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The Relationship between Trace Elements and Depression among Older Patients with Chronic Liver Disease

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ABSTRACT

Introduction: The prevalence of Chronic Liver Disease (CLD) is rising in the older population, older patients with CLD had a Poor Quality of Life (QOL) as they may present with emotional reactions reaching to depression with a deleterious effect on their life. Trace Elements (TEs) and macro-minerals levels may be varied in CLD**.** They are linked with depression.

Objective: Our aim is to detect the association between TEs, macro-minerals, and depression among older patients with CLD.

Materials and Methods: A cross-sectional study was conducted among 147 older patients with CLD. Depression was confirmed by the Patient Health Questionnaire (PHQ-9). Liver function tests, electrolytes and TEs (zinc (Zn) and copper (Cu)) were measured.

Results: The prevalence of depression was 53.7%. Low serum sodium (Na) and calcium (Ca) levels were statistically significantly related to depression (P-value: 0.020 and 0.000 respectively) with lower serum Magnesium(Mg), serum Phosphorous(P) compared to higher serum Cu levels among depressed than non-depressed CLD, however no difference regarding serum Potassium (K) and Zn levels.By using univariate logistic regression, lower serum Na and Ca levels, malnutrition and diuretics were related to depression among CLD patients (P-value: 0.023, 0.001,0.000, 0.013 respectively). While by using multivariate logistic regression, malnutrition and low serum Ca levels were significantly associated with depression among older CLD patients (P-value: 0.001 and 0.014 respectively)

Conclusion: Using diuretics and malnutrition are associated with depression through their effect on serum TEs and macro-minerals. Treating malnutrition and adjusting the dose of diuretics may decrease the risk of depression.

Keywords: chronic liver disease, trace elements, macro-minerals, depression

INTRODUCTION

The prevalence of Chronic Liver Disease (CLD) is rising in the older population. CLD increases morbidity and mortality worldwide (1).

It is also well recognized that older patients with viral hepatitis have higher mortality rates than younger patients (2).

CLD has a significant economic and social burden (3), older patients with CLD had a poor Quality Of Life (QOL) as they may present with a wide range of emotional reactions starting from worry, fear, hopelessness and reaching to depression ,and anger that had a deleterious effect on their life (4).

Depression is one of the most common mental disorders seen among the older population and is expected to become the second leading cause of disability in all age groups by 2020, depression and subsyndromal depressive are represented between (1-4%) and (10-15%), respectively (5,6).

It has been demonstrated that patients with depression have worse health outcomes, reduced QOL and increased morbidity and mortality compared to patients without depression (7).

Patients with CLD had a higher incidence of depression than that in a healthy population, Major Depression Disorder (MDD) is present in up to 15% of patients on the Liver Transplant (LT) waiting list and in up to 57% of patients with cirrhosis (8,9).

Pathogenesis of depression in patients with CLD is inadequately explained, it may be due to accumulation of neurotoxin in the blood due to the inadequate clearance by a cirrhotic liver and the accumulation of the proinflammatory cytokines in the brain that decreases the ability of astrocytes to detoxify ammonia in the brain, that leads to its accumulation that may interfere with neurotransmitter transport and activity (10).

The liver regulates the transport, and excretion of TEs through bile formation (11). Most of TEs are bounded to plasma proteins which are important for their transport and distribution. The concentration of each TEs varies with different types of CLD since these elements may have direct hepatic toxicity or may be decreased as a result of liver function impairment (12).

There is a relation between TEs and the neurobiology of psychiatric disorders in which enzymes like MonoAmine Oxidase (MAO), Dopamine β-Hydroxylase (DBH), and tyrosine hydroxylase which is used in the synthesis and metabolism of neurotransmitters such as Serotonin (5- HT), Noradrenaline (NE), and Dopamine (DA) implicated in the pathophysiology and treatment of affective disorders or anxiety disorders might require TEs as cofactors (13). Moreover, there is an association between TEs concerning the role of oxidative stress in affective disorders or anxiety disorders (14).

