

DEPRESSION AND SERUM INTERLEUKIN-6 LEVELS IN PATIENTS ON DIALYSIS

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SUMMARY

Background: Depression is a common psychiatric problem in patients undergoing dialysis. Several studies have been performed to validate the association between depression and inflammation in haemodialysis patients. The levels of proinflammatory cytokines are increased in chronic renal failure patients, as in depression. The objective of this study was to compare the incidence of depression in the patients on dialysis (on hemodialysis /HD/ and on continuous ambulatory peritoneal dialysis /CAPD/), and a relationship between depression and the presence of inflammation.

Subjects and methods: 88 patients (52 on HD and 36 on CAPD) were enrolled in this study.

Depressive symptoms were measured with the Beck Depression Inventory (BDI). The BDI is a 21-item self-report instrument, and the elevated symptoms of depression were defined as a BDI score ≥ 16 . HD patients were treated with high-flux polysulphone biocompatible dialyzers and CAPD patients were treated with usual dwell time (4-6 hours during the day and 8-10 hours at night). The presence of an inflammatory state was assessed by determinations of plasma interleukin-6 (IL-6) levels.

Results: Depression (BDI ≥ 16) was present in 28.4% of dialysis patients, 35% of patients on hemodialysis (HD) and 18.1% of patients on continuous ambulatory peritoneal dialysis (CAPD). The BDI score was significantly lower in CAPD patients comparing to HD patients, as well as the levels of albumin, C-reactive protein (CRP) and interleukin-6 (IL-6). IL-6 serum levels were similar in patients with depression and patients without depression in the whole group, as in HD patients. In CAPD patients without depression IL-6 levels were significantly lower.

Conclusions: The prevalence of depression was higher in HD comparing to CAPD patients. Although IL-6 level was higher in HD compared to CAPD patients, the relationship between depression and presence of inflammation parameters were observed in CAPD, but not in HD patients.

Key words: depression - interleukin-6 - hemodialysis - continuous ambulatory peritoneal dialysis

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INTRODUCTION

Depression is the most common psychopathological condition among hemodialysis patients, it reduces quality of life and has a negative clinical impact upon sufferers with chronic illness, including the end-stage renal disease (ESRD) (Chilcot et al. 2008). According to the National Comorbidity Survey, lifetime prevalence of depression in the general population is 21.3% among women and 12.7% among men (Cohen et al. 2007). Although depression may be associated with worse medical outcomes, including increased mortality, it is still under-recognized and misdiagnosed. Depression is the most prevalent comorbid psychiatric condition, estimated at about 25% of end-stage renal disease samples (Halen et al. 2012). As depression, the ESRD is growing in prevalence and incidence. In patients with ESRD depression can be secondary to loss of a primary role in their occupation or family and decreased physical function (Cohen et al. 2007). Cukor et al. (2008) identified 29% of urban hemodialysis sample as having either a current major depressive disorder or a

milder more chronic depression, dysthymia, using the 'gold standard' of psychiatric diagnosis, the Structured Clinical Interview for the DSM-IV (SCID-I). Furthermore, it seems that the prevalence of depression in patients on continuous ambulatory peritoneal dialysis (CAPD) is lower than in those on hemodialysis (HD), patients treated with PD may have better independence, mobility, and quality of life than patients treated with hemodialysis (Kalender et al. 2007, Dervisoglu et al. 2008).

Kimmel et al. (2001) demonstrated the need to track the course of depression, as there were significant differences in morbidity and mortality for subjects with persistently high levels of depressive affect when compared with those with intermittently high levels or low levels of depressive affect. Accurate estimation of the prevalence of depression in the ESRD population has been difficult due to the overlap of depressive symptomatology with symptoms of uremia, the confounding effects of medications and the varied assessment techniques. Several studies have been performed to validate the more common depression screening measures in patients with chronic kidney disease. The Beck De-

pression Inventory, the Hamilton Rating Scale for Depression, the Nine-Question Patient Health Questionnaire, and the Center for Epidemiologic Studies Depression Scale are some of the measures that have been used to screen for depression in patients with ESRD. The most common validated depression screening measure in ESRD patients is the Beck Depression Inventory (BDI). The BDI is a 21-item self-report instrument, used for screening and evaluation of the severity 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. It has been used extensively in ESRD populations (Cohen et al. 2007).

