

Psychosocial Aspects of Chronic Disease: ESRD as a Paradigmatic Illness

Daniel Cukor,* Scott D. Cohen,[†] Rolf A. Peterson,[†] and Paul L. Kimmel[†]

*Department of Psychiatry and Behavioral Sciences, SUNY Downstate Medical Center, Brooklyn, New York; and

[†]Division of Renal Diseases and Hypertension, Department of Medicine, George Washington University, Washington, DC

ABSTRACT

Psychosocial issues are an understudied yet important concern in the overall health of hemodialysis (HD) patients. Stress is a concomitant of chronic illness and its treatment, and may have meaningful influences on psychological and medical outcomes. This article reviews the influences of psychopathology, social support, family issues, dialysis unit culture, and socioeconomic status on patients treated with center HD. Depressive affect and decreased perception of social support have been linked with mortality in several studies of ESRD patients. Decreased marital satisfaction, disturbances in family dynamics, and lower socioeconomic status (SES) have been associated with poorer health outcomes and can affect patients' perception of social support and depressive affect. Chronically ill ESRD patients who undergo treatment with constant interaction and observation by medical staff are potentially an ideal group for evaluation of the effects of stress and psychosocial factors on outcomes in those with chronic disease, as well as an excellent patient population for intervention to reduce morbidity and mortality. These interactions between potentially modifiable psychosocial risk factors for disease and medical aspects of illness form a paradigm for the study of interventions related to adjustment to chronic illness in the ESRD population.

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Remarkable advances in the understanding and treatment of ESRD have been achieved over the last 20 yr. However, most of the investigations have focused on medical factors, many of which are fixed features. Over recent years, there has been increasing attention given to the individual characteristics of patients with an emphasis placed on understanding the effects the patients' social situation, perceptions and responses to the illness, their physicians and healthcare providers, their spouses and families, and their SES have on outcomes. Although this area of "psychonephrology"¹ has been a subject of research for many years, recent work in patients with^{2,3} and without renal disease^{4–12} has advanced

our understanding of the interaction of psychological factors with medical outcomes. The notion of "stress" serves to provide a research context for the study of such interactions.

The concept of stress has resisted definition since it was first introduced in the 1930s by Hans Selye,¹³ but the word has since permeated the popular cultural idiom. Stress may be thought of as a disruption in the physical condition, environment, or psychosocial setting of an organism.¹⁴ The concept of stress has been operationalized through the notion of "stress mediators," typically hormones that affect or are produced by the central nervous system or hypothalamic-pituitary-ad-

renal (HPA) axis. Stress mediators are thought to potentially have both protective and maladaptive consequences, depending on their peak intensity and the temporal associations of the response. A further refinement of the idea of stress includes the ability to achieve stability through change, or "allostasis".^{14,15} The construct of allostasis was first developed in an effort to understand the physiological basis for disparate patterns of morbidity and mortality unexplained by SES, access issues, or lifestyle choices.¹⁶ McEwen and Stellar¹⁷ proposed the construct of allostatic load to convey the cumulative impact of progressive physiological wear and tear that could predispose biologic organisms to disease. Interestingly, the factors that comprise the Allostatic Index are weighted toward risk factors for cardiovascular disease (such as systolic BP, cortisol and catecholamine excretion, the waist/hip ratio, glycosylated hemoglobin, and the ratio of serum HDL to total serum cholesterol concentration).¹⁵ McEwen^{15,18} suggested several response patterns that are indicative of excessive wear and tear: 1) a response pattern with ex-

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Address correspondence to: Dr. Paul Kimmel, Department of Medicine, George Washington University, 2150 Pennsylvania Avenue NW, Washington, DC 20037. Phone: 202-741-2283; Fax: 202-741-2285; E-mail: pkimmel@mfa.gwu.edu

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cessive and repeated insults over time, 2) a pattern where the organism is unable to habituate to stressful stimuli, 3) a pattern that is activated but remains at a heightened level of activation without sufficient recovery to baseline status, and 4) a pattern where the primary mechanisms are inadequate to the challenge, resulting in the activation of compensatory mechanisms. These four response patterns may lead to variable end-organ responses that may characterize patients with chronic illness, and in particular ESRD.

The ability of stress mediators to return to baseline is a particularly salient issue for patients with renal dysfunction. Because peptide and steroid hormones undergo metabolism by the kidney and often circulate at levels higher than in patients without renal disease,^{19–21} the patient with chronic kidney disease (CKD) can be considered to exist in an internal biochemical milieu that is similar to a chronic stress response.

People’s variability in their perception of “stress” is critical, because outcomes may be quite variable in patients with similar allostatic loads.¹⁵ Therefore, age, gender, presence of comorbid illness, developmental history, and genetic heterogeneity may be associated with different outcomes, but personality, mood, habits and behaviors (such as diet, level of exercise, use of tobacco, alcohol and regulated substances, and spirituality and religious observance) may play roles in modifying disposition of allostatic load as well. In particular, some of the stressors in the life of a dialysis patient may cause modifications to the patients’ status in a variety of marital, familial, and occupational and societal contexts (Figure 1). However, to fully appreciate the dynamic nature of these demands one must also understand the patient’s perspective on his or her ability to cope with these stressors. The person’s personality, psychological functioning, resources, and even cultural beliefs may all affect the perception of the ability to respond successfully to a challenge (Figure 1).