Previous studies tackled the association of depression with CLD (15,16) while other studies search the relationship between trace elements and depression (17,18) but data about the association between depression in CLD and macro-elements and TEs are limited. So the aim of our study is to detect the relationship between TEs, macro-minerals, and depression among older patients with CLD.

MATERIALS AND METHODS

A Cross-Sectional study included older patients aged 60 years old or more with CLD. They were recruited either during their hospital admission or attendance outpatient clinics of Ain Shams University hospitals.

We collected data of 148 CLD patients and divided into 2 groups: the first group included 79 CLD patients with depression. The second group included 68 CLD patients who were not depressed.

Exclusion criteria included patients on anti-depressant therapy, hepatic encephalopathy, treated with interferon, taking mineral supplements, renal impairment, alcohol abuse, cognitive impairment, and those who refused participation in the study.

Data from each patient was collected including demographic data (age, sex and special habits of medical importance including smoking, alcohol intake or substance addiction), past history including comorbid conditions and drug history.

Patients with CLD were diagnosed by careful history taking, physical examination for detection signs of CLD (jaundice, gynecomastia, palmar erythema, hepatomegaly, splenomegaly, ascites, …) and laboratory tests (liver function tests including total and direct bilirubin, ALT, AST,HCV AB, HBsAG, albumin, International Normalized Ratio (INR) and Complete Blood Count (CBC), and imaging studies (Pelvi-abdominal ultrasound in patients with CLD may show hepatomegaly, or cirrhotic liver, ascites, portal hypertension, and splenomegaly).

Prognosis of CLD patients was assessed by Child-Pugh's classification which has scored for five parameters including serum bilirubin, serum albumin, Prothtrombin Time (PT) or INR, ascites and hepatic encephalopathy. It is graded into Child-Pugh's 'A' grade (score less than 7), Child-Pugh's 'B' grade (score 7-9) and Child-Pugh's 'C' grade (score more than 9). Child's grade A patients have the best prognosis, while Child's grade C patients have the worst prognosis (19).

Depression was assessed by The Patient Health Questionnaire 2 (PHQ-2) which comprises the first 2 items of the PHQ-9, asking about the degree to which the patient has experienced depressed mood and loss of interest in the last two weeks. PHQ-2 scores are calculated as 0, 1, 2, and 3, which are corresponding to answers, not at all, several days, more than half the days, and nearly every day respectively. This tool is used for screening of depression and if the patient had a score > or = 3 this indicates a high probability of depressive disorders and the patient will be further evaluated with the PHQ-9 for confirming the diagnosis of depression (20).

The PHQ-9 questions are based on diagnostic criteria of depression from the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-V). Questions are about the loss of interest, depressed mood, having troubles in falling asleep, feeling tired, eating habits, feeling bad about yourself, troubles concentrating on things, speed of functioning, suicidal ideation , and a 10th question which asks about the difficulty of the problems that the above questions make it function in daily life. The 10th question is not added into the final score and it is used to measure the patient's opinion of the level of impairment caused by their mental health. PHQ 9 scores are calculated as 0, 1, 2, and 3, which are corresponding to answers not at all, several days, more than half the days, and nearly every day respectively. Its total score ranges from 0 to 27. Scores of 5, 10, 15, and 20 represent cut points for mild, moderate, moderately severe and severe depression, respectively (21).

The nutritional state was assessed by the Mini-Nutritional Assessment (MNA) long form. It was developed for screening the risk of malnutrition in older people (22). It is composed of four parts: anthropometric measurements (weight, height, and weight loss), general status (the lifestyle of the individual, drug history, and mobility), diet information (ability to feed independently, fluid intake and number of meals) and subjective assessment (self-view of nutrition and health status). The sum of 18 questions provide a maximum score of 30, a score of less than 17 points is an indication of malnutrition, 17-23.5 points is a risk for malnutrition and 23.5 points is a normal nutritional status (23,24).

