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Depression and high sensitivity C reactive protein in regular hemodialysis patients

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Abstract

Depression is a common psychiatric problem in patients undergoing hemodialysis. Depression is associated with increased mortality in these patients. Chronic hemodialysis is associated with high levels of proinflammatory cytokines, recent studies suggest that inflammation may play a role in the pathogenesis of depression. The aim of the study was to estimate the prevalence of depressive symptoms in haemodialyzed patients in Ain Shams University hemodialysis unit and the possible association between inflammation and depression in these patients. **Patients and Methods:** Seventy haemodialyzed patients from Hemodialysis unit of Ain Shams University Hospital were enrolled into the study. Meanage was 48.59 ± 11.59 years .Each patient received21-item Beck Depression Inventory (BDI) questionnaire for depression screening. Additional questions considering length of dialysis treatment, concomitant diseases and number of days spent in hospitals during the last year were also asked. **Results:** Depressive symptoms were found in 43(61.4%) patients. Patients with depressive symptoms when compared with the patients without them tended to have higher High sensitivity C-reactive protein(hs-CRP) plasma concentration(29.35 ± 15.83 vs. 3.09 ± 3.23 mg/l; $p < 0.001$). During the last year, patients with depressive symptoms spent in hospitals more days than patients without depressive symptoms (10.23 vs.2.07 days, respectively; $p<0.001$). using logistic regression analysis, only hs-CRP level has an independent effect on the presence of depressive symptoms among studied hemodialysis patients. **Conclusions**: (1) Depressive symptoms are frequently found (61.4 %) in haemodialyzed patients in Ain Shams University hospital . (2) inflammation seems to play an important role in the pathogenesis of depression in haemodialysis patients.

Keywords: Depression, Hemodialysis, Inflammation.

Introduction

Major depression is the most common psychiatric disorder in patients with end-stage renal disease (ESRD)[(1)]and reported prevalence of depression in ESRD patients is much higher than in general population[(2)]Depression is associated with a 30-48% increased risk of mortality in ESRD after adjustment for age, race, socioeconomic status, and medical comorbidities.[(3)] Dialysis patients with depression have lower quality of life, lower adherence to drug treatment, higher rates of hospitalization, cardiovascular disease events, and mortality[(3,4)]

It is important to distinguish between depressive symptoms in dialysis patients and the syndrome of clinical depression, recent studies that have employed the Beck's Depression Inventory (BDI)—a standard self-administered questionnaire commonly used in psychiatric practice to screen patients for depression-have reported remarkably similar findings[(3,5,6)]. These studies note that between one-third and one-half of dialysis patients have scores suggesting the presence of at least a moderate degree of depression.

The BDI is a 21-item self-report instrument, used for screening and evaluation of thes everity of depressive symptoms with scores ranging from zero to 63, Scores higher than 10 for the general population and scores equal to higher than 15 for hemodialysis patients are defined as indication of clinical depression and it has been used extensively in ESRD populations[9]

Chronic inflammatory state is greatly prevalent among advanced chronic kidney disease (CKD) patients.[7,8] The etiology of inflammation in patients with advanced CKD is multifactorial. Decreased renal function,[10]persistent infections,[11] obesity,[12] the dialysis procedure itself,[13] retention of circulating cytokines,[14] pro-oxidants[15] contribute to a proinflammatory environment in CKD and dialysis patients.

Patients with major depression have been found to exhibit increased peripheral blood inflammatory biomarkers, including inflammatory cytokines, which have been shown to access the brain and interact with virtually every pathophysiologic domain known to be involved in depression, including neurotransmitter metabolism, neuroendocrine function, and neural plasticity. Indeed, activation of inflammatory pathways within the brain is believed to contribute to a confluence of decreased neurotrophic supportand altered glutamate release/reuptake, as well as oxidative stress, leading to excitotoxicity and loss of glial elements, consistent with neuropathologic findings that characterize depressive disorders.[16]

Furthermore, depressive behaviors and mood alterations, including sadness, depressed mood, and suicidal ideation, were observed in patients who received repeated injections of recombinant cytokines for the treatment of autoimmunediseases, viral infections or cancer[17,18]

This study aimed to evaluate the prevalence of depression in hemodialysis patients in hemodialysis unit of Ain Shams University hospital and to identify its possible association with inflammation.

Subjects and Methods

Seventy hemodialysis patients from hemodialysis unit of Ain Shams University hospital were enrolled into the study. patients were treated with low-flux polysulphone biocompatible dialyzersthree times weekly. Oral and written information about the study was provided to all patients, and their consent was obtained before participation.

