5 mg/dL.They showed that nonadherent patients had lower quality of life (P = .04) and higher depression scores (P = .01) than did adherent patients.We could not show a relationship between quality of life and overall adherence to medications. However, in patients with higher adherence to antihypertensive medications, the SF-36 score was significantly higher (data not shown). This entity may need examination of more detailed aspects of quality of life and the long-term effect of various medications on quality of life.

Our limitation in this study was use of self-reported measures, including BDI; which is a highly sensitive but a moderately specific test, compared to the structured interview based on the Diagnostic and Statistical Manual of Mental Disorders revised 4th edition, which is the gold standard for diagnosis of major depressive disorder. Also lack of a standard method of evaluation of adherence to different aspects of hemodialysis and medications makes it difficult to compare our results with the results of similar studies, which have used a number of different methods for evaluation of adherence to dialysis and the related medications.

CONSLUSIONS

Adherence to medication was mainly associated with hemodialysis patients' depressive symptoms scores and was poorer in depressed patients. Nonadherenec to calcium carbonate was linked to a higher level of serum phosphorus concentration as well as elevated PTH levels. Control of depression may significantly improve adherence to medications and patient management.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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