The number of comorbid conditions was assessed by Charlson Comorbidity Index (CCI). It is used for classifying comorbid conditions that might alter the risk of mortality. The one-year mortality rate for different scores were 0: 12%; 1-2: 26%; 3-4: 52%; and greater than or equal to 5: 85%. The predicted risk of death from comorbid disease at a 10-year follow up is 0: 8%; 1: 25%; 2: 48%; and greater than or equal to 3: 59%. Assigned weight for each patient's condition. The total equals the score. 1 point: Myocardial infarct, congestive HF, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, ulcer disease, mild liver disease, and DM.2 points: hemiplegia, moderate or severe renal disease, DM with end-organ damage, any malignancy, leukemia, and lymphoma.3 points: Moderate or severe liver disease.6 points: Metastatic solid malignancy, and Acquired Immunodeficiency Syndrome (AIDS) (25).

Besides laboratory investigations to confirm CLD, serum electrolytes and TEs including Sodium(Na), Potassium (K), Calcium(Ca), Phosphorus (P)and Magnesium (Mg) were measured automatically via Beckman Coulter AU 480 analyser

Table 1. Socio-demographic characteristics among depressed and non-depressed CLD patients

		Not depressed		Depressed		P-value
		No	%	No.	%	
Age	60-69	42	61.8%	52	65.8%	0.233
	70-79	25	36.8%	21	26.6%	
	80-89	1	1.5%	5	6.3%	
	90-100	0	0.0%	1	1.3%	
Gender	Female	14	20.6%	21	26.6%	0.395
	Male	54	79.4%	58	73.4%	
Educational levels	Illiterate	49	72.1%	58	73.4%	0.978
	Primary	9	13.2%	11	13.9%	
	Preparatory	3	4.4%	3	3.8%	
	Secondary	2	2.9%	3	3.8%	
	University	5	7.4%	4	5.1%	
Smoking habits	Non-smoker	30	44.1%	37	46.8%	0.817
	Current smoker	25	36.8%	30	38.0%	
	Ex-smoker	13	19.1%	12	15.2%	

Chi-square test

(Beckman Coulter, USA) while Zinc(Zn) and Copper(Cu) were also measured using Centronic GmbH analyser (Centronic GmbH, Germany).

Ethical Considerations: Our study is approved by the ethical committee of the faculty of medicine Ain Shams University. Informed consent was obtained from the patients or the next of kin.

Sample size: To estimate the sample size needed to establish a difference in the means of certain electrolytes and trace elements between the two groups (depressed and those free from depression) and due to lack of information, the effect size approach was used assuming equal number of the two groups. Group sample sizes of at least 65 cases per group achieve 80% power to reject the null hypothesis of zero effect size when the population effect size is 0.50 (a medium sized effect size) and the significance level (alpha) is 0.05 using a two-sided two-sample equal-variance t-test. The sample size that will be satisfactory for the whole study will be at least 130 cases.

Statistical analysis: Appropriate statistical methods were used to present and analyze the data. Quantitative variables were presented as mean and standard deviation and the independent t-test was used to compare the two groups. Qualitative data were presented as frequency and proportion and the chi-square test was used to compare the two groups. Multivariable techniques including logistic regression were used to evaluate the independent effect of each risk factor of depression.

The level of significance was taken at P-value < 0.05 is significant, otherwise is non-significant. The P-value is a statistical measure for the probability that the results observed in a study could have occurred by chance.

Data entry and statistical analysis were on a personal computer using a statistical package for social science (SPSS) version 20.0.

RESULTS

The mean age of the studied population was 67.65± 6.53. Males were 112 (76.2%). 107 (72.8%) of the sample were illiterate. 55 (37.4%) were a current smokers. Viral liver disease was 133 (90.5%) of older CLD patients while HCV was the most common cause of viral chronic liver disease reaching 128 (87%). The prevalence of depression was 79(53.7%) among CLD patients.