Anderson and Armstead²² advanced the biopsychosocial model first elabo-

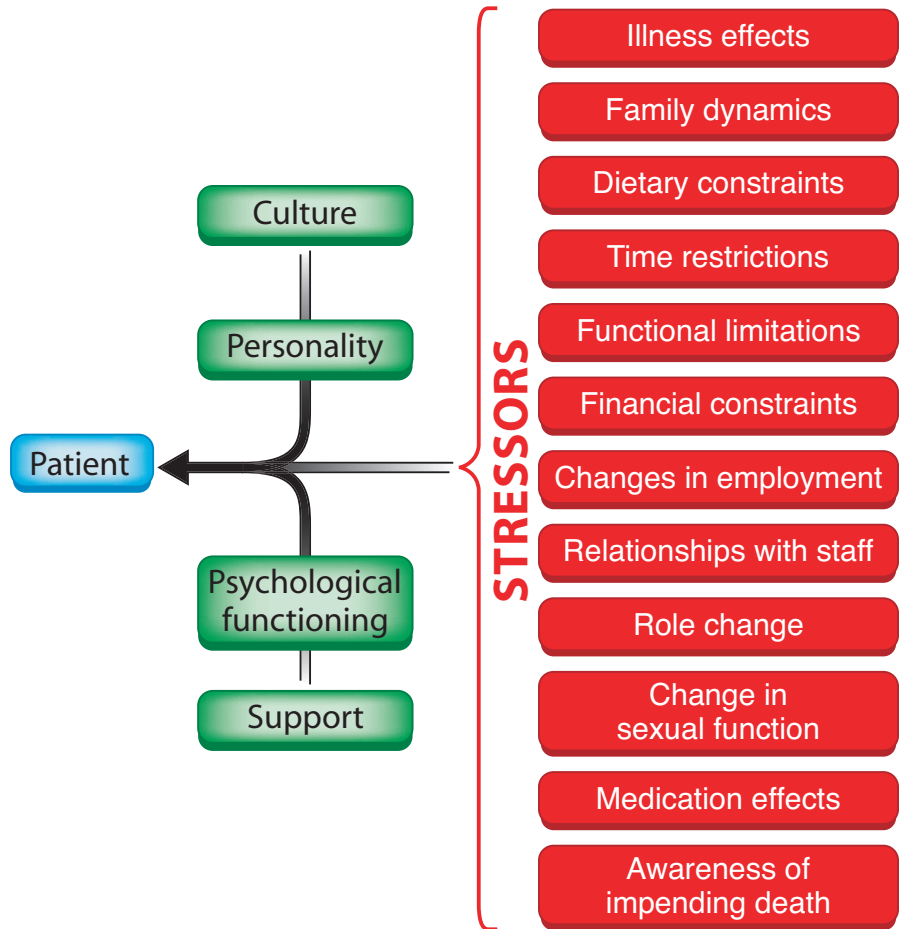


Figure 1. Patient characteristics and stressors that may affect perceived stress in HD patients.

rated by Engel²³ to encompass many levels that may interact to determine health status. Some of these stratifications include individual demographic data (age, ethnicity, gender), physiological measures (e.g., body mass index, cardiovascular, immunologic and conditioning status), psychological and behavioral parameters (distress, personality factors, health-promoting or -damaging habits), and social or environmental factors (occupational imperatives, level of social support, access to health care, residential characteristics, and SES). Psychological and social parameters (Table 1) might include personality factors, affect, and perceptions of distress, well-being, or illness, whereas social measures include marital satisfaction, satisfaction with health care, compliance with the dialysis regimen, and level, number, and quality of interactions with dialysis personnel

Table 1. Selected psychosocial parameters in chronic disease

Individual psychological variables
psychopathology
personality
illness perception
Behavioral compliance variables
nutrition
exercise
sleep
medication
attendance at treatment sessions
Social variables
social support
family/dyad/other
religion
occupation
residence
race/ethnicity
socioeconomic status

and staff. ESRD patients exist in a complex network encompassing, at the min-

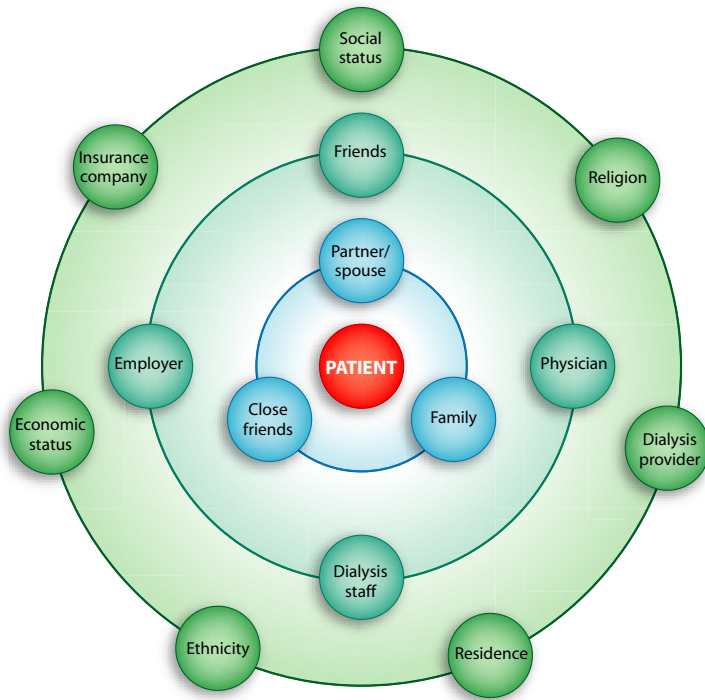


Figure 2. Psychosocial parameters: Spheres of influence.