Socio-demographic data on patients were collected by a general questionnaire (age, sex, body weight, blood pressure). General questionnaire for patients contained questions to collect data related to the kidney disease: diagnosis, current treatment, hospitalizations and duration of illness.

Depressive symptoms were measured with the Beck Depression Inventory (BDI). The BDI is a 21-questionmultiple-choice self-report inventory used for measuring the severity of depression. A BDI cutoff score of>16 was our cut-off point to define depression in patients on dialysis.

In each patient, the following laboratory results were obtained: Complete blood cell count including hemoglobin (Hb), blood urea nitrogen, serum creatinine, serum albumin, serum bilirubin, serum alanine transaminase (ALT), serum high-sensitivity C-reactive protein (hs-CRP).

All venous blood samples were drawn after fasting for 12 hours. The samples were also immediately centrifuged and stored at -20°C until assayed for hs- CRP. Serum hs CRPwas analyzed by an ELISA kit. All biochemical analyses were performed at the Department of Medical Laboratory Diagnosis of Ain Shams University Hospital.

To describe the studied data, quantitative data e.g. age were presented as minimum, maximum, mean and standard deviation. Qualitative data e.g. sex, were presented as count and percentage.

Student t test was used to compare quantitative data between the two groups (those with depressive symptoms and those without) and Chi-Square test was used to compare qualitative data between them. Logistic regression analysis was used to measure the independent effect of different variables on the presence of depressive symptoms. P value < 0.05 was considered significant.

Results

Tables 1, 2 and 3 showed the demographic and laboratory parameters.

70 patients were enrolled in this study, 43 males and 27 females, age was48.59±11.59 years.

The length of hospital stay during the last year was 7.94±7.11. The level of hs-CRP was 19.22±17.95 and hemoglobin concentration was 9.31±1.9.

Moderate to severe depressive symptoms of depression (BDI>16) were found in 43(61.4%) patients as shown in table 4.

Comparison between groups with or without depression is shown in tables 5, 6 and 7.If compared with patients without depressive symptoms, patients with depressive symptoms spent more days in hospitals during the last year (10.23 vs. 4.3 days, respectively; p<0.001), spent less time on hemodialysis sessions (3.23 ± .37 vs 3.89 ±.25 hours per session, respectively; p<.001), tended to have higherhs- C-reactive protein plasma concentration (29.35 ± 15.83 vs.3.09 ± 3.23 mg/l, respectively; p < 0.001), had a lower hemoglobin concentration (8.35 ± 1.36 vs 10.82 ± 1.64, respectively; p< 0.001) and had more vascular comorbidities (ischemic heart disease (IHD) and cerebro vascular strokes (CVS)) (23.3% vs 3.7% respectively; p = 0.04).

There were no significant differences between the two groups with regard to age, gender, marital status and the cause of end stage kidney disease.

Table 8 shows the independent effect of different variables on the presence of depressive symptoms. Only the level of hs-CRP had an independent significant effect on the presence of depressive symptoms (p =0.03).

Table 1: demographic data of studied patients:

		N	Min.	Max.	Mean	SD
Age		70	27.00	75.00	48.59	11.59
				N	%	
Sex	Male			43	61.4%	
	Female			27	38.6%	
	Total			70	100.0%	
Marital status	Married			51	72.9%	
	Single			19	27.1%	
	Total			70	100.0%	

Table 2: clinical data of studied patients:

		N	Min.	Max.	Mean	SD
Duration of HD sessions (hr)		70	3.00	4.00	3.49	.46
Duration of hospital stay during last year (days)		70	1.00	30.00	7.94	7.11
				N	**%**	
Cause of ESRD	DM			18	25.7%	
	HTN			22	31.4%	
	GN			13	18.6%	
	SLE			7	10.0%	
	Analgesic nephropathy			3	4.3%	
	Stones			7	10.0%	
Co-morbidity	Absent			14	20.0%	
	Present			56	80.0%	
Co-morbidities:						
DM	No			38	54.3%	
	Yes			32	45.7%	
HTN	No			29	41.4%	
	Yes			41	58.6%	
COPD	No			64	91.4%	
	Yes			6	8.6%	
IHD/CVS	No			59	84.3%	
	Yes			11	15.7%	

Diabetes Mellitus (DM), Hypertension (HTN), Glomerulonephritis (GN), Systemic lupus erythromatosis(SLE), Chronic obstructive pulmonary disease (COPD), Ischemic heart disease (IHD), Cerebrovascular stroke (CVS).