There were no statistically significant differences between depressed and non-depressed CLD patients regarding different age groups, gender, educational level and, smoking habits (**Table 1**).

Regarding the type of liver disease, there was a statistically significant difference between both groups (P-value: 0.037) as viral liver disease is more prevalent among the depressed group. However, there was no statistically significant difference between depressed and non-depressed patients regarding chronic hepatitis C virus (HCV) or hepatitis B virus (HBV) (P-value: 0.399,0.739 respectively) (**Table 2**).

As regard child classification, a highly statistically significant difference were found between depressed and non-depressed CLD patients as Child B and C was more prevalent among depressed patients in comparison to non-depressed patients as 60.8% and 32.9% of depressed patients were child B and C in comparison to 55.9% and 16.2% of non-depressed patients respectively (P-value: 0.001) (**Table 2**).

There was a highly statistically significant difference between depressed and non-depressed CLD patients as regards nutritional status using MNA (P-value was 0.000). Risk of malnutrition and malnutrition were more prevalent in depressed CLD patients in comparison to non-depressed patients, in which 39.2% (no=31) of depressed patients were at risk of malnutrition, while 26.5% (no=18) of non-depressed patients and, 57.0% (no=45) of depressed patients were malnourished, while 30.9% (no=21) of non-depressed patients (**Table 2**).

The results found that there was a statistically significant difference between depressed and non-depressed CLD patients as regards increase the number of diseases by using CCI (P-value: 0.005). Also, using diuretics and the number of drugs were concluded to increase the risk of depression (P-value: 0.012 and 0.005 respectively) (**Table 2**).

Regarding macro-minerals and TEs, both serum Na and Ca levels were statistically significantly related with depression (P-value: 0.020 and 0.000 respectively). While serum P and Mg were lower in depressed CLD patients with no statistically significant difference (P-value: 0.757 and 0.219 respectively) but serum zinc and copper were higher in depressed CLD patients in comparison to non-depressed CLD while there was

Table 2. Comparison between depressed and non-depressed CLD patients as regard Clinical data

		Non-depressed	Depressed	P-value
		No = 68	No = 79	
Charlson Comorbidity Index	Mean ± SD	5.22 ± 1.44	5.99 ± 1.77	0.005**
	Range	3 – 8.00	3 – 11	
Type of liver disease	Non-viral	6 (8.8%)	2 (2.5%)	
	Viral	57 (83.8%)	76 (96.2%)	0.037*
	Mixed	5 (7.4%)	1 (1.3%)	
HBV	No	63 (92.6%)	72 (91.1%)	
	Yes	4 (7.4%)	7 (8.9%)	0.739
HCV	No	11 (16.2%)	9 (11.4%)	
	Yes	57 (83.8%)	71 (88.6%)	0.399
Child-Pugh Classification	Child A	19 (27.9%)	5 (6.3%)	
	Child B	38 (55.9%)	48 (60.8%)	0.001**
	Child C	11 (16.2%)	26 (32.9%)	
Number of drugs	Mean ± SD	1.65 ± 0.75	2.14 ± 0.91	
	Range	1.00 – 3.00	1.00 – 5	0.005**
Diuretics use	No	49 (72.1%)	41 (51.9%)	
	Yes	19 (27.9%)	38 (48.1%)	0.012*
Mini-nutritional assessment	Normal	29 (42.6%)	3 (3.8%)	
	At risk of malnutrition	18 (26.5%)	31 (39.2%)	0.000**
	Malnourished	21 (30.9%)	45 (57.0%)	

HBV: *Hepatitis B Virus*, **HCV:** *Hepatitis C Virus*
*P-value <0.05: Significant (S); **P-value< 0.01: highly significant (HS)
Chi-square test

