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Association of brain-derived neurotrophic factor and interleukin-6 serum levels with depressive and anxiety symptoms in hemodialysis patients

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ABSTRACT

Objective: This study assessed the possible association of serum brain-derived neurotrophic factor (BDNF) and interleukin-6 (IL-6) with depressive and anxiety symptoms in hemodialysis (HD) patients.
Method: An analytical cross-sectional study was conducted over 274 HD patients from March to October 2017. The Hospital Anxiety and Depression Scale (HADS) was utilized to evaluate depressive (HADS-D) and anxiety (HADS-A) symptoms. The HADS-D/A is a self-report instrument that has a maximum score of 21. Serum BDNF and IL-6 were measured using enzyme-linked immunosorbant assay (ELISA).
Results: Serum IL-6 was significantly higher in patients with depressive symptoms compared to normal (20.47 ± 4.27 pg/mL for HADS-D ≥11 versus 9.26 ± 1.59 pg/mL for HADS-D < 7, p = 0.014). Multivariable regression analysis revealed that IL-6, education level, hypertension, and dialysis duration were significant predictors of HADS-D. Also, gender, education level, hypertension, and the number of dialysis sessions/week were significant predictors of HADS-A. Significant positive correlation was shown between HADS-D and IL-6 (r = 0.1729, p = 0.004).
Conclusion: Collectively, HD patients with depressive symptoms showed higher levels of IL-6, supporting previous findings that the circulating inflammatory mediator IL-6 can be used as a biomarker for prediction of depressive symptoms in HD patients. Further longitudinal or interventional studies are needed to further validate this association.

1. Introduction

Chronic kidney disease (CKD) is a growing and prevalent worldwide major public health problem. While the early stages of CKD are generally asymptomatic, the progressive decline in kidney function becomes irreversible leading to end-stage renal disease (ESRD), which requires renal replacement therapy including dialysis or kidney transplantation [1,2].

Patients on long-term hemodialysis (HD) treatment are more prone to changes in their lifestyle, daily performance, quality of life, and increased risk of psychological disorders [3]. Several observational studies have shown that symptoms of depression and anxiety are prevalent among HD patients, and are highly associated with poor health outcomes. The prevalence of depression, the most common psychological problem among HD patients, is estimated to be 22.8% using interview-based diagnosis and 39.3% using self-administered or clinician-administered questionnaires [4,5]. Increased adverse clinical outcomes such as hospitalization rates, emergency department visits, dialysis nonadherence, and mortality have been observed with increased depression in HD patients [6,7]. Depressive and anxiety symptoms can coexist, and the latter can be presented in about 50% of dialysis patients [8].

Environmental, social, and biological factors have been implicated in the pathogenesis of psychosocial disorders [9]. The brain-derived neurotrophic factor (BDNF) is a neuroprotein that promotes the survival and differentiation of neurons. BDNF is highly expressed in the hippocampus and cerebral cortex [10] and has been implicated as a regulatory protein in the pathophysiology of mood disorders [11]. Reduced BDNF plasma or serum concentrations have been reported in patients with depression [12] and in women with anxiety disorder [13] in comparison to healthy controls. Also, evidence suggests that treatment with antidepressants elevates the peripheral BDNF concentration [14]. Although BDNF has been extensively studied in psychological disorders [14,15], very little is known regarding the behavior of this

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protein in HD patients with depressive and anxiety symptoms. One investigation conducted with over 188 HD patients revealed that BDNF levels are not correlated with depression [9]. Authors suggested that other studies with larger sample size are warranted to further clarify this association.

Inflammatory mediators could also influence the risk of psychiatric illness. For instance, upregulation of multiple inflammatory cytokines has been documented in brain tissue samples of depressed patients [16]. The pro-inflammatory cytokine Interleukin-6 (IL-6) has gained much attention as it was found to be consistently elevated in patients with depression [17] and was shown to be correlated with anxiety symptoms in the different patient populations [18,19]. Chronic inflammation is highly represented in patients with ESRD, evidenced by increased levels of C-reactive protein, IL-1, IL-6, and tumor necrosis factor-alpha [20,21]. A recent review reported that the correlation between IL-6 and depressive symptoms in HD patients is highly controversial, and highlighted the need for additional investigations in this area [22]. Moreover, the role that IL-6 plays in the etiology of anxiety in HD patients has not been studied clearly [8,23].

Collectively, while depression and anxiety are common in HD patients, their association with BDNF and IL-6 has not been clearly elucidated. Therefore, this study was conducted to illustrate the possible association of these symptoms with serum BDNF and IL-6 levels in a representative group of HD patients.

