Original Article

An Observational Study on Depressive Illness in Hemodialysis Recipients: A Review on its Association and Prognostication

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Abstract:

Major Depressive Disorder (MDD) is one of the most common psychiatric illnesses. The effect of depression on one's physical health is well-known, which can include anything from weight gain or loss to chronic illnesses such as heart disease, kidney or gastrointestinal problems. Provided the increasing prevalence of patients suffering from End Stage Renal Disease (ESRD) and receiving hemodialysis treatment, it is important to investigate how MDD affects the outcome of their treatment. The incidence of depression in dialysis patients ranges from 10% to 66% in various studies, with prevalence reaching as high as 100%. The purpose of this article is to find the prevalence and severity of major depressive disorder in dialysis patients as well as to describe the possible pathways MDD worsens the dialysis outcome. Our study population consisted of 51 End Stage Renal Disease (ESRD) patients sampled from the Department of Nephrology at BIRDEM General Hospital. Neurocognitive, physical symptoms, the severity of MDD and presence of comorbid conditions including diabetics and hypertension, were measured in our study. The ESRD patient sample consisted 47.7% moderately depressed patients, 34% severely depressed, 11.4% mild and 6.8% with minimal MDD patients. Analogous to Hypertension and Diabetic patients with depression, the number of Chronic Kidney Disease (CKD) patients with mostly moderate severe depression increased with the duration of the disease. The article explains a myriad of biologic, behavioral, genetic and social factors underlying the association of depression and adverse medical outcomes in patients with CKD and ESRD. Moreover, neuroimaging data is required for further discussion on relationship between Depression and CKD. The implication of this study is to emphasize the importance of dialysis patients' overall health and to serve as a pretext for further research into depression in dialysis patients.

Keywords : *Compound depression, Major depressive disorder (MDD), Major depressive episode (MDE), Dialysis, End stage renal disease (ESRD), chronic kidney disease (CKD)*

Abbreviations

MDD: Major Depressive Disorder; MDE: Major Depressive Episode; HD: Hemodialysis; rCBF: Right Cerebral Blood Flow; ESRD: End Stage Renal Disease; CKD: Chronic Kidney Disease; RRT: Renal Replacement Therapy; DSMV: Diagnostic and Statistical Manual of Mental Disorders; BDI II: Beck Depression Inventory Second Edition; DM: Diabetes Mellitus; HTN: Hypertension; AKI: Acute Kidney Injury; WMHs: White Matter Hyperintensities; IHD: Ischemic Heart Disease; MRI: Magnetic Resonance Imaging.

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Introduction:

There are approximately two million End Stage Renal Disease (ESRD) patients worldwide, who regularly receive Renal Replacement Therapy (RRT) in the form of hemodialysis[1]. Depression has been associated with poor quality of life and adverse medical outcomes in patients with CKD or ESRD [2-5] . The etiology of compound depression in ESRD is dynamic complicated by both neurocognitive somatic features. While prevalent, depression is still often unrecognized, reflecting a lack of routine psychological evaluation among this patient population[6-7]. The consequences of unidentified depression among dialysis patients are significant. Comorbid depressive illnesses amplify the impact of chronic illnesses, increasing functional disability as well as the use of healthcare services. Most common psychopathological condition occurring in patients with Hemodialysis (HD) is depression[8-10]. This article describes the possible pathways MDD worsens the dialysis outcome.

Methodology

This was an observational, cross-sectional and prospective study on recently diagnosed ESRD patients. 51 ESRD patients were sampled from Department of Nephrology at BIRDEM General Hospital (A tertiary care hospital) during July 2017 to December 2017. Informed written consent was taken from patient and privacy was maintained. Diagnostic and Statistical Manual of mental disorders (DSM-V) was used as a diagnostic tool. Major Depressive Disorder (MDD) was graded as minimal, mild, moderate and severe by Beck