Table 3. Comparison between depressed and non-depressed CLD patients as regard serum electrolyte levels and trace elements

		Non-depressed	Depressed	P-value
		No = 68	No = 79	
Serum Na (mmol/L)	Mean ± SD	135.32 ± 3.80	133.38± 5.81	0.020*
	Range	126 – 145.00	117 – 148	
Serum K (mmol/L)	Mean ± SD	3.87 ± 0.58	3.97 ± 0.60	0.315
	Range	2 – 5.50	2.9 – 5.5	
Serum Ca (mg/dL)	Mean ± SD	8.94 ± 0.50	8.60 ± 0.64	0.000**
	Range	7.8 – 10.80	6.7 – 10	
Serum P (mg/dL)	Mean ± SD	2.60 ± 0.67	2.56 ± 0.70	0.757
	Range	1 – 5.30	1.5 – 4.6	
Serum Mg (mg/dL)	Mean ± SD	1.91 ± 0.31	1.85 ± 0.34	0.219
	Range	1 – 2.70	1.2 – 3	
Serum Zn (µg/dL)	Median (IQR)	131.75 (72.4 - 238.25)	150 (99.7 – 255.4)	0.147 †
	Range	12.8 – 380	33.2 – 538.9	
Serum Cu (µg/dL)	Median (IQR)	101.63 (76.38 - 125)	105 (79.5 – 134.2)	0.557 †
	Range	38.2 – 489.5	23 – 650	

* P-value <0.05: Significant (S); **P-value< 0.01: highly significant (HS)
Mann Whitney test †

Table 4. Univariate and multivariate logistic regression analysis for factors of depression among CLD patients

	Univariate				Multivariate			
	P-value	Odds ratio (OR)	95% C.I. for OR		P-value	Odds ratio (OR)	95% C.I. for OR	
			Lower	Upper			Lower	Upper
Types of liver disease	0.968	1.022	0.357	2.925	-	-	-	-
Child-Pugh Classification	0.000**	2.772	1.561	4.922	0.300	1.662	0.636	4.339
Diuretics use	0.013*	2.390	1.200	4.763	0.898	1.077	0.345	3.362
Number of drugs	0.010*	1.482	1.099	1.999	0.589	1.134	0.719	1.787
Serum Na level	0.023*	0.922	0.860	0.989	0.998	1.000	0.917	1.091
Serum Ca level	0.001**	0.341	0.181	0.643	0.014*	0.401	0.193	0.832
Mini-nutritional assessment	0.000**	3.217	1.982	5.222	0.001*	2.786	1.483	5.233
Charlson Comorbidity index	0.007**	1.347	1.086	1.671	0.-532	1.102	0.813	1.492

* P-value <0.05: Significant (S); **P-value< 0.01: highly significant (HS)
CI = confidence interval, *Significant.

no difference between depressed and non-depressed CLD as regard serum K(P-value: 0.315) (**Table 3**).

By using univariate logistic regression, the results showed that the severity of liver disease by Child-Pugh Classification, using diuretics, number of drugs, lower serum Na level, lower serum Ca level, malnutrition by using MNA and increase the number of diseases by using CCI were independent risk factors of depression among CLD patients (P-value: 0.000, 0.013, 0.010, 0.023, 0.001, 0.000, 0.007 respectively). While by using multivariate logistic regression, it was found that malnutrition by using MNA and low serum Ca levels were significantly associated with depression among CLD patients after adjustment of other variables (P-value: 0.001 and 0.014 respectively) (**Table 4**).

DISCUSSION

CLD has a long duration and poor prognosis with harmful effect on patient psychological health. When a patient with an end-stage liver disease has a mental health problem, it is commonly misdiagnosed as a complication of hepatic encephalopathy, which leads to ineffective treatment and delays the diagnosis and treatment of the emotional disorder like depression (26). Some patients with end-stage liver disease have suicidal ideation due to depression (27).

