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Depression in patients with chronic renal disease
What we know and what we need to know

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Abstract

Depression is a common, but underdiagnosed and understudied problem in patients with renal disease. The overlap between symptoms of chronic medical illness and those of depression make for a particularly challenging diagnosis in this illness. The prevalence of depression varies with the diagnostic tool employed. The gold standard for the psychiatric diagnosis is the interview, using DSM-IV TR criteria. Researchers in the field of renal disease have often not distinguished between the diagnosis of major depression and high levels of depressive affect in studies. There are almost no data regarding the magnitude of depression in patients with chronic renal insufficiency, patients treated with peritoneal dialysis, and children with renal disease, compared with adults with end-stage renal disease treated with hemodialysis. The relationships between age, ethnicity, marital status and satisfaction, and perception of quality of life and level of depressive affect and diagnosis of depression, and medical outcomes have not been determined in patients with renal disease. The mediators which may underlie the deleterious effects of depression in patients with renal disease, and their relationship with stage of renal dysfunction have not been delineated. More emphasis must be placed on well-designed treatment studies and survival analyses in these populations, using longitudinal techniques.

Keywords: Depression; Chronic kidney disease; Prevalence; Survival; Peritoneal dialysis; Hemodialysis; Chronic renal insufficiency; Compliance; Suicide; Immune dysfunction; Marriage

Introduction

Although depression has been regarded as the most common psychiatric abnormality in patients with end-stage renal disease (ESRD) treated with hemodialysis (HD) [1–5], there is a paucity of large-scale, well-designed epidemiologic studies to provide solid findings regarding this issue. Indeed, one of the classic articles in the field cited studies describing the prevalence of depression in dialysis patients ranged from zero to 100%, suggesting that the real extent of this problem in this population is unknown [6]. Large surveys of the prevalence of depression in the population of ESRD patients treated with chronic peritoneal dialysis (PD) have not been undertaken, and there are even fewer data regarding possible associations of magnitude of depressive affect and level of renal functional impairment in patients with chronic renal insufficiency (CRI) [7].

Depression has been associated in the psychodynamic literature with the response to a loss of some kind (reviewed in Refs. [3,4]). ESRD patients, and to a lesser extent, patients with CRI, have sustained multiple losses, including loss of role within the family and workplace, loss of renal function and mobility, loss of physical skills and cognitive abilities and loss of sexual function [2,4]. In addition, the symptoms of medical illness and the pathophysiologic responses engendered by a chronic, debilitating disease might cause depression. Medications used to treat patients with ESRD and CRI might also cause depression or have side effects that mimic its symptomatology. Indeed, the overlap between the symptoms of depression and those of chronic medical illness is a critical problem for investigators in the field of chronic renal disease (as well as other chronic conditions) (Table 1). The stresses associated with the

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Table 1
Comparison of symptoms of depression and uremia

Symptoms of depression	Uremic symptoms
Depressed mood	
Psychomotor agitation or retardation	Encephalopathy
Loss of interest or pleasure	
Difficulty concentrating	
Decreased appetite or weight change	Anorexia/Edema
Sleep disturbance/Fatigue	Sleep apnea, anemia, volume overload, congestive heart failure
Aches and pains	Neuropathy/Arthropathy
Feelings of worthlessness or guilt	
Preoccupation with death	
Suicidal ideation	

disease, as well as its treatment, might predispose to an increased level of depressive symptoms, or increase the risk of developing or exacerbating depression itself (Table 2). Finally, several minority populations are overrepresented in the ESRD population in the United States [8]. These groups may be at particularly high risk for the development of depression [9].

The diagnosis of depression in dialysis patients may be determined by the choice of screening method [2,6]. To delineate the cognitive and somatic aspects of depression in patients with renal disease, we used a ''Cognitive Depression Index'' (CDI) (excluding items dealing with somatic symptoms from the Beck Depression Inventory [BDI]) [10,11]. The CDI correlates highly with the BDI in our HD patient population. Although several other groups have attempted to create a tool to differentiate the somatic and cognitive components of depression, our tool and these others have not been determined to provide predictive power [2,4,12,13]. Almost half the dialysis patients in one study were categorized as depressed using the BDI, compared with 10% using the Multiple Affect Adjective Check List (MAACL), but only 5% of the patient population by clinical interview using DSM-III criteria [6]. The index of crude agreement between the BDI and the MAACL was 0.633, and between the BDI and a DSM-III diagnosis was 0.583. Of note, the index of crude agreement between the MAACL and the DSM-III diagnosis was 0.950.