Table 3: laboratory investigations of studied patients:

	N	Minimum	Maximum	Mean	SD
hs-CRP	70	.00	48.80	19.22	17.95
s.creatinine	70	3.60	9.00	6.26	1.60
Hb	70	5.80	14.00	9.31	1.90
ALT	70	18.00	40.00	31.65	4.58
s.albumin	70	2.50	4.00	3.21	.35
bilirubin	69	.70	1.20	.94	.14

Table 4: results of Beck Depression Inventory:

	N	%
Non-depressive symptoms	**27**	**38.6%**
Depressive symptoms	**43**	**61.4%**
Total	**70**	**100.0**

Table 5: relation between demographic data of patients and presence of depressive symptoms:

		BDI results				Student t test	P value
		depressive symptoms group (N=43)		non-depressive symptoms group (N=27)			
		Mean	SD	Mean	SD		
Age		48.60	11.39	48.56	12.12	.02	.99
		N	%	N	%	Chi Square test	P value
Sex	**Male**	25	58.1%	18	66.7%	.51	.48
	Female	18	41.9%	9	33.3%		
Marital status	**Married**	31	72.1%	20	74.1%	.03	.86
	Single	12	27.9%	7	25.9%		

Table 6: relation between clinical data of patients and presence of depressive symptoms:

		BDI results				Student t test	P value
		depressive symptoms group (N=43)		non-depressive symptoms group (N=27)			
		Mean	SD	Mean	SD		
Duration of HD sessions (hr)		3.23	.37	3.89	.25	8.84	<.001
Duration of hospital stay during last year (days)		10.23	8.15	4.30	2.07	4.55	<.001
		N	%	N	%	Chi Square test	P value
Cause of ESRD	**DM**	8	18.6%	10	37.0%	7.44 (Exact)	.18
	HTN	15	34.9%	7	25.9%		
	GN	10	23.3%	3	11.1%		
	SLE	6	14.0%	1	3.7%		
	analgesic nephropathy	1	2.3%	2	7.4%		
	stones	3	7.0%	4	14.8%		
Co-morbidity	**Absent**	9	20.9%	5	18.5%	0.06	.53
	Present	34	79.1%	22	81.5%		

Co-morbidities:							
DM	no	26	60.5%	12	44.4%	1.72	.14
	yes	17	39.5%	15	55.6%		
HTN	no	15	34.9%	14	51.9%	1.97	.16
	yes	28	65.1%	13	48.1%		
COPD	no	37	86.0%	27	100.0%	4.12 (Exact)	.08
	yes	6	14.0%	0	.0%		
IHD/CVS	no	33	76.7%	26	96.3%	4.79 (Exact)	.04(S)
	yes	10	23.3%	1	3.7%		

Table 7: relation between laboratory investigations of patients and presence of depressive symptoms:

	BDI results				Student t test	P value
	depressive symptoms group (N=43)		non-depressive symptoms group (N=27)			
	Mean	SD	Mean	SD		
hs-CRP	29.35	15.83	3.09	3.23	10.53	<.001
S.creatinine	6.51	1.48	5.86	1.72	1.67	.100
Hb	8.35	1.36	10.82	1.64	6.83	<.001
ALT	31.21	4.92	32.34	3.97	1.00	.322
s.albumin	3.26	.35	3.14	.35	1.46	.150
bilirubin	.95	.14	.93	.13	.54	.594

Table 8 :Logistic regression predicting likelyhood of depressive symptoms based on CRP, Hb, HD duration, duration of hospital stay, and IHD/CVS as comorbidity

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	**crp**	.503	.206	5.960	1	.015	1.654	1.104	2.476
	hb	.020	.469	.002	1	.967	1.020	.407	2.558
	HD_duration	-1.803-	1.876	.924	1	.337	.165	.004	6.513
	hospital_stay	.227	.254	.799	1	.372	1.255	.763	2.063
	ihd_cvs(1)	.594	5.441	.012	1	.913	1.812	.000	77515.941
	Constant	1.225	8.542	.021	1	.886	3.405		

Discussion

The prevalence of depression in hemodialysis (HD) patients in this study (61.4%) is higher than the prevalence observed in many other similar studies(20% to 41%).[19-21]

Dervisoglu et al.(2008) using BDI of ≥17 as a cut-off found a prevalence of 40% in examined patients.[22]Hung et al. (2011) found the prevalence of 49.5%using BDI cutoff score ≥14 in 147 HD patients.[23]Kimmel et al.(2001) using BDI cutoff score ≥15 found the prevalence of depression was 46.6%).[24]Wilson et al. (2006) using BDI of ≥14found Prevalence of depression of 38.7% in 124 HDpatients.[25]

These differences can be explained by varying criteria, methodology, and screening tools used to diagnose depression.