In addition to known risk factors causing depression in CLD, our study highlighted that macro-minerals and TEs abnormalities could increase the risk of depression among older patients with CLD through either using diuretics or malnutrition.

Using diuretics among our participants was a risk factor for depression in CLD patients (48.1% of depressed patients were using diuretics compared to 27.9% of non-depressed patients) (P-value: 0.012).

There are no direct data to support a direct significant effect of diuretics on depression, but this could be explained by using diuretics that can promote the elimination of various electrolytes that leads to electrolyte disturbances like decreasing serum Na and K levels that could increase the risk of depression (28).

In-addition, our current study suggested that the risk of malnutrition and malnutrition using MNA were more prevalent in depressed older CLD patients in comparison to non-depressed patients and was confirmed by univariate and multivariate regression analysis.

As the study was done by Vafaei et al. (2013) on 370 older people living in 36 rural in Isfahan, revealed that depressed older patients were susceptible to malnutrition (16.4%) (29).

Moreover, Cabrera et al. (2007) performed a cross-sectional study included 267 individuals aged 60 to 74 year old analyzed the association between nutritional deficiency and the presence of depression among community-dwelling older people showed that their nutritional deficit presented a significant association with depression, even after adjusting for control variables such as low schooling, low socioeconomic level, and smoking (P-value < 0.001) (30).

Malnutrition among CLD patients is multifactorial, in which CLD may be accompanied by loss of appetite, and the presence of ascites causes early satiety. Also, malabsorption may occur due to portal hypertension due to the congestion of the intestinal mucosa. As well as the liver is the main organ that stores many nutrients, so, CLD can lead to loss of storage capacity that exacerbates micronutrient deficiencies due to low or unbalanced dietary intake (31).

In addition, depression affects appetite, and food intake which causes weight loss and increases the risk of malnutrition. Also, malnutrition might cause TEs and mineral deficiencies that could affect depression, and malnourished patients always complain of easy fatigability that may increase the risk of depression. So, nutritional deficiency can play an important role in the onset as well as severity and duration of depression (32).

Regarding macro-minerals and TEs, our study revealed that low serum Na and Ca levels were statistically significantly related with depression (P-value: 0.020 and 0.000 respectively) with lower serum Mg, serum P compared to higher serum Cu levels among depressed than non-depressed CLD, however no difference regarding serum K and Zn levels.

This is consistent with the study of Ozdemir et al. (2014) who found that patients with depression had statistically significant lower serum Na levels than healthy control subjects (P value: 0.04) (33).

This could be explained by decreased Na levels causes cellular edema, that affects the central nervous system (CNS), causing CNS depression and edema of the brain cells, resulting in neurologic and psychiatric symptoms as lethargy, restlessness, behavioral changes, confusion, seizures, irritability, depression, and manic behavior (34).

Our study showed that depression was highly statistically related to serum Ca level, in which lower Ca serum levels were more prevalent among depressed patients in comparison to non-depressed patients and this relation was confirmed by univaraite and multivariate regression analysis.

It was confirmed by a study done by Islam et al. (2018) who proved that significantly decreased serum Ca level among depressed patients compared with control subjects (P-value: < 0.05) (17).

Thi Thu Nguyen et al. (2019) stated that a strong statistically inverse relation between depressive symptoms and serum Ca level (18). Also, the study by Miki et al.2015 suggested that a higher dietary intake of Ca was associated with a lower prevalence of depressive symptoms (35).

This could be explained by Ca dysregulation could have stimulatory effects on neuromuscular junctions, depression, agitation, and mania which have been described with hypocalcemia (36).

As regard serum Mg levels, a study was done by Zieba et al. (2000) concluded that patients with unipolar depression exhibit significantly lower serum Mg levels than the control group (37) and was confirmed by our results.

A systematic review was done by Dermo et al,2013 and proved that Mg rich diet reduces the depressive symptoms (38).