The mechanism which underlying depression in dialysis patients has not been cleared yet. Actually, there are two theories: first one connects depression in these patients with the loss of internal control, and second one view depression as a direct or indirect consequence of the renal failure (Kimmel et al. 2002, Kimmel et al. 2005, Chilcot et al. 2008). There are numerous reports which connect depression with inflammatory status. Indeed, a chronic renal failure is a well known state of chronic inflammation: there are increased levels of cytokines and acute-phase reactants in uremic patients implicating cytokine-induced depression in the pathogenesis of depression in dialysis patients (Chilcot et al. 2008). Many of the same inflammatory biomarkers are known to be dysregulated in ESRD patients, so perhaps there is a direct biologic link between increased levels of depression and renal disease.

Cytokine secretion is known to play an important role in the pathophysiology of depression, and levels of proinflammatory cytokines are increased in chronic renal failure (CRF) patients. Much recent attention has focused on the role of increased inflammation in promoting progression of underlying comorbid illnesses, thus leading to increased mortality among ESRD patients. Several studies have shown an association between inflammatory markers and survival on dialysis. There is concern that, by reactivation of the inflammatory cascade, the dialysis procedure may increase mortality (Halen et al. 2012). Evidence linking inflammation to MDD comes from three different observations (a) elevated levels of inflammatory markers in patients with MDD, even in the absence of illness, (b) co-occurrence of MDD with inflammatory illnesses and (c) increased risk of MDD with cytokine treatment. Cytokines have been found to influence almost every pathway involved in the pathogenesis of depression including alterations to the expression of neurotransmitters, neuroendocrine function, synaptic plasticity and basal ganglia. The similarities between cytokine-induced sickness behaviour and MDD further support a role of inflammation in depression as well as the anti-inflammatory effects of successful antidepressant treatment (Patel 2013).

One mechanism of action of proinflammatory cytokines in MD is the increased production of quinolinic acid, another is the contribution of indoleamine 2,3-dioxygenase (IDO) to the serotonergic deficiency. Moreover, effects on other neurotransmitters, for example on glutamatergic neurotransmission, are well known. Although IL-6 does not directly act on (IDO), its elevated levels in serum may contribute to (IDO) activation within the central nervous system (CNS) through the stimulatory effect on PGE₂, which acts as a cofactor in the activation of (IDO). This fits with a report on the correlation of increased in vitro IL-6 production with decreased tryptophan levels in depressed patients (Müller 2013).

The aim of this study was to find out how many patients on hemodialysis and those on continuous ambulatory peritoneal dialysis have depression, and if there is relationship between depression and the level of proinflammatory cytokines such as IL-6.

SUBJECTS AND METHODS

Subjects

Eighty eight (88) patients (52 on hemodialysis /HD/ and 36 on continuous ambulatory peritoneal dialysis /CAPD/) were enrolled in this study. HD patients were treated with high-flux polysulphone biocompatible dialyzers three times weekly. Continuous ambulatory peritoneal dialysis (CAPD) patients were treated with usual dwell time (4–6 hours during the day and 8–10 hours at night), clinically stable and without evidence of an active infection, and all received conventional glucose-based dialysates. Oral and written information about the study was provided to all patients, and their consent was obtained before participation. The study received appropriate ethical approvals from the Human Research Ethics Committee of the University Hospital Centre Split.

Measures

Socio-demographic data on patients were collected by a general questionnaire (age, sex, somatic anamnesis, 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.