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Table 1

Parameters		Frequency	Percentage
Sex	Male	25	47.2
	Female	26	49.1
Age (in years)	> 30	1	1.9
	30-50	14	26.4
	50 and above	34	64.2
Marital status	Married	44	83
	Unmarried	1	1.9
	Widow	1	1.9
Occupation status	Employed	11	20.8
	Unemployed	11	20.8
	Widow	23	43.4
Habitat	Urban	26	49.1
	Rural	16	30.2
	Semi Urban	4	7.5
Educational status	Uneducated	3	5.7
	Below SSC*	23	37.7
	SSC*	7	13.2
	HSC*	8	15.1
	Graduate	7	13.2
Monthly income (in BDT)	Less than 10000	2	3.8
	10000	6	11.3
	20000 and above	34	64.2
Family members	2	2	3.8
	3	3	5.7
	4	10	18.9
	More than 5	27	50.9

SSC: Secondary School Certificate (equivalent of grade 10 completion; *HSC: Higher Secondary School Certificate (equivalent of grade 12 completion).

Depression Inventory. The Beck Depression Inventory Second Edition (BDI II) was a 21 items self-reported instrument for measuring the severity of Depression in adults and adolescents aged 13 years and older[11] . Exclusion criteria included refusal to participate in the psychiatric interview, patients who were diagnosed with psychiatric disorders other than MDD and patients with prior history of any psychiatric illness. A single psychiatrist interviewed all study subjects.

Results

The following comorbid conditions were present among the study subjects- Alport syndrome, Epilepsy, Kidney TB, Antral gastritis, Acute Respiratory Failure (ARF), Obstructive sleep apnea, Ischemic Heart Disease (IHD), Acute Suppurative Otitis Media (ASOM), Electrolyte imbalance, Chronic Glomerulonephritis (CGN), Hyperkalemia, hyperparathyroidism, Coronary Artery Bypass Graft (CABG), Cholelithiasis, Hypoalbuminemia, Hypokalemia, Hypothyroidism Urinary tract infection (UTI), Asthma, Diabetic retinopathy (DR), Fracture, Xerotic dermatitis, Eczema, Pulmonary Tuberculosis (PTB). Hemorrhoids, Sepsis, Stroke, Facial palsy, Thyroidectomy, Benign Enlargement of Prostate (BEP). The most frequent comorbid condition was Diabetes and Hypertension and followed by Ischemic Heart Disease (IHD) which constitutes around 13.5% of the study subjects.

All the patients in the study population had Diabetes Mellitus (DM), Hypertension (HTN) and Major Depressive Disorder (MDD).Table 1 shows the sociodemographic parameters of the study sample which belongs to the moderate socioeconomic class with the bulk educated up to less than HSC and mostly female. Table 2 gives the picture of CKD with depression

Table 2

MDD Severity	Duration of CKD			
	1 yr	**2-5 yrs**	**More than 5yrs**	**Total**
Minimal	0 (0.0%)	1 (3.1%)	0 (0.0%)	1 (3.1%)
Mild	1 (3.1%)	1 (3.1%)	1 (3.1%)	3 (9.4%)
Moderate	7 (21.9%)	10 (31.2%)	3 (9.4%)	20 (62.5%)
Severe	1 (3.1%)	6 (18.8%)	1 (3.1%)	8 (25%)
Total	9 (28.1%)	18 (56.2%)	5 (15.6%)	32 (100%)

Table 3: Frequency distribution of depression with DM duration

MDD severity	Duration of DM			
	1-3 yr	**3-10 yrs**	**10 and > 10yrs**	**Total**
Minimal	0 (0.0%)	1 (2.4%)	3 (7.1%)	4 (9.5%)
Mild	0 (0.0%)	0 (0.0%)	4 (9.5%)	4 (9.5%)
Moderate	2 (4.8%)	2 (4.8%)	17 (40.5%)	21 (50%)
Severe	0 (0.0%)	1 (2.4%)	12 (28.6%)	13 (31%)
Total	2 (4.8%)	4 (9.6%)	36 (85.5%)	42 (100%)

Table 4: Frequency distribution of depression with the duration of Hypertension.