Low serum Mg level is associated with depression through its role as a protector of the nervous system, as it has a strong anti-inflammatory effect. Furthermore, Mg is a Ca antagonist and voltage-dependent blocker of the N-methyl-D-aspartate channel that regulates Ca flow into the neuron. So, low serum Mg levels causing high levels of Ca and glutamate that may deregulate synaptic function, resulting in depression (39).

Glutamate is the most abundant excitatory neurotransmitter in the brain, an abnormally high level of glutamate can lead to neuron damage, and mood disorders like depression (40).

Our study proved that depression was not statistically related to the serum Zn level. In contrast to the study by Islam et al. (2018) that revealed that decreased level of serum Zn was statistically significantly related to depression (17). Another two studies were done by Gronli et al. (2013) and Siwek et al. (2013) (41,42) concluded the similar findings.

This controversy with our results may be contributed to the fact that serum Zn level was significantly lower with increasing the severity and progression of liver damage, due to poor appetite, and malabsorption of Zn due to portal hypertensive gastropathy (43,44). As, Most of our participants were Child B, with a lower percentage of Child C patients (16.3%, of our CLD patients were Child A, 58.5% were Child B, and 25.2% were Child C), as by the progression of liver cirrhosis, Child C patients

suffer from several complications as renal impairment or hepatic encephalopathy so, most of them were excluded from our study and consequently this relation was not significantly proved.

As regard elevated cu levels among depressed CLD older patients in our study group. It agreed with Schlegel-Zawadzka et al. (1999) who found that serum Cu level was significantly increased in 19 unipolar depressed patients compared to 16 non-depressed patients (45).

Also, Islam et al. (2018) in a case-control study recruited 247 patients and 248 healthy volunteers which analyzed the association of serum macro-minerals and TEs with MDD, revealed that depression was related to increased serum Cu level (17).

This may be contributed to increased serum Cu levels may be injurious to the cells and leads to cellular instability and damage due to the oxidative potential of the free metal, so it may increase the possibility of depression (46).

The current study found lower serum P levels among older CLD with depression in comparison with non-depressed older CLD patients.

No direct study report relationship of serum P levels with depression but it was proved by Kaner et al. (2015) (47) that a lower amount of P intake in the group with depressive symptoms was observed in comparison to the group without such symptoms.

However, Thi Thu Nguyen et al. (2019) and Kaner et al. (2015) revealed that a lower amount of K intake was statistically significantly in a group with depression (18,47). This relationship was not confirmed in our study.

This disagreement can be explained by our patients were using K sparing diuretics with furosemide which keep serum K levels within the normal range (Mean ± SD of serum K levels was 3.97 ± 0.60 among depressed patients compared to 3.87 ± 0.58 among non-depressed patients).

According to our study, the previous macro-minerals and trace elements abnormalities can be explained either by using diuretics or malnutrition which are associated with depression among older CLD patients. So by treating malnutrition and adjusting the dose of diuretics may decrease the risk of depression in CLD older patients.

The strength of our study is that we excluded subjects with other psychiatric and co-morbidities like renal impairment that affect serum TEs and micro-mineral levels, which could potentially confound the results. Moreover, according to our knowledge, our study was the first research that studied the association between depression in CLD and macro-minerals and TEs. However, the limitation is that we did not study the dose and duration of diuretics used, so the actual effect of diuretics on the level of macro-minerals and TEs is not obtained. So, future studies are needed to reveal the effect of the dose and duration of diuretics on macro-minerals and TEs that could affect depression.

CONCLUSION

In addition to known risk factors causing depression in CLD, our study revealed that using diuretics and malnutrition are associated with depression among older CLD patients through their effect on serum TEs and macro-minerals. So, screening for depression and malnutrition, in addition, follow up of serum TEs and macro-minerals with adjusting the dose of diuretics are recommended for decreasing the risk of depression and consequently reducing the suffering of older patients with CLD and improving their quality of life.

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