Weight, height and waist circumferences (measured in duplicate at the level with the navel in thin subjects) were measured with an accuracy of 0.1 kg and 0.5 cm. Body mass index was calculated using the formula: $weight/height^2$ [kg/m^2]. Blood pressure was measured by using a random zero sphygmomanometer in supine position from the right arm after fasting for 12 hours. All venous blood samples were drawn from the right antecubital vein after fasting for 12 hours. Complete blood cell count, blood urea nitrogen, urinary urea nitrogen, serum creatinine, dialysate creatinine, urinary creatinine, serum high-sensitivity C-reactive protein (hs-

CRP), total cholesterol, triglyceride, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, serum glucose, dialysate glucose, glycated hemoglobin, serum albumin, ferritin, iron, transferrin, and intact parathormone levels were measured using standardized procedures. The samples were also immediately centrifuged and stored at -20°C until assayed for IL-6. Serum IL-6 was analyzed by an ELISA kit (R&D Quantikine HS IL-6 Immunoassay kit No. HS600B). All biochemical analyses were performed at the Department of Medical Laboratory Diagnosis of the University Hospital Centre Split. The laboratory is certified for performing all of the stated analyses and is under supervision of Croatian Society for Clinical Chemistry through quality control for the stated analyses.

Depressive symptoms were measured with the Beck Depression Inventory (BDI). The BDI is a 21-question multiple-choice self-report inventory used for measuring the severity of depression. A BDI cutoff score of ≥ 16 was the standard cut-off point to define depression in patients on dialysis, thus this value was used to classify patients with elevated symptoms of depression.

Statistical analysis

The analysis was based on both parametric and non-parametric methods, depending on the data distribution. We used Kolmogorov-Smirnov test to infer the data distribution type. In case of normal distribution, mean and standard deviation (SD) of the numerical variables were used, followed by the unpaired Student t-test and chi square tests were used for group comparison (with Fisher's exact test used in situation with too few cases for a chi-square test). For variables that did not follow the normal distribution Mann-Whitney test was used. We employed either Pearson correlation coefficient for variables with normal distribution, or the Spearman rank correlation test (for variables with non-normal

distribution). $P < 0.05$ is considered significant. Statistical analysis were performed using the statistical package SPSS version 15.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

88 patients (52 on HD and 36 on CAPD) were enrolled in this study, 47 males and 41 females, age 62 ± 11.8 years. End-stage renal disease (ESRD) in the HD patients were of the following etiology: nephroathia diabetica (n=10), uropathia obstructiva (n=2), pyelonephritis (n=9), nephropathia hypertensiva (n=5), binephrectomia (n=3), nephrolithiasis (n=2), nephritis tubulointestinalis (n=2), glomerulonephritis (n=12), and polycystosis renalis (n=6). In CAPD patients, the cause of ESRD was: nephropathia diabetica (n=7), pyelonephritis (n=2), nephropathia hypertensiva (n=12), nephrolithiasis (n=2), glomerulonephritis (n=9), and polycystosis renalis (n=3). The basic characteristics of the patients are presented in Table 1. HD patients were significantly older, and were longer on dialysis. Depression (BDI ≥ 16) was present in 28.4% of dialysis patients, in 35% of patients on hemodialysis (HD) and 18.1% of patients on CAPD. Depression rate, as well as the level of CRP and IL-6 were significantly lower in CAPD patients. Levels of albumin were lower in CAPD patients, either (Table 2 and Table 3). There was a significant correlation in HD patients between age and BDI score. Significant correlation was between body weight (before and after dialysis) and IL-6 level too. In CAPD patients the significant correlation were between BDI and IL-6 level, also between the levels of albumin and BDI score. There were no correlation between two inflammation parameters, CRP and IL-6. We have not found the correlation between inflammation parameter CRP and depression in both groups. The relationship between BDI and IL-6 level in CAPD patient is presented in Figure 1.

