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Association between vitamin D status and depression in children with chronic liver disease

Ola G. Behairy[1*], Al Rawhaa A. Abo Amer[1], Amira I. Mansour[2] and Karim I. Mohamed[1]

Abstract

Background: Deficiency of vitamin D and depression are commonly occurring in patients with chronic liver diseases. This study aimed to determine the association between 25-OH-vitamin D status and depressive symptoms among children with chronic liver diseases. Eighty children were enrolled and divided into 2 groups: the patients' group (60 children with chronic hepatitis) and the control group (20 healthy children). All children have been analyzed for their clinical, biochemical features, histological profile, serum 25-OH-vitamin D levels, and assessment of childhood depression using Arabic form based on Kovacs Children's Depression Inventory.

Results: Serum level of 25(OH) D was significantly lower in the hepatic group than the control group [17 (5–52) ng/ml, 45 (13–95) ng/ml, $p = <0001$ respectively]. Depression score was significantly higher in the hepatic group as 30% of the control group had mild depression, while 36.7% of the hepatic group had mild depression, 16.7% had moderate depression, and 10% had severe depression. There was a statistically significant difference between children with depressive symptoms and non-depressive symptoms as regards the level of serum vitamin D as it was lower in children with depressive symptoms [median (range) 17 (5–40) ng/ml, 27.5 (8–52) ng/ml, $p = 0.04$ respectively]. There were statistically significant differences between the serum level of 25(OH) D and depression as it decreases with increasing severity of depression.

Conclusion: Children with chronic liver disease who had depressive symptoms showed significantly lower levels of vitamin D when compared with those without depressive symptoms; also, vitamin D had an inverse correlation with depression scores in these children.

Keywords: Children, Depression, Chronic liver diseases, 25-OH-vitamin D

Background

Chronic liver disease (CLD) is a progressive liver parenchyma destruction and regeneration which leading to fibrosis and cirrhosis (normally lasts 6 months). CLD's etiological agents include hepatotropic viruses (HCV and HBV), fatty liver, and autoimmune hepatitis [1].

Depression, also known as major depressive disorder (MDD), major depressive episode (MDE), or clinical depression, is a mental disorder marked by pervasive and persistent low mood, followed by low self-esteem and loss of interest or enjoyment in usually pleasurable activities. CLD was long known and associated with depression [2–4].

Liver diseases may interfere with the development of the active vitamin D metabolites leading to abnormal calcium and bone metabolism [5, 6]. Vitamin D also had several other roles, including cell growth and control of the neuromuscular and immune system. Vitamin D deficiency is highly prevalent globally and is believed to be associated with an increased risk of major depressive disorder and anxiety disorders [7]. So this work aimed to

* Correspondence: olaped99@yahoo.com; ola.behery@fmed.bu.edu.eg
[1]Pediatrics Department, Faculty of Medicine, Benha University, Benha, Qualiopia, Egypt
Full list of author information is available at the end of the article

investigate the association between vitamin D status and depressive symptoms among children with CLD.

Subject and methods

This case-controlled study was conducted on children diagnosed with CLD who attending the outpatient hepatology clinic after obtaining informed written consent from each parent of enrolled children in the period from October 2018 to July 2019 and apparently healthy children of matched age and sex acted as the control group. Children with comorbidity like renal diseases, heart diseases or parathyroid disease, prior parathyroid surgery, concurrent anticonvulsant treatment metabolized by cytochrome P450 activity, psychiatric disorders (psychosis or dementia), hepatic encephalopathy, and liver transplantation were excluded from this study, and the number of each category of the excluded patients was not recorded. The study was approved by Ethical Scientific Committee according to guidelines of the Helsinki Declaration [8].

❖ All the following were collected based on medical records and anamnesis: sociodemographic, clinical examination, abdominal ultrasonography, result of hepatic needle biopsy, laboratory parameters: hematological (complete blood picture (CBC), biochemical (liver function tests: [aspartate aminotransferase (AST), alanine aminotransferase (ALT)), alkaline phosphatase(ALP), gamma-glutamyl transpeptidase(GGT), total and direct bilirubin, serum protein and albumin] and serum creatinine) autoantibodies (anti-nuclear antibodies (ANA), smooth muscle antibodies (ASMA), liver-kidney microsome antibodies (LKM-1) and anti-mitochondrial antibodies(AMA)), and viral hepatitis profile.

❖ The severity of liver disease was quantified using Child-Pugh score [9], model for end-stage liver disease (MELD) score [10] for teens older than 12 years of age, and pediatric-related end-stage liver disease (PELD) score [11] for participants younger than 12 years of age.