MDD Severity	Duration of Hypertension in Years			
	1-3 year	3-10 yrs	10 and < 10 yrs	Total
Minimal	2 (4.9%)	2 (4.9%)	0 (0.0%)	4 (9.8%)
Mild	0 (0.0%)	2 (4.9%)	2 (4.9%)	4 (9.8%)
Moderate	3 (7.3%)	7 (17.1%)	12 (29.3%)	22 (53.7%)
Severe	1 (2.4%)	6 (14.6%)	4 (9.8%)	11 (26.8%)
Total	6 (14.6%)	17 (41.5%)	18 (43.9%)	41 (100%)

Table 5: Co-morbid condition and depression among the study subjects.

Parameters		Duration (in years)	Number of patients with MDD	
Co-morbid condition	**Diabetes**	1-3	2 (4.8)	Total 42 (100%)
		3-10	5 (11.9%)	
		> 10	35 (83.3)	
	Hypertension	1-3 yrs	7 (17.1%)	Total 41 (100%)
		3-10	17 (41.5%)	
		> 10 yrs	17 (41.5%)	
	Chronic Kidney Disease	1 yr	10 (28.6%)	Total 35 (100%)
		2-5 yrs	17 (48.6%)	
		> 5 yrs	8.75 (25.0%)	

Table 6: Severity of depression among the study subjects

Depression Severity	Frequency (percentage)
Minimal	3 (6.8%)
Mild	5 (11.4%)
Moderate	21 (47.7%)
Severe	15 (34.1%)
Total	44 (100%)

With mostly moderate severity and the number increasing with the duration of kidney disease i.e. from 2 to 5 years. Table 3, Table 4 show frequency of distribution of depression in DM and Hypertension respectively. Table 5 shows frequency of distribution of depression in DM, Hypertension and CKD as co morbidity.

Discussion

This study result can compare and contrast with the studies done home and abroad. The severity of MDD are measured in our study [12, 13]. Depression increase the risk of chronic diseases such as diabetes, chronic heart disease, and heart failure with their accompanying complex medical regimen and poly pharmacy. Other pathways include poor adherence to medical regimen and other adverse health behaviors such as smoking and alcohol over use. Depression is also related to delay health care seeking behaviors, difficulties in patient-physician communications, and possibly medical errors leading to Acute Kidney Injury (AKI). Substantial variability is noted in the consideration of depression severity. Some studies indicated that moderate depressive syndromes are common in approximately 25% of ESRD patients, and that severe major depression in 5%- 22% of ESRD patients, coinciding with the present study. Dialysis is an unstable and critical period, and that levels of depression may change over times[14, 15].

Mechanisms by which depression associates with adverse outcome

There are several potential biologic mechanisms that can explain the association between depression and poorer medical outcomes in patients with CKD and ESRD[16]. There are behavioral consequences of depression, which may adversely affect medical outcomes. Inpatients with ESRD, depression has been associated with medication

noncompliance, dietary indiscretion, inter dialytic weight gain, and missed dialysis. In a study of 65 hemodialysis patients and 94 kidney transplant patients. Cukor, et al. evaluated the association between psychological measures and self-reported medication adherence, and found that depressive symptoms are a significant independent predictor of lower medication adherence[17]. Furthermore, in a study of 295 hemodialysis patients by Kimmel, et al. worsening depressive symptoms are correlated with worse compliance with total dialysis time[8]. Noncompliance with self-care behaviors could worsen blood pressure, blood glucose, cholesterol, bone metabolism, anemia, phosphorus, and volume status in patients with CKD and ESRD, and ultimately lead to adverse health outcomes[16] Hypothesized mechanisms include biologic, behavioral, genetic, and social factors[9], ranging from inflammatory factors (e.g., C-reactive protein, cytokines) or chemical imbalances (e.g., higher levels of phosphorus, uremia and lower levels of hemoglobin[18], hormones like high levels of cortisol, etc.) to physical inactivity and lack of social support[10]. There is evidence of an association between Malnutrition, Inflammation, and Atherosclerosis (MIA) in ESRD patients, and some researchers have suggested that depression might be involved in the MIA syndrome. Others have demonstrated frequent and close relationships between serum albumin levels and depression[19].