imum, family, physicians, dialysis staff, clinic personnel, hospitals, and dialysis and insurance companies (Figure 2). This paper updates the literature on the mechanisms and impact of these psychosocial influences on HD patients, first outlined in 2001.²⁴

PSYCHOPATHOLOGY

In a review of hospitalization data from US Medicare ESRD patients who were treated with dialysis in 1993, the most common psychiatric disorders in the population were depression and affective disorders (26%), organic brain syndromes and dementia (26%), schizophrenia and other psychoses (22%), and drug and alcohol abuse (15%).²⁵ In our Brooklyn data, 19% of urban HD patients had an active substance abuse diagnosis and 10% had a diagnosis of psychosis.²⁶ In an in-depth analysis of

alcohol use in 163 urban HD patients, 27.6% were found to have troublesome use of alcohol.²⁷

DEPRESSION

The assessment of depression is complicated by the considerable overlap of depressive and uremic symptoms.^{2,3,28,29} However, the Beck Depression Inventory (BDI),³⁰ a measure of depressive symptomatology, has been shown to be a valid measure of depressive affect in HD populations.^{3,26,28,31–33} A BDI cut-off score of 14 to 16 appears to best approximate a psychiatric diagnosis of major depressive disorder in HD patients.^{3,26,31–33} The prevalence of a current depressive disorder in HD patients is estimated at 20% to 30% if all depressive disorders are included.³

There was no correlation between time since initiation of renal replacement

therapy (RRT) and BDI scores in our studies.^{34,35} We did not detect differences between mean BDI scores in incident and prevalent hemodialysis populations.³⁶ Using US administrative data, we showed that hospitalization for depression in ESRD patients treated with dialysis was a late event, occurring more frequently in patients treated for more than 2 yr rather than an early characteristic of the response to RRT.²⁵ Lopes *et al.* found a trend toward greater prevalence of depression, measured using subsets of Kidney Disease Quality of Life questions, in patients treated for ESRD for >1 yr.³⁷ In a recent study, Hedayati *et al.*³⁸ used the Veterans Administration database to identify 1588 male HD patients. The physician-diagnosed rate of depression was 14.7%. Over the course of 2 yr, a diagnosis of depression was associated with more hospitalizations and increased duration of hospitalization but not with overall mortality when variation in demographic and medical factors was controlled.³⁸

Depression possibly affects medical outcomes in ESRD patients through modification of immunologic and stress responses, impact on nutritional status, and/or reduction of compliance with, or access to, prescribed dialysis and medical regimens^{2,3,28,34} (Figure 3). Recent studies^{2,3,24,39,40} have described preliminary data regarding these mechanisms in patients with and without renal disease.^{41,42}

Immunologic Response

The “cytokine theory of depression”⁴³ posits that proinflammatory cytokines,

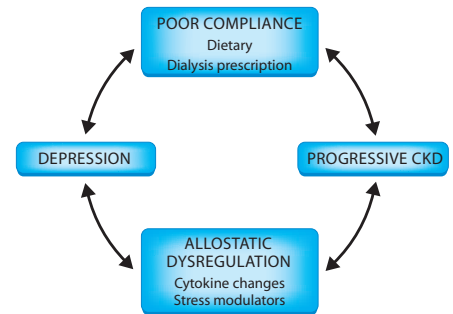


Figure 3. Potential mechanism of vicious cycle between depression and ESRD.

acting as neuromodulators, mediate the behavioral and neurochemical features of depression.^{44–49} There are several suggested mechanisms that might underlie this effect.^{50,51} One suggestion is that cytokine-induced hyperactivity of the HPA axis causes interference in the negative feedback of circulating corticosteroids.⁵² This dysregulation may also lower the availability of tryptophan by reducing levels of its precursor, 5-hydroxytryptamine (5-HT), an essential component of neurocellular function. Additionally, there is evidence that inflammatory biomarkers such as C-reactive protein are dysregulated and predict outcome in general^{53,54} and in ESRD patients.^{55–59} We^{55,60} and others^{56–59} showed cytokine levels were elevated in HD patients, and proinflammatory cytokines were associated with mortality. In subanalyses, increased cytokines were associated with increased depressive affect.⁶⁰ Stenvinkel *et al.*⁶¹ identified specific immunologic factors such as TNF- α and IL-6 that alter the cytokine network in uremia in ESRD patients. The chronic proinflammatory state intrinsic to ESRD is related to the higher than expected rates of cardiovascular disease and other medical causes of increased mortality in this population.^{55,62–65}

There is increasing literature to support an association between depression and risk factors for cardiovascular disease in patients without kidney disease.⁶⁶ Stress levels have modulating influences on the autonomic nervous system, which can lead to coronary vessel vasoconstriction, tachyarrhythmias, and other adverse cardiac events.⁶⁶ In addition, increased depressive affect has been associated with the production of various inflammatory cytokines including IL-6 and C-reactive protein in some studies.^{67–69} Inflammation is known to play a key role in the generation and progression of atherosclerosis.^{66,67,70} Depression is also associated with enhanced platelet aggregation *via* alterations in serotonin and catecholamine pathways.⁶⁶