Craven et al. [14] showed that 45.4% of patients had depression assessed by the BDI. They showed that a BDI score ≥ 15 had high sensitivity and specificity for the diagnosis of depressive disorder in patients with ESRD treated with dialysis, with the Diagnostic Interview Schedule (DIS) used as the gold standard [14]. The cutoff score used in patients without renal disease (≥ 10) was associated with more false negatives and a lower positive predictive value [14]. Suicidal ideation and depressed mood were key discriminators between patients with and without depression in the studies of Hinrichsen et al. [15] and Smith et al. [6] (reviewed in Refs. [2,4]).

Lowry and Atcherson [16] reported an 18% prevalence of major depression, using DSM-III-R criteria in a group of primarily Caucasian patients beginning home HD in Iowa. Hinrichsen et al. [15] found that 17.7% of center HD patients met criteria for minor depressive disorder, while 6.5% could be diagnosed with major depression, using the Schedule for Affective Disorders and Schizophrenia. Craven et al. [14] found that 8.1% of dialysis patients met DSM-III criteria for major depressive disorder, while 6.1% could be diagnosed with dysthymic disorder.

In our studies of a predominantly African-American population of urban patients with ESRD treated with HD, almost half had a BDI score >10 [2,12], consistent with the findings of Smith et al. [6]. Almost a quarter of patients had a BDI score >15. Approximately 1 in 20 patients was determined to have a psychiatric diagnosis of depression, using the DIS (unpublished data), again consistent with other studies [6,14].

Few studies have compared the incidence and prevalence of depression, and assessed its consequences in patients with ESRD treated with chronic PD. Small studies have suggested that up to one third of chronic PD patients may be depressed (reviewed in Ref. [17]). Depressed ESRD patients treated with PD had a tendency towards higher complication rates with peritonitis [17]. Valid comparisons of any associations of treatment modality and depressive affect, and the influence of depression on course, morbidity and outcome of PD patients have not been fully determined.

We reviewed data from the almost 200,000 US ESRD patients who were treated with dialysis in 1993. Almost 10% of the patients were hospitalized with a psychiatric diagnosis [18]. In approximately 25% of these patients, the psychiatric diagnosis was the primary reason for the admission. The most common psychiatric disorder in the population was depression and affective disorders, with dementia and organic brain syndromes constituting another large category of psychiatric complications, expected in an elderly, chronically ill population. Rates of hospitalization for a primary diagnosis of depression were higher in ESRD patients than for patients with ischemic heart disease and cerebrovascular disease, and equaled those for patients with

Table 2
Stresses for dialysis patients

Dietary constraints
Time restrictions
Functional limitations
Loss of employment
Loss of role in intimate dyad/family/workplace/society
Change in sexual function
Illness effects
Medication effects
Fear of death

diabetes mellitus. There were differences between the risk of hospitalization with a diagnosis of depression in different groups of patients. There was no difference between the risk of hospitalization with a diagnosis of depression in men and women. Interestingly, patients between 18 and 64 years of age were more likely to be hospitalized with a diagnosis of depression compared with those over 65. White patients were more likely to be hospitalized with a diagnosis of depression than were Black patients.

Patients treated with PD were less likely to be hospitalized with a diagnosis of depression than HD patients. This may reflect selection processes in determining treatment modalities more than medical factors. ESRD patients were more likely to be hospitalized with a diagnosis of depression after their first year of receiving ESRD therapy, suggesting the diagnosis is not simply a result of adjustment to a new and exacting medical therapy. Rather, the unrelenting, long-term nature of the disease and the intensity and duration of its treatment may be associated with the development of the psychiatric syndrome.

Few studies have assessed the prevalence and correlates of depression and depressive affect in patients with CRI. CRI represents a much larger population than the ESRD patients, and they are the virtual "tip of the iceberg" when considering the number of patients with chronic renal disease [19]. In a small, preliminary study of outpatients with CRI, we found that BDI and CDI scores correlated with measures of patient perception of the burden of illness, patient general physical functional status and assessments of satisfaction with life [7]. Interestingly, in this study, there was no correlation of level of depressive symptoms and level of renal functional impairment, inversely related to the serum creatinine concentration. Stage of disease in patients with chronic renal dysfunction may however be associated with level of depressive affect. In a small population of outpatients with CRI at an advanced stage of disease, about to embark on ESRD therapy, with a mean creatinine concentration of 5.4 ± 3.4 mg/dl, the mean BDI score was significantly higher (14.1 ± 10.4) than in the group of patients with a mean serum creatinine concentration of 3.5 ± 2.1 mg/dl (mean BDI score 8.0 ± 3.7) [7,11].