Depression is associated with dialysis shift, psychological and social factors which include feelings of hopelessness, perceptions of loss and lack of control, job loss, and altered family and social relationships. Approximately 60%-97% of patients on HD experience some fatigue, which is negatively correlated with quality of life[20]. In a study, 83.49% of harem dialyzed patients have depressive disorders, including 54.85% mild and 28.64% moderate depression. In the subgroup of peritoneal dialyzed patients, moderate depression is identified in 15.63% of respondents[21].In another study[22] on 241 Maintenance Hemodialysis (MHD) patients in Boston (USA) area, 57 (23.7%) participants with significant depressive symptoms are found. In another research, 323 patients with End Stage Renal Disease (ESRN) were compared with a control group of primary health care patients[23]. The group of patients with end stage renal disease got significantly higher scores in (Beck Depression Inventory) BDI[21] compared to primary health care patients. The BDI results indicate that depression is present in patients with mild or medium renal insufficiency. The incidence of depression in dialysis patients ranges from 10% to 66% in various studies [24-29].

Depressive disorder is the most frequently described psychiatric condition in patients with End-Stage Renal Disease (ESRD). Prevalence can be as high as 100%[30]. Depressive symptoms are more likely to develop rapid declines in kidney function and develop clinical renal outcomes including ESRD and hospitalization with AKI during follow-up[31]. Depression predicts subsequent rapid decline in kidney function, in new onset clinically severe kidney disease (or end-stage renal disease), and hospitalizations that are complicated by acute kidney injury. Substance abuse, alcoholism and suicidal tendency are common in depressive illness[32]. In our study, substance abuse, alcoholism and suicidal thoughts, attempts and deliberate self-harm are absent. The difference may be due to the collectivistic nature of the study population that promotes increased family support, religious and social constraints as well as emotional resilience[33]. The lurking crisis of Bangladeshi dialysis patients, represented in this study is recent unemployment due to CKD which comes as a curse along with the profound physical disability. In a recent meta-analysis, patients on dialysis were reported to have higher rates of depression and increased risk of hospitalization due to psychiatric disorders than individuals undergoing conservative treatment and post-transplant patients. Those with Major Depressive Episode (MDE) had a higher risk of death, hospitalization, or maintenance dialysis initiation within 12 months of MDE diagnosis compared with those without an MDE[34]. Patients with both CKD and MDE have almost twice the risk of being hospitalized[31,35-37]. Several comorbidity conditions like cerebrovascular disease, hypertension, and diabetes are found in the present study and others[38]. In patients on chronic hemodialysis therapy, depression is related closely to nutritional status and could be an independent risk factor for malnutrition[39].

The relationship between CKD and depression in neuroimaging

Kim, et al. demonstrated that in 27 patients with CKD, regional cerebral blood flow (rob) patterns correlate with symptom clusters of depressive mood[40]. More recently, Nam, et al. studied 14 patients with CKD before and 6 months after HD and found correlations between reduced levels of depression, higher perfusion in the left middle temporal gyrus, and higher rCBF in the right Para hippocampal gyrus[41]. These latter findings implicate the importance of the kidney-brain connection, not only in the neurologic aspect of cognition and learning but also in the affective presentation of many individuals with CKD, particularly with respect to the appearance of affective disorders[40]. Hemodialysis patients had more severe white matter disease and cerebral atrophy (sulci prominence=2.3 vs 0.6; ventricular enlargement=2.3 vs 0.9; hippocampal size=1.3 vs 1.0) with all p-values <0.001. Hemodialysis patients also had a higher prevalence of small (17.8%) and large (7.8%) vessel infarcts than controls (combined 22% *vs.* 0%, p <0.001)[42]. Patients with vascular diseases often have depression. In a sample of 15186 patients treated in a primary care setting, we observed that those with significant depressive symptomatology had a higher frequency of vascular disease than non-depressed patients[43]. Approximately 8% of depressed patients had hypertension, 9% had ischemic heart disease, 13% had peripheral vascular disease, 7% had stroke, and 9% had heart failure. The corresponding percentages for non-depressed patients were 4%, 4%, 4%, 5%, and 4%, respectively. Silent stroke, stroke without neurological signs, is frequent in elderly depressed populations. In a Japanese sample, silent cerebral infarction was found in 83% of major depressives older than 65 years. Silent cerebral infarction was observed in 94% of patients