Malnutrition

Although we were unable to detect an association between depression and mark-

ers of malnutrition in a group of 295 primarily black patients,⁷¹ other studies have demonstrated such links.^{72,73} Diversity in the study samples or treatment conditions may explain these disparate findings. In an interesting but methodologically flawed study, Friend *et al.* showed that depression preceded the decrease in serum albumin concentration in dialysis patients, implying that depression causes malnutrition and not the reverse.⁷⁴ There has also been increasing evidence for a molecular mechanism for the cachexia that occurs in CKD patients.^{75,76} Levels of TNF- α , a cytokine associated with cachexia, and cortisol, a stress hormone associated with depression and dysregulated carbohydrate metabolism, as well as other such mediators have also been shown to be elevated in ESRD patients treated with HD.^{55,77,78}

Treatment Compliance

Studies have indicated a relationship between depressive affect and both laboratory and behavioral markers of poor compliance in dialysis patients.^{79,80} Decreased behavioral compliance with the dialysis prescription correlated with increased depressive affect in prevalent HD patients.^{24,40,71,72,81} Decreased compliance with HD prescription has also been associated with poor medical outcomes and increased mortality.^{71,79,80,82,83}

Depression and Mortality

Depression has been associated with increased mortality in the general medical population.^{84–88} Gallo *et al.* performed a randomized controlled trial to study the effect of a depression intervention in twenty general medicine clinics from the Northeastern United States. They found a decrease in 5-yr mortality rates in the group randomized to the depression intervention.⁸⁹

A connection between depression and mortality in ESRD patients has been difficult to demonstrate. Some studies^{90–93} and our own work⁹⁴ initially indicated that depression was associated with mortality in this patient population. These studies, however, often compared means between groups of deceased and surviving patients without accounting for fun-

damental, potentially confounding medical and demographic factors (reviewed by Kimmel^{2,24}). Several more recent studies had been unable to detect associations between depression and mortality in HD patients.^{2,24,28,71,95–97} However, in a large multinational sample, ESRD patients treated with hemodialysis who were classified as depressed and those who reported frequent depressive affect had higher risk of mortality, withdrawal from therapy, and hospitalization.³⁷ The nontraditional assessment of depression used in this study make these results difficult to interpret. Nevertheless, the results seem to indicate a robust relationship between depressive affect and medical sequelae in contemporary HD patients around the world.⁷¹ Although we were able to detect associations between perception of increased burden of illness and mortality, and between perception of a high level of perceived social support and improved survival,⁷¹ the baseline level of depressive affect proved not to be a risk factor for increased mortality in our population of almost 300 HD patients. More recently, we performed longitudinal assessments of our study population to evaluate BDI scores obtained up to six times (mean 2.9) over a period of 20 mo to 5 yr. The scores were used as time varying covariates in Cox regression models of patient mortality.³⁵ An increased level of depressive affect over time was associated with increased mortality risk, even when analyses controlled for medical parameters.³⁵ We concluded that models incorporating multiple assessments of depression more accurately predict outcome while still accounting for patients' medical and nutritional status. The effect of timing of assessments, baseline conditions, and averaging depressive affect over time could prove critical when outcomes are assessed. Recently, Boulware and colleagues generated similar results when they evaluated baseline and longitudinal data from the Choices for Healthy Outcomes in Caring for End-Stage Renal Disease (CHOICE) study, a large cohort of incident patients starting peritoneal dialysis and hemodialysis.⁹⁸ Boulware *et al.* determined that levels of depressive

affect at the beginning of the study were not associated with increased overall mortality. However, similar to our findings, using several different time-dependent analyses, the investigators demonstrated that persistently higher levels of depressive affect over time were associated with increased risk of death and cardiovascular events in both adjusted and unadjusted analyses. From the currently available evidence, it is not clear whether depression has a direct causal role in poor outcomes associated with ESRD or if depression is merely a marker of increased disease comorbidity and illness severity.

Withdrawal from Dialysis

Estimates indicate that approximately 20% of US dialysis patients voluntarily choose to discontinue ESRD therapy.^{24,99–104} Interestingly, black patients are much less likely to withdraw from care than white patients across all ages.^{24,100} Age, medical complications, and failure to thrive are commonly associated with the decision to withdraw from ESRD therapy.^{24,100,101} A recent study found that depression was a predictor of the decision to withdraw from dialysis.¹⁰⁵ Despite the high rate of withdrawal from dialysis, the extent to which it should be considered a suicide equivalent is unclear and controversial.^{24,102,104} It is known that ESRD patients have the potential to commit suicide with relative ease through noncompliance, and, in fact, an early study reported rates of suicide to be 100 to 400 times higher in dialysis patients compared with the general population.¹⁰⁶ Another study of predominantly white patients from Minnesota found suicide rates of ESRD patients to be 0.2%, approximately 15 times greater than that of the general population.¹⁰¹ However, true suicidal behavior and ideation might be more difficult to differentiate in this population.^{24,34,103,105} The early findings might have been a result of evaluating white populations at high risk in an era of relatively primitive dialytic delivery techniques. More recent studies show suicide to be less prevalent in contemporary ESRD populations,^{24,99} although the rate

is 84% higher than in the general population.⁹⁹ Alcohol dependence and hospitalization for substance abuse and mental illness were strongly associated with subsequent suicide in the ESRD population.⁹⁹ This recent study shows definitively that populations that withdraw from treatment and those that actively commit suicide represent different clinical entities, highlighting that suicide is associated with alcohol and drug dependency and the presence of mental illness.⁹⁹ The complex relationship between depression, suicide, and withdrawal from treatment needs further clarification.