2. Materials and methods

2.1. Study population and setting

In this cross-sectional study, participants were recruited from dialysis units at five primary governmental, military and educational hospitals in Jordan during the period of March–October 2017. Eligible patients were adults (age > 18 years) on maintenance HD of at least three months and not known to have any psychiatric or mental disease. History of psychiatric illness was queried from participants and confirmed from the patient's medical records. Patients with severe liver disease, active inflammatory or infectious conditions, and those receiving anti-depressant or anxiety medications were excluded as those may impact the level of the biomarkers. Patients' demographic criteria, daily habits, socioeconomic status, laboratory, and dialysis information were collected from the participants, their medical records, and the dialysis staff. These data include age, gender, marital status, educational level, smoking status, income, predialysis serum, creatinine and urea, hemodialysis duration, number of dialysis sessions per week, length of each dialysis session, comorbid conditions (hypertension and diabetes), and current medications. The study has been approved by the local institutional review board committee at each hospital. A written informed consent was obtained from each individual prior to participation.

2.2. Psychological measures

The Hospital Anxiety and Depression Scale (HADS), that is widely implemented in medical patients, was employed in the current study. It is a self-administered questionnaire which comprises a total of 14 easy to understand items that reflect depressive and anxiety symptoms (7 each) [24]. Each item is rated on a 4-point Likert scale, ranging from 0 to 3, with total scores of 0 to 42 for the total depression and anxiety scale, and 0 to 21 for each of the depression (HADS-D) and anxiety (HADS-A) subscales. Higher scores indicate that the patient is highly distressed by depressive or anxiety symptoms. Total scores were separated into three groups as follows: normal (< 7), mild (8 to 10), and moderate-severe symptoms (11 to 21) [25]. Completion of the questionnaire was performed during the first 90 min of the dialysis session. To assure consistency in understanding and answering the research questionnaire, a trained nurse was employed in the study who assisted with filling out the questionnaire data. Most participants were met at the open hemodialysis suites while few of them had private rooms. Confidentiality and privacy were maintained during the completion of the questionnaire. Also, we have obtained information from patients' medical records for participants who were unable to provide all required information. The HADS scale has been frequently tested on dialysis patients [23,26] and validated in Arabic speaking countries [27,28] with high levels of reliability. The research questionnaire was also piloted and tested among a group of patients to receive feedback about understandability and clarity of the questions. The Cronbach alpha of the current study was 0.84 for HADS-D and 0.85 for HADS-A subscales.

2.3. Blood samples and laboratory analyses

Blood samples were collected from patients at the time of needling before their scheduled dialysis session. Blood was centrifuged at 10,000 rpm for 10 min to obtain the serum which was aliquoted and stored at -70° C until analysis. Human serum BDNF was quantified using the DueSet enzyme-linked immunosorbent assay (ELISA) kit (DY248, R&D Systems, UK), and IL-6 was measured using high sensitivity ELISA kits (BMS213HS and 88-7066-22, Invitrogen, USA). All assays (standards and samples) were performed in duplicate according to the manufacturer's recommended instructions. The absorbances of the samples were measured at 450 nm using an Epoch Biotek microplate reader (BioTek, Winooski, VT, USA). The concentrations of BDNF and IL-6 in samples were calculated from the corresponding standard curves. Few samples were located above the given range and diluted with the kit buffer. The detection sensitivity of BDNF and IL-6 were 23.4 pg/mL and 0.03 pg/mL, respectively.

2.4. Data and statistical analyses

Descriptive statistics (mean, standard deviation, frequency, and percentages) were used, as appropriate, to describe patient characteristics. As described earlier, patients were separated into three groups based on the depression or anxiety scores, and demographic and clinical factors were compared between groups using ANOVA for continuous variables and chi-square test for categorical data. Differences in BDNF and IL-6 levels between patients at different psychological scores were determined using ANOVA test. Pearson's correlation was conducted to examine the relationship between BDNF or IL-6 concentrations and HADS scores of depression and anxiety. Multivariable linear regression analysis was performed to identify variables that predict depression and anxiety scores after adjusting for demographic, serum BDNF and IL-6, clinical and dialysis-related covariates. Variables included in the regression model were age, gender, marital status, education level, BMI, smoking status, the presence of hypertension or diabetes, income level, numbers of years under dialysis and weekly dialysis sessions, length of each dialysis session, serum levels of urea, creatinine, BDNF, and IL-6. Because BDNF and IL-6 concentrations were not normally distributed, regression analysis was also performed using the log-transformed BDNF and IL6. Statistical analyses were conducted using STATA version 12 (STATA, College Station, TX, USA) at the level of significance of < 0.05. Graphs were generated using GraphPad Prism (Version 6; GraphPad Software Inc., San Diego, CA).

3. Results

3.1. Sociodemographic, clinical, and psychological characteristics of participants

The total number of patients who participated in the study was 274, with a response rate of about 95% at each dialysis unit. Only a limited number of subjects were excluded due to: age < 18 (n = 15), being under dialysis for < 3 months (n = 9) or because of active liver