Table 1. Basic characteristics of the patients

	Hemodialysis (N=52)	Peritoneal dialysis (N=36)	t	p
	X \pm SD	X \pm SD		
Age (years)	66.38 \pm 9.9	55.78 \pm 11.7	4.447	<0.001
Duration of Dialysis (months)	48.9 \pm 32.9	31.65 \pm 26.7	2.638	0.013
Hemoglobin (g/L)	118.08 \pm 11.21	114.66 \pm 11.62	1.323	0.190
Thrombocytes	191.9 \pm 56.3	270.97 \pm 77.3	-5.380	<0.001
Glucose (mmol/L)	6.85 \pm 2.65	6.32 \pm 2.16	0.950	0.345
Fe (mmol/L)	12.56 \pm 6.5	11.27 \pm 3.87	1.007	0.317
Ca (mmol/L)	2.39 \pm 0.19	2.36 \pm 0.16	0.835	0.407
Cholesterol (mmol/L)	4.16 \pm 0.93	4.82 \pm 1.5	-2.164	0.036
Triglycerides (mmol/L)	2.07 \pm 1.36	2.28 \pm 0.92	-0.828	0.410
Albumin (g/L)	41.02 \pm 5.99	38.47 \pm 3.39	2.475	0.015
PTH	57.4 \pm 84.8	29.9 \pm 29.9	1.762	0.082
CRP (mg/L)	7.71 \pm 7.44	4.15 \pm 3.5	2.536	0.013
IL-6 (pg/mL)	4.26 \pm 2.83	0.92 \pm 0.99	6.771	<0.001
BDI score	14.67 \pm 7.58	9.94 \pm 6.33	3.176	0.002

Table 2. The relationship between examined variables in hemodialysis patients

	IL-6		BDI score	
	r	p	r	p
BDI score	0.109	0.447	-	-
Age	-0.079	0.580	0.311	0.025
BW (bHD)	0.358	0.012	-0.202	0.160
BW (eHD)	0.372	0.008	-0.204	0.155
Hgb	-0.039	0.786	0.052	0.715
Albumin	0.192	0.182	0.031	0.828
URR	-0.022	0.879	0.094	0.515
CRP	-0.001	0.994	0.003	0.986

HD - hemodialysis; BW (bHD) – body weight before HD; BW (eHD) – body weight after HD

Table 3. The relationship between examined variables in continuous ambulatory peritoneal dialysis patients

	IL-6		BDI score	
	r	p	r	p
BDI score	0.580	<0.001	-	-
Age	0.303	0.072	0.257	0.131
Hgb	0.166	0.364	-0.006	0.975
Urea	-0.061	0.741	-0.269	0.136
Albumin	-0.092	0.617	-0.447	0.010
CRP	0.178	0.330	0.183	0.317
LDH	0.331	0.064	0.488	0.005

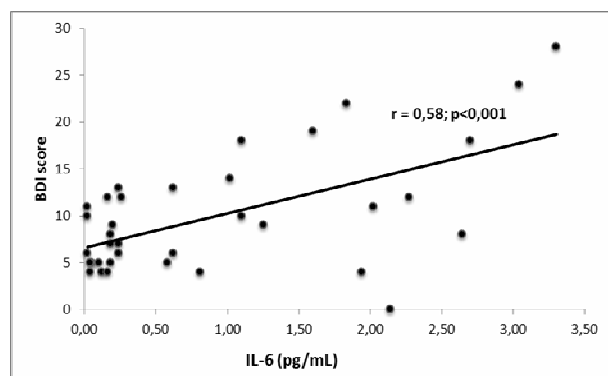


Figure 1. The relationship between the BDI score and IL-6 level in patients on continuous ambulatory peritoneal dialysis