ANXIETY

In comparison to depression, anxiety disorders have received little clinical attention in the ESRD population. Most studies rely exclusively on self-report scales as a broad measure of anxious distress.^{107–109} Some of our unpublished data suggest that there is poor agreement between self-report measures of anxiety and a formal anxiety diagnosis in an urban HD population. Other studies have used structured clinical interviews to provide a formal anxiety disorder diagnosis. One study found a 30% rate of anxiety disorders in HD patients using the Primary Care Evaluation of Mental Disorders (PRIME-MD) as a diagnostic tool.¹¹⁰ By comparison, the same PRIME-MD questionnaire was given to 2316 general medical patients, and a 19% prevalence of anxiety disorders was found.¹¹¹ Our work in Brooklyn demonstrated a 27% prevalence of anxiety disorders using the Structured Clinical Interview for the DSM-IV (SCID).²⁶ The impact of high levels of anxiety or an anxiety diagnosis on outcomes is also unclear. Anxiety's negative impact on quality of life (QOL) and disability across multiple illnesses has been demonstrated, but its specific effect in ESRD has not been studied.¹¹² One study from Turkey found that depression but not anxiety correlated with interdialytic weight gain.¹¹⁰ Another Turkish study found that teaching progressive muscle

relaxation over a 6-wk course reduced both state and trait anxiety and improved QOL.¹¹³

Patients with depression and anxiety, or depression and another psychiatric diagnosis, may represent a population at particular risk. Comorbid (so-called "compound") depression has been associated with more profound physiological abnormalities and treatment resistance.^{34,114}

Treatment

Few studies have focused on the treatment of depression and anxiety disorders in ESRD patients. Treatment options including psychotherapy, cognitive behavioral therapy, and pharmacologic agents are similar to those used in the general patient population.^{24,115–118} However, treatment of psychological disease in the ESRD population presents unique challenges. Careful consideration of dose adjustments for level of GFR and dialysis schedule must be addressed each time medical therapy is being considered.

The challenges of treating depression in ESRD patients should not serve to limit use of appropriate therapy. Depression may be undertreated in ESRD patients. Watnick *et al.* reported that just 16% of HD patients with depression were receiving treatment.¹¹⁹ Ameliorating the symptoms of depression is important because it may improve other adverse outcomes associated with ESRD, including poor nutritional status and treatment compliance. This may in turn affect survival.^{2,3,34,120,121}

Pharmacologic options to treat depression include selective serotonin reuptake inhibitors (SSRIs), as well as the newer selective serotonin and norepinephrine reuptake inhibitors.^{24,34,115,122–125} Other agents such as tricyclic antidepressants, monoamine oxidase inhibitors, and St. John's wort should be avoided if possible because of potential exacerbation of common adverse events in dialysis patients, including drug–drug interactions, arrhythmias, and orthostatic hypotension.^{24,115,122,125} Patients who receive these antidepressant medications should be closely monitored for development of a prolonged corrected

QT interval.^{126,127} If this complication occurs, the antidepressant medication should be discontinued.

There have been limited studies evaluating the efficacy of SSRIs in ESRD patients.^{128–131} SSRIs should be favored over other antidepressant medication options because of their relatively limited side effect profiles, as well as their favorable potential to reduce the symptoms of orthostatic hypotension, a potentially debilitating problem for patients with ESRD treated with hemodialysis.^{24,115,132} A strategy is to reduce the initial starting dose of SSRIs by one third.^{115,125,133}

An important adverse event associated with SSRIs that should be considered before prescribing these agents is the potential to increase the risk of mania in bipolar disorder patients who are improperly diagnosed with depression.^{115,134–137} Initial administration of SSRIs may also be associated with an increased risk of suicide during the initial period of administration; however, this issue remains controversial.^{138–140} SSRIs may also exacerbate nausea and bleeding, two common uremic symptoms.^{115,121,141–147}

There have been no randomized clinical trials assessing the efficacy of psychotherapy for treating depression in this population,^{120,148} but there is some clinical evidence that these interventions might be effective.¹⁴⁹ Optimal treatment of depressive disorders in ESRD patients, therefore, may involve medical treatment, psychotherapy, or their combination.