Although other groups have assessed psychological distress and functional status of patients with CRI [20,21], there are no well-designed epidemiologic studies specifically addressing the issue of prevalence of depression in patients with CRI.

Few studies have assessed depressive affect in a longitudinal manner, or in relation to the stage of CRI or ESRD. In addition, there have been few studies that assess possible differences in relationships between level of depressive affect or the diagnosis of depression and medical factors between the genders or in patients of different ethnic groups.

Husebye et al. [22] showed that almost half of elderly HD and PD patients had no change in level of depressive affect after a 3-year period. More than 25% of patients had lower levels of depressive affect at a second assessment, but almost a third had an increased depression score. In our baseline evaluations, there was no statistically significant correlation between the time since initiation of renal replacement therapy and BDI scores. Although mean level of depressive affect correlated highly over time, there was variation in individuals [12,13]. In our follow-up studies, there was a tendency for level of depressive affect to decrease [12]. It is unclear whether this represents normal variation, successful adjustment, or selection bias. About one third of patients changed level of depressive affect (either increasing or decreasing) over a 6-month period.

Relatively little work has been done on the prevalence and consequences of depression in children treated for ESRD [23]. In a study of 73 adolescents and children, no differences could be demonstrated in levels of depressive affect of patients with ESRD, using the Childhood Depression Inventory, treated with different modalities, including transplantation [24]. Home dialysis patients had lower levels of depressive affect than patients treated in the hospital. These same researchers showed that higher levels of depressive affect in children were related to their increased functional disability [25].

Potential mediators of deleterious effects of depression in patients with renal disease

Depression could affect medical outcome through several mechanisms (Table 3). For example, depression could alter the medical aspects of disease by influencing access to or utilization of health care, by modifying compliance with the dialytic and medication prescription, by impacting nutritional status, and by mediating changes in immune function. Any relationships between these factors and mortality in HD patients, however, have been incompletely or poorly delineated. Depression could effect survival of patients through the use of medications, through effects on the underlying illness, by influencing interpersonal dynamics, or by suicide. The existence of robust relationships between level of depressive affect and compliance has not been established in studies of HD patients, and fewer data on this matter exist in patients treated with PD [26]. Perception of stress was related to increased weight gain between dialysis sessions in one study of HD patients, but for unclear reasons, there was an association of increased depression

Table 3
Depression and outcome in patients with ESRD: potential mediators

Access to medical care
Compliance with dialysis regimen
Nutritional status
Neuroendocrine/Immune function
Medication effects
Interpersonal relationships
Suicide

with lower levels of IDWG, perhaps because of appetite disturbances [27]. Many studies have not been able to establish a clear association between depressive symptoms and compliance with fluid restrictions [2,26,28].

In our studies, increased level of depressive affect was associated with both standard medical and behavioral markers of poor compliance, and poorer compliance with the dialysis prescription in longstanding HD patients [2,26,28] was directly associated with increased depressive affect (Ref. [2] and unpublished data). Higher levels of depressive affect in children with end-stage renal failure were related to poorer adherence to treatment [29], and to greater functional disability [25].

An extensive and growing literature has linked depression with immune dysfunction (reviewed in Refs. [4,30–35]). Careful studies have demonstrated decreased cellular immunity in unmedicated patients with depression, in the absence of medical illness [33]. Depressed patients have higher circulating levels of cytokines and acute phase reactants [2,31,35,36] compared to control subjects, as is the case with patients with ESRD [37]. It is noteworthy that administration of interleukin-1 to animals produces a "sickness profile" that is similar to uremia (reviewed in Refs. [2,38]).

Friend et al. [39] showed that depression preceded the decrease in a survival marker, serum albumin concentration, in dialysis patients. We also found that higher BDI scores were correlated with lower serum albumin concentrations, and immune parameters that have been associated with differential mortality in ESRD patients (unpublished data).

In recent studies, we showed that depressive affect in African-American women HD patients functioning in dyadic relationships was associated with increased levels of circulating β-endorphin, a mortality marker [38]. Depression may be an important stressor in women dialysis patients, who often have diverse roles to play in the dyad, family and workplace. Responses to depression might underlie different adaptation and coping mechanisms between genders or ethnic groups.