with onset of first depressive episode after 65 years of age [44]. Elderly depressives and especially late onset depressives have white matter hyper intensities (WMHs) more frequently than no depressed individuals. WMHs correspond to areas of arteriolar ectasia, enlargement of perivascular spaces, and myelin pallor associated with arteriosclerotic changes of perforating arteries. Lesions in the basal ganglia are associated with depression. Approximately 40% to 75% of depressed elderly patients have lesions of the thalamus and basal ganglia, while only 5% of normal elderly controls have such lesions, and their lesions are smaller than the lesions of elderly depressives[45].

End stage renal disease patients who have been on long-term hemodialysis tend to develop central nervous system complications. The most common neurologic complications in the dialysis patient group include white matter changes, cerebral atrophy, osmotic demyelination syndrome, dialysis encephalopathy, hypertensive encephalopathy, intracranial hemorrhage, infarct, sinus thrombosis, and infection[46]. Lesion generation has been attributed to endothelial damage, giving rise to a pathological hemodynamic and cerebrovascular regulation which, in turn, is unable to maintain stable cerebral blood flow. This hypo-perfusion model has been shown to lead initially to an impaired protein synthesis, crucial in both cognitive and affective processing. Further vascular dysfunction culminates in the ischemic injury of specific tissue, sub-cortical white matter being especially sensitive due to its limited supply by terminal arterioles with little to no collateral flow[47]. The majority of studies in patients with ESRD have reported an association between depression and poor psychosocial and medical outcomes, with only a minority reporting no association. In a recent systematic review, Farrokhi, et al. identified 31 studies of 67,075 patients examining the association between depression and mortality in patients with ESRD receiving long-term dialysis[48]. In 18 studies, the authors found that the mortality risk in patients on dialysis was 1.5 times higher in the presence of depressive symptoms independent of other confounding factors. They also found that this relationship was dose dependent, that is, the more severe the depression, the higher the risk of mortality[16]. Another potential biological mechanism that may lead to depression in patients with CKD and ESRD is the direct effect of comorbid cerebrovascular disease, which is highly prevalent in patients with kidney disease, on the mood regulatory functions of the brain. For example, specific post stroke lesions in the left anterior and left basal ganglia, and those close to the frontal pole, have been associated with depression. Cerebrovascular disease may also indirectly affect mood by increasing inflammation [49-51].

Further research is needed to identify bio behavioral mechanisms by which depression adversely affects renal disease outcomes[31].

Limitation and Future Research

Psychiatry is a stigmatized subject among common people in Bangladesh. Moreover, CKD patients were already irritable and noncompliant which made the data collection challenging. More finance would have increased the study sample. Neuroimaging using MRI would have added more information to our research. Further research is needed to identify bio-behavioral mechanisms by which dialysis treatment outcome may improve.

Conclusion

Prevalence of MDD among CKD and ESRD patients propels the vicious cycle where dialysis treatment is undermined and the patients' overall health outcomes are compromised. Treatment of the physical ailments become more challenging when it is compounded with mental disorders such as MDD. Lack of education, shortage of overall government health funding, stigma of mental health conditions and scarcity of desired resources, especially in developing countries such as Bangladesh, means that issue of MDD goes seemingly unaddressed, which further enhances the complexity of the issue. Thus, depressive disorder deserves more attention in context to the management of dialysis patients. Improvement of dialysis treatment outcome relies on utilization of a multifaceted intervention approach that encompasses social, political, biological and cultural models of health to address the proper diagnosis and treatment of depressive disorder.

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