The treatment options for anxiety disorders are similar. Like antidepressants, adjustment of anxiolytic dose for level of GFR is needed when these agents are prescribed.¹²⁵ Older treatment options for anxiety were limited to barbiturates and benzodiazepines. However, their unfavorable side effect profiles, particularly in patients with hepatic or renal failure, have led to the use of newer psychotropic agents including buspirone, a partial agonist of cerebral serotonin 5-HT_{1A} receptors.^{125,150–154} Antidepressant agents may also have a role in therapy for anxiety, including SSRIs such as paroxetine and the newer serotonin and norepi-

nephrine reuptake inhibitor venlafaxine.^{150–154} In clinical practice, anxiety may coexist with depression.²⁶ Additional studies are needed to determine the specific efficacy of these agents for treatment of anxiety in ESRD as well as general medical patients.¹⁵⁵ Close consultation with mental health professionals is always advised before the prescription of any psychotropic agents, particularly if ESRD patients display any complicated clinical symptoms suggesting suicidal ideation or mania.¹¹⁵

SOCIAL SUPPORT

Social support refers to a social network's provision of psychological and material resources intended to benefit an individual's ability to cope with stress.^{24,156–158} It is often divided into three types: instrumental, informational, and emotional.¹⁵⁷ Instrumental support involves the provision of material aid (e.g., financial assistance). Informational support refers to the provision of helpful information (e.g., guidance). Finally, emotional support involves the expression of empathy and provides opportunities for emotional expression. Another relevant concept is social integration, defined as participation in a broad range of social relationships.¹⁵⁸ It includes a behavioral component, active engagement in a wide range of social activities or relationships, and a cognitive component, a sense of communality and identification with one's social roles.¹⁵⁸

Social support and integration are now acknowledged as important factors in adjustment to chronic and acute illness.^{24,71,95,156–161} For example, one study of social integration in healthy participants demonstrated that the diversity of one's social network protected against developing the common cold after exposure to the virus.¹⁵⁹ Social support has been broadly and consistently linked to improved health outcomes in a variety of chronic illnesses in numerous studies independent of geographic settings, SES, and ethnic backgrounds.¹⁵⁶ In fact, differences in social support between groups has been suggested to underlie

differences in mortality of dialysis patients between units^{24,162} or among national populations,²⁴ perhaps as a result of differences in compliance.^{2,28,79} Although the relationships between social support, social integration, and health are robust, the mechanisms underlying the linkages have not been clearly delineated.^{24,71,156,163} Suggested mediators for improved health resulting from more developed social support and integration include better access to and utilization of health care, better compliance, and better "stress buffering" through improved psychological, neuroendocrine, nutritional, or immunologic functioning.^{156,161,163,164}

Several studies have shown an association between survival and perception of social support in ESRD patients of different ethnic backgrounds.^{71,95,160,161,165–167} McClellan *et al.* showed, in a prospective study, that a QOL measure, which included social support, predicted survival of HD patients.¹⁶⁶ Christensen *et al.* showed family cohesion, as a social support indicator measured by the Family Environment Scale, predicted survival in HD patients.⁹⁵ The effects of medical and treatment parameters such as nutritional status, delivery and intensity of dialysis, and patient compliance were not controlled in these studies, however. McClellan and colleagues further showed patients' assessment of level of giving social support predicted improved survival in HD patients.¹⁶⁷ The relationship of social support to other medical and psychosocial parameters, and functional status in particular, was not assessed. Most previous studies also did not include longitudinal reappraisals of psychological or compliance parameters. We showed increased perception of social support, measured by the Multidimensional Scale of Perceived Social Support, predicted survival even when variation in age, severity of comorbid illness, level of serum albumin, dialysis membrane type, and study site were controlled.⁷¹

High levels of social support have been associated with increased utilization of medical services (reviewed by Kimmel *et al.*⁷¹, Cohen *et al.*¹⁶¹, and Patel

*et al.*¹⁶⁸). Social support may affect compliance of ESRD patients treated with HD,^{24,71,79,157,161,168} although the findings have been variable, in part dependent on the parameters assessed in different populations. Support from family and caregivers correlated with a composite compliance measure in HD patients in an urban population (reviewed by Kimmel *et al.*⁷¹). Several studies have suggested that perception of social support was associated with increased compliance.^{71,79,160,161,169} In a study of HD patients in Utah, patients who perceived high family support had lower levels of interdialytic weight gain and better biochemical compliance measures.¹⁶⁰ Leggat *et al.*, in a large study performed using data from the United States Renal Data System, found patients living with someone, rather than living alone, were less likely to shorten HD treatments.⁸³ There was, however, no association of household composition with attendance, interdialytic weight gain, or level of serum phosphate. Moreover, other studies either could not establish relationships between measures of social support from family and friends and compliance measures of HD patients, and such studies have also failed to show a correlation between greater perception of social support and compliance.⁷¹

Indices of social support correlated with level of depressive symptoms, perception of illness effects, and satisfaction with life in our studies.^{24,35,36,168–171} One recent ESRD study found that optimism was a mediating influence between social support and depression.¹⁷² Another recent study¹⁷³ highlighted the need to account for the role of individual differences in the relationship between support and depression. The investigators found that greater social support among individuals high in the personality trait of “agreeableness” was associated with a decrease in depressive symptoms over time, whereas support had little effect on depression change for individuals low in “agreeableness.” Social support may affect psychological, medical, and biochemical factors in other unknown ways to engender better health outcomes.^{71,156,168,169}

MARITAL AND FAMILIAL ISSUES

The intimacy of a relationship with a life partner may be intense and complex. Such relationships may have positive aspects, such as associations with greater perceived social support, or negative ones, perhaps associated with hostility. Marital stability, satisfaction, and perceptions of hostility have been associated with differential health outcomes in the general population.^{60,174–178} Unhappily married individuals report poorer health than do happily married or divorced people with similar demographic and health characteristics. Marital quality has predicted length of stay after bypass surgery for women, but not for men.¹⁷⁹ Declines in reported marital satisfaction have been associated with subsequent poorer health evaluations. One fascinating study¹⁸⁰ found that couples’ blister wounds healed more slowly and local cytokine production (IL-6, TNF- α , and IL-1) was lower at wound sites after marital conflicts than after social support interactions. Kiecolt-Glaser and colleagues also found that hostile couples produced relatively larger increases in plasma IL-6 and TNF- α values the morning after a conflict than after a social support interaction compared with couples without conflict.¹⁸⁰ Marital conflict may affect perceptions of illness and interfere with the ability of a patient to comply with the complex regimen entailed by RRT.