It was proven that proinflammatory cytokines play an important role in the pathogenesis of depression in general population.[26]several inflammatory markers are increased in ESRD patients.[27]C-reactive protein is an acute phase reactant that rises rapidly following an inflammatory stimulus. The synthesis of CRP in

the liver is induced by proinflammatory cytokines, such as IL-1, IL-6, and TNF-α.20,92 High-sensitivity CRP (hs-CRP) is the most widely used inflammatory biomarker in the clinical setting.[27]

We found that depressive symptoms were significantly associated with high levels of hs-CRP in hemodialysis patients. This agreed with Simic-Ogrizovic et al. who found that 77 dialysis patients with depression had significantly higher serum hs-CRP concentrations than patients withoutdepression.[28] Li et al., Su et al. and Dogan et al. showed that dialysis patients with depression had significantly higher serum CRP levels compared with patients without depression.[29-31]

In contrast with the above mentioned studies, Boulware et al. assessed depressives ymptoms in 917 dialysis patients (688 HD) and did not find significant differences in mean serum levels of CRP in patients with and without depression.[32]

Also, Hung et al.in 146 HDpatients,[23]Chilcot et al.in 132 HD patients,[33] and Taraz et al.in 83 HD patients[34] did not find significant correlation between depression scores and serum CRP orhs-CRP levels.

Using different cut-off points for screening and diagnosis of depression symptoms by Beck Depression Inventory (BDI) or using different methods for screening of depression like Hamilton score may be a possible explanation for these different results.

Using regression analysis we found that CRP levels have an independent effect on the presence of depressive symptoms among studied hemodialysis patients. This independent effect of hs-CRP on depression scores was reported in other similar studies.[30,35]

Su et al. found significantly lower prevalence of depression and lower levels of hs-CRP in patients on hemodiafilteration (HDF) than in patients on standard hemodialysis (HD).[30]

Hemodiafilteration (HDF) is a technique that depends on hemofilteration which is superior to standard hemodialysis in removing middle molecules.HDF has been reported to decrease levels of a variety of inflammatory cytokines and mediators, including IL-6, CRP, complement C3d and advanced glycated end products that have a close relationship with depression.[36]

Unfortunately, we do not have patients on HDF in Ain Shams University Hospital to be enrolled into our study. But our findings of high prevalence of depression and its significant association with hs-CRP can be one of the encouraging factors to introduce this new modality of dialysis in Ain Shams University Hospital.

We found that depressed hemodialysis patients had a significantly lower hemoglobin concentration with the mean hemoglobin of 8.35 g/dl. Similar result was found by Nowak et al.[35] our depressed dialysis patients had a significant higher levels of hs-CRP which is a marker for inflammation, and it is known that the presence of inflammation and the acute-phase response interact with the hematopoietic system at several levels to result in reduced erythropoiesis, accelerated destruction of erythrocytes leading to anemia.[37]

Another suggested explanation is the expected poor compliance of the depressed patients. Patients with depression symptoms tend not to have their medications including erythropoietin injections needed for treatment of renal anemia. On the other side chronic anemia has been associated with low quality of life[38] which can be a factor increasing depressive symptoms.

Another interesting finding in our study was that dialysis patients with depressive symptoms tend not to complete the 4 hours HD session, they have significantly shorter HD sessions (with the mean 3.23 hours).This can be explained by the poor compliance of patients with depression symptoms. This signifies that the depression in our hemodialysis patients is not well treated. Better attention to depression among our hemodialysis patients and proper treatment should be applied.

There was a significant association between depressive symptoms in our HD patients and the duration of hospital stay during the last year. Abbas et al. found that depression in haemodialysis patients is associated with the higher rate of hospital admissions.[39]

The relation between hospital admissions and depression can be bidirectional, Long hospital stay can be a factor contributing to depression or depressed hemodialysis patients had more comorbidities that led to long hospital stay.

We acknowledge that there are few limitations to our study. First, the cutoff value of BDI score for the diagnosis of major depressive symptoms remains uncertain[19]. Second, we used a self report depression screening tool instead of the gold standard, Diagnostic and Statistical Manual of Mental Disorder (DSM-IV) to investigate the depressive symptoms. Compared with DSM-IV, BDI is easier to administer.

Conclusion

The prevalence of depression was high among our chronic hemodialysis patients. Depressive symptoms were highly linked to the inflammatory marker hs-CRP.

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