We have previously noted the overlap between symptoms of depression [38] and abnormal cytokine regulation ("sickness behavior") (reviewed in Refs. [2,38]) such as fatigue, cognitive defects, and appetite and sleep disturbances and those of uremia (Table 1). Cytokine metabolism may be similarly deranged in patients with depression and with ESRD. In the latter case, abnormal clearance of immune mediators may play a linked pathophysiologic role [2,38].

Suicide is the ultimate complication of depression. It has been frequently pointed out that ESRD patients may commit suicide easily, by increasing noncompliant behaviors or manipulating their vascular access sites, and that suicidal behaviors may have different expressions in this population (reviewed in Ref. [2] and Refs. [4,40]). An extremely high rate of suicide was reported in ESRD patients in an early study [40], but recent data suggest that suicide is less prevalent in contemporary populations, perhaps as a function of changes in therapy, patient selection biases, or reporting mechanisms [2,4]. Withdrawal from ESRD therapy has been a focus of health policy planners since 1986 [41] when a survey from Minnesota reported an incidence of withdrawal from dialysis of 9%, accounting for 22% of deaths. Since that time, it has become apparent that there are differences in the withdrawal rate from dialysis in different ethnic groups, with white patients having a relatively high death rate due to this cause [2,8]. Approximately one fifth of dialysis patients discontinue this life-sustaining therapy voluntarily [2,8]. Medical complications, age, diabetes, cerebrovascular disease and irreversible dementia, and failure to thrive are common current causes for withdrawal, while access failure is rarely cited as a reason for discontinuing dialysis treatment [2,8]. Women are slightly more likely to withdraw from dialysis therapy compared with men. Suicide accounts for a death rate of approximately 0.2% per 1000 dialysis patients years at risk [2,8]. The relationship of antecedent depression to withdrawal and suicide, however, has been poorly delineated. While the growth of the hospice movement may have changed contemporary end-of-life practice in ESRD programs, there are few data regarding the results of psychological interventions on withdrawal rates and outcomes.

Depression and survival in ESRD patients

Studies have assessed the relationship between depression and mortality in HD patients, but the conclusions have been contradictory. Ziarnik et al. [42], Wai et al. [43], Burton et al. [44], Shulman et al. [45], and our group [10] presented data suggesting that increased depressive affect was associated with poorer survival of dialysis patients (reviewed in Refs. [2,4]). With the exception of the data of Shulman et al. [45], and our preliminary studies [10], the analyses were often poorly performed, not using contemporary survival analyses. None of the studies were large, nor did these cross-sectional baseline evaluations account for variation in multiple demographic, treatment and nutritional risk factors (such as age, race, gender, medical comorbidities, serum albumin concentration, dose of dialysis, and time since starting ESRD therapy, among other important parameters) [2].

More recent, better designed studies using improved analytic techniques, however, failed to implicate depressive affect as a risk factor for ESRD patients. Devins et al. [46], Husebye et al. [22], and Christensen et al. [47] were unable to define a link between depression and mortality in dialysis patients. We could not demonstrate that depressive affect was a mortality risk factor in a large population comprised mostly of African-American urban HD patients, using Cox regression analyses, when the variation in several medical risk factors was controlled [13].

We performed longitudinal follow-up in our study, collecting several evaluations of BDI and CDI scores over prolonged periods of time, which were used as time-varying covariates in Cox regression models of patient survival [12]. A one standard deviation increase in level of depressive affect evaluated over time was associated with an 18–32% increased risk of mortality, when variations in medical parameters were controlled. We concluded that time-varying models may enhance predictive accuracy, and allow different patterns of change and stability to be quantified and evaluated.

Conclusions

Depression is a common, but underdiagnosed and understudied problem in ESRD patients. There are almost no data regarding the magnitude of this problem in patients with CRI, who represent a much larger population, with significant medical comorbidity. The prevalence of depression varies with the population studied, the modality of ESRD therapy provided and the diagnostic tool employed. The extent of depression in the PD population and its association with outcomes has not been thoroughly investigated. Researchers in the field of renal disease have often not distinguished between the diagnosis of major depression and high levels of depressive affect in studies. The relationships between age, marital status and satisfaction, ethnicity, and perception of quality of life and level of depressive affect and diagnosis of depression, and medical outcomes have not been determined in the ESRD population. The mediators that may underlie the deleterious effects of depression in ESRD patients, and their relationship with stage of renal dysfunction have not been delineated. More emphasis must be placed on well-designed survival analyses, in incident populations, using longitudinal study techniques.

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