The development of a chronic illness in a couple may place strain on usual marital roles. Spouses can become caregivers and may experience depression and/or hostility. There also might be changes in the patient’s ability to work, forcing a further shift in the individual’s roles within the dyad. In addition, the spouse may be the object of the patients’ negative emotions. Finally, sexual dysfunction can change the dynamics of the relationship.^{181,182} Few studies exist on spousal or family relations in ESRD patients, and almost none focus on outcomes.^{182–190} Most studies performed within families of HD patients have assessed comparisons of members of dyads or families on psychosocial tests.

More than half of couples including a patient with ESRD had evidence of marital disruption.¹⁸² Chowanec and Binik¹⁸⁷ showed dialysis patients and spouses had strong links between psychological distress and perceptions of marital strain. Twenty percent of spouses of dialysis patients had “significant depressive symptoms” in a Canadian study.¹⁸⁷ Spouses’ level of distress was not correlated with level of patient function or depression. Social support received from the patient and social and financial stressors experienced by the spouse accounted for a large proportion of spouse perceptions. Another study suggested women caregivers of ESRD patients perceived good QOL and no evidence of burden, but these two parameters were correlated.¹⁹¹ Lowry and Atcherson found lower levels of anxiety, depression, and marital problems in a group of carefully screened home dialysis spouse partners in Iowa than others reported,¹⁹² although the reasons underlying differences between this study and others are unclear and may relate to selection bias. Berkman, Katz, and Weissman found that, although there was a high prevalence of sexual dysfunction in home dialysis patients, marital and social adjustment scores were comparable to those of the general population.¹⁹³ Moquilner, Bauman, and De-Nour found a correlation between patient and spouse BDI scores.¹⁹⁴ We found that spousal levels of depression correlated with extent of HD patients’ depressive affect, and the greater the level of social support the spouse reported, the less strain they identified in the marriage.¹⁸⁶

Marital conflict has been associated with endocrinological and immunologic changes in women, but not men, in subjects without renal disease.¹⁹⁵ A study of 68 Israeli prevalent HD patients and their spouses revealed high levels of distress compared with normative groups and high correlations between distress scores of spouses.¹⁸⁴ Married female patients had less anxiety than married male patients. However, male spouses had higher levels of distress than female spouses. Giving and receipt of social support within a marriage may also change

during the ESRD life cycle. In Canadian couples including a patient with ESRD, women patients felt that family support declined after the onset of illness, but no change in perceived support was noted by male ESRD patients.¹⁸⁵

We studied the relationships between medical factors, neuro-endocrinological and immunologic factors, and outcome in a subset of 174 male and female HD patients functioning in dyadic relationships.⁶⁰ Dyadic satisfaction scores were comparable to those of normative populations, although the women had more negative assessments of their marriages than the men. Interestingly, a different pattern of interactions for men and women was noted. For women, higher levels of depressive affect and increased perception of the burden of illness correlated with increased severity of illness, and greater circulating levels of IL-1 and β -endorphin. Marital satisfaction and conflict scores correlated with medical risk factors, psychosocial parameters, and circulating IL-1 and β -endorphin levels, but again, only in the women in the study. Finally, neurologic, immunologic, and marital indices predicted differential survival in the study group, but the dyadic indices were associated with outcome only in the women. It appears that strong negative emotion, such as perception of dyadic conflict, may be a particularly important stressor in women HD patients, activating physiological and neuroendocrinological pathways.

To expand our understanding of familial support beyond the dyad, we surveyed a prevalent population of almost 500 black HD patients. We defined family composition in terms of size and structure, with a simple household defined as one in which the patient lived alone or only with a spouse or partner, and a complex household as being characterized by patients living with various combinations of relatives and nonrelatives, often in multigenerational groups. After an approximately 3-yr observation period, Cox regression analyses revealed only age and household structure emerged as associated with survival. Patients who lived in complex households

had significantly increased risk of mortality, but once again the findings were driven solely by the effects in the group of women.¹⁹⁶

These data suggest that black women with ESRD treated with HD functioning in complex households or in difficult marital situations may be at particular risk. This risk may relate to their gender roles or expectations regarding family duties in people with limited economic resources and/or diminished social support in such settings.^{24,168} Because previous studies have suggested stress and inflammatory responses, and depressive symptoms are greater in women than men,¹⁹⁵ perhaps these factors mediate outcomes for women more than men with ESRD.