DISCUSSION

The prevalence of depression patients with ESRD obtained in presented study (28.4%) is within range of 20-30%, suggested in similar studies (Chilcot et al. 2008). As previously mentioned, screening for depression in dialysis patients and its prevalence depends on assesment tool chosen for screening. Cohen et al. (2007) identified a higher BDI cutoff score, of >14 to 16, having increased positive predictive value at diagnosing depression in patients with end-stage renal disease, with sensitivity of 88.5% and specificity of 8.71% as compared to a diagnostic interview. Sacks et al. (1990) found almost the same prevalence of depression (26%), using BDI cutoff score ≥ 16 in 57 patients on HD and CAPD while Wilson et al. (2006) using BDI of ≥ 14

found prevalence of depression of 38.7% in 124 HD patients. In the research conducted by Kimmel et al. (2001) using BDI cutoff score ≥ 15 depression prevalence was 26.7% in 300 HD patients (but, when BDI cutoff score was ≥ 10 the prevalence of depression was 46.6%). Wuerth et al. (2001) used BDI cutoff score ≥ 11 and found prevalence of 49% in 380 CAPD patients and Hung et al. (2011) found the prevalence of 49.5% using BDI cutoff score ≥ 14 in 147 HD patients. The frequency of depressive symptoms indicating clinical depression according to the BDI scores was 45.3% in the study conducted by Simic-Ogrizovic et al. (2009). Other authors published similar data; Guney et al. (2010) found 70% patients on automated PD and 62.5% on CAPD depressive, and Dervisoglu et al. (2008) using BDI of ≥ 17 as a cut-off found a prevalence of 40% in examined patients (CRF, HD and PD together). Performed studies lead us to conclusion that the prevalence of depression is higher in HD comparing to CAPD patients.

A lower level of IL-6 in patients on CAPD was found in our research. This may be because PD provided better clearance of middle-molecule-weight uremic toxins than HD. The same finding was in study done by Dervisoglu et al. (2008). A relationship between IL-6 level and BDI score in our HD patients was not found as it was similarly presented by Hung et al. (2011) with sample of patients 3 times larger than our (147 patients) which may be part of the explanation. The relationship between IL-6 and depression was also found by Sonikian et al. (2010) and Kalender et al. (2006).

We did not find any relationship between BDI score and the level of IL-6 neither in the whole group of patients with ESRD, nor in the group of patients on the HD. The lack of relation between BDI score and the level of IL-6 can be explained with the fact that HD patients in our sample were more numerous, and in the fact that HD patients are exposed to several cytokine – inducing factors, such as contact with dialysis membranes, contamination by endotoxin and non-endotoxin cytokine-inducing factors what can disturb their relationship (Dervishoglu et al. 2008, Higuchi et al. 1997). What we did find in our research is a significant relationship between IL-6 level and BDI score in CAPD patients: connecting depression and chronic inflammation. The latest advancement in neurobiological research provided an increased evidence that inflammatory and neurodegenerative pathways play a relevant role in depression (Zeugman et al. 2013). Preclinical and clinical studies on depression highlighted and increased production of inflammatory markers such as interleukin (IL)-1, IL-6, TNF- α and γ . On the other hand, acute and chronic administrations of cytokines or cytokine inducers were found to trigger depressive symptoms (Catena-Dell'Osso et al. 2011). Patients treated with immunotherapy develop neurovegetative and somatic symptoms and cognitive impairment (Konsman et al. 2002, Raison et al. 2006, Valentine et al. 2005). These symptoms are related to the immunotherapy and are ameliorated by antidepressant treatment (Musselman et al. 2001). Further, antidepressant treatment alters serum cytokine levels in patients with depression (Frommberger et al. 1997, Lanquillon et al. 2000). According to the cytokine hypothesis, depression could be due to a stress-related increased production of pro-inflammatory cytokines that, in turn, would lead to increased oxidative and nitrosative brain damage (Catena-Dell'Osso et al. 2011).

Some limitations of the present study warrant consideration. A larger sample size of the both groups would be more beneficial. One limitation of this study might be use of the self report measure, the BDI, which is a highly sensitive but a moderately specific test. Additional studies are necessary to further evaluate the optimal methods to screen for and treat depression in patients with chronic kidney disease.

CONCLUSION

The prevalence of depression was higher in HD comparing to CAPD patients. Although IL-6 level was higher in HD compared to CAPD patients, the relationship between depression and presence of inflammation parameters were observed in CAPD, but not in HD patients. Identifying depression in HD patients is important because the disorder is likely to be persistent in a substantial proportion of patients.

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