UNIT CULTURE

Given the amount of time most HD patients spend at their dialysis site, it is reasonable to speculate that their relationships within the dialysis unit play an important role in determining adjustment and outcomes, but there are few data available on these issues. One study showed that unmeasured dialysis unit characteristics predicted survival better than the characteristics predicted by differences in case-mix.¹⁶² We have demonstrated that dialysis unit staff exhibit sustained characteristics over time in spite of the high turnover of individual employees, suggesting that a particular “culture” typifies each dialysis unit.¹⁹⁷ To understand the relationship between patients’ feelings about the dialysis staff and outcomes, we surveyed HD patients regarding their level of satisfaction with their nurses, technicians, and nephrologists. Patients’ increased satisfaction with staff and their perception that staff cared about them correlated with better dietary compliance. Interestingly, patients’ increased satisfaction with physicians, but not nursing or technical personnel, correlated with improved attendance and greater total time compliance with the dialysis prescription.¹⁹⁸

The impact of social work groups on the unit or organized social activities are

unknown and should also be explored further. It is clear that the culture of the dialysis unit and the connectedness the patient feels to the dialysis staff are important factors and may mediate differential outcomes in dialysis programs with similar patient populations. Specifically, the role of dialysis providers, particularly physicians, may impact HD patients’ compliance.

SOCIOECONOMIC AND CULTURAL ISSUES

SES has been shown to have a significant impact on the incidence and treatment of ESRD.^{199,200} Norris and Agodoa²⁰¹ have developed a model highlighting how socioeconomic factors such as low income, poor education, residence in low-income areas, and poor access to health care are strong predictors of the development of ESRD. Not enough study has been given to the notion that differential quality of physician care may characterize programs in different neighborhoods. The relationships between race, SES, and ESRD outcomes are quite complex and may result from their synergistic combination.^{24,202} Few studies have assessed the relationship between survival and SES in the ESRD population. Dialysis Outcomes and Practice Pattern Study (DOPPS) data have suggested that higher SES was associated with improved survival, regardless of race.²⁰³ A startling finding is the differential survival of black patients compared with whites in the United States ESRD program^{100,199,202} because in almost all cases higher SES is associated with improved survival in chronic illnesses.²⁰⁴ Rodriguez *et al.* recently found higher mortality rates among white and black dialysis patients living in areas with zip codes that were predominately composed of blacks. They also found lower rates of transplantation in communities that were made up of a majority of blacks.²⁰⁵ In a preliminary investigation,²⁰⁶ we found a paradoxical association in which minority patients living in areas with higher in-

equality of distribution of income in the United States had poorer outcomes. These findings are tentative and the underlying reasons are unclear, but they may reflect different allocation of resources between groups in the same residential area, differential access to health care and services, discordance between viewpoints of physicians and patients, or the effects of discrimination.²⁰⁷ Another factor to consider is the interplay of the ethnicities of the patient and the physician. There is evidence that there is decreased trust on behalf of patients when they are of a different ethnicity than the physician.²⁰⁸ The influence of residential factors on ESRD patient outcomes requires further study.

According to a 2001 survey, 55% of Hispanic and 45% of black populations were uninsured or received publicly funded health care, compared with 22% of the white population.²⁰⁹ Minority populations in the ESRD program in the United States may be subject to the consequences of inequitable distribution of resources.

Culture may also play an important role in forming attitudes to health care, including how illness is perceived and what form treatment should take.²¹⁰ For instance, many minority and immigrant populations may have attitudes toward illness and health care that put them in intellectual conflict with the views of their physicians.^{79,210,211} These attitudes may be based on spiritual and religious beliefs, and there may even be a general skepticism toward Western medicine. Cultural beliefs may also affect lifestyle factors, such as diet, exercise, and body image, contributing to differential rates of obesity, hypertension, and diabetes among racial and ethnic minorities.^{200,201,212} The relationship between psychosocial functioning, culture, and SES may explain their connection to health outcomes in the ESRD population.²¹²

CONCLUSIONS

Patients with ESRD treated with HD deal with the multiple stressors of their illness

and attempt to make their way through life in the context of their intimate relationships, families, social networks, treatment programs, and cultures. They must cope with the demands of their occupations, the changes in their life roles, and the challenges and opportunities that life exposes them to while balancing the restrictions that life on HD entails. As opposed to the mostly invariant biological factors, psychosocial factors are a potential target for successful intervention.^{2,3,24,28,120,149,213,214}

Over the past decades, a tremendous amount has been learned about the physiological and psychological reactions of dialysis patients. Despite this growing body of research, there are many essential elements that are still unknown. The impact that mental health treatment has on outcomes is still unclear. Some evidence^{2,3,28,120,123,124,149} suggests that depression can be successfully treated in ESRD populations, but the potentially greater impact of improved psychological functioning on burden of care, intimate relationships, compliance, QOL, and mortality is largely unexplored. The results of interventions in earlier stages of renal disease are also unknown, as well as the role of interventions in children.^{2,120} The role that quotidian dialysis might have upon psychosocial variables has also not been studied in a rigorous manner.²¹⁵

Although this field of research is still in its infancy, the fields of stress medicine and psychoneuroimmunology are beginning to make connections between emotions and their biological mediators. In many ways ESRD is an excellent research paradigm for the study of the intertwined effects of medical and psychosocial factors in chronic disease, as patients are available for assessment on a consistent basis, standard biochemical markers that are related to outcome are easily measurable and obtainable, and the patients are in great need of supportive services. Nephrologists, psychosocial researchers, and ESRD patients can collaboratively contribute to understanding the impact of stress and the body's attempts to regain allostasis by helping

make the connections between psychosocial and biological variables.

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DISCLOSURES

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