❖ All the participants were evaluated for depression level based on Children's Depression Inventory (CDI), a commonly used scale that tests depression symptoms in children and adolescents ages 7 to 17 years within the last 2 weeks [12] with the use of Arabic-translated form [13]. It measures negative mood (irrational thinking about people or events which means focusing on the negative and not seeing the positive in life), negative self-esteem (lack of confidence and feeling badly about oneself), anhedonia (loss of the capacity to experience pleasure), ineffectiveness (low capability of producing the desired result or the inability to produce desired output), and indecisiveness (not decisive or conclusive). The scale includes 27 items; each item consists of three choices of answers and the patient should choose one. Those 3 choices represent 3 degrees of severity of symptoms. According to the severity, the degree ranges from 0 to 2 as follows: no symptom, 0; mild to moderate, 1; and severe symptoms, 2. The score for both male and female ranging from 0 to 9 was considered normal, while mild depression in males was considered at 9–14 and in females at score 9–16, moderate depression in males at 15–18 and in females at 17–22, and severe depression in males at score > 18 and in females at score > 22. The questionnaire was administered by the same interviewer.

❖ Laboratory investigations*:* 3-ml venous blood was drawn by aseptic venipuncture using a disposable sterile syringe. Blood was used for the assessment of serum levels of 25-hydroxyvitamin D by enzyme-linked immunosorbent assay (ELISA). Quantitative measurement of bioactive Vit D was carried out using sensitive competitive ELISA kits supplied from WKEA Med Supplies Corporation, China. The normal level of vitamin D is defined as a 25-OH Vit D concentration greater than 20 ng/ml (> 50 nmol/L). Vitamin D insufficiency is defined as a 25-OH-Vit D concentration of 12–20 ng/ml (30–50 nmol/L). Vitamin D deficiency is defined as a 25-OH-Vit D level less than 12 ng/ml (< 30 nmol/L) [14] for all the participants.

Statistical analysis

Data were tabulated, coded, and then analyzed using the computer program SPSS (statistical package for social science) version 16. Quantitative data were presented as mean ± SD. The χ^2 test and Fisher exact test were used to compare proportions as appropriate. The Student's t test and the Mann–Whitney (Z) test were used to test differences between the two groups regarding parametric and non-parametric data, respectively. Spearman's correlation coefficient was used to test the correlation between variables. For all analyses, the level of significance was set at $p < 0.05$.

Results

Study population characteristics

The mean age of the studied 60 children suffering from chronic liver disease of different etiologies is 12 ± 3 years; they were 33 (55%) male and 27 (45%) female. Twenty-one (35%) of them had positive consanguinity, while the 20 control children were 10 females (50%) and 10 males (50%) with mean age 12 ± 4 years with 4 (20%) of them had positive consanguinity with no statistically significant difference between both groups as regards age, gender, and consanguinity. Regarding diagnosis of chronic liver disease group, 25% had metabolic and genetic liver diseases (3.3% Dubin Johnson syndrome, 15% glycogen storage disease, and 6.7% Wilson disease), 43.4% were diagnosed with chronic hepatitis [autoimmune hepatitis 20%, chronic hepatitis of unknown etiology 11.7%, steatohepatitis 6.7%, and congenital hepatic

fibrosis 5%], 21.6% had infective hepatitis (18.3% HCV and 3.3% HBV), and 10% had cholestatic liver disease (5% Alagille syndrome and 5% progressive familial intrahepatic cholestasis). The studied CLD patients were presented clinically with jaundice (66.6%), abdominal pain (20%), abdominal distention (58.4%), fever (15%), faltering of growth (24.5%), and pallor (16.6%). Abdominal ultrasonography of patients revealed hepatomegaly (80%), splenomegaly (50%), and ascites (6.6%).

All the patients had increased levels of liver enzymes and regard histopathological evaluation of liver biopsy according to the Ishak score revealed that the majority of the studied patients (80%) showed mild disease activity. Regarding the degree of fibrosis, 45% had mild fibrosis (F1), 33.3% had moderate fibrosis (F2), and severe fibrosis (F3) was present in 16.7% of patients (Table 1).

Vitamin D and depression score in CLD patients and controls

There was a statistically significant difference between the studied groups regarding the level of serum 25-OH-vitamin D as it was lower in the hepatic group (Fig. 1 and Table 2). There was a statistically significant difference between studied groups regarding depression score as all degrees of depression (mild, moderate, and severe) were statistically higher in the hepatic group (Table 2).

Regarding liver biopsy, there was a statistically significant association between the serum level of 25-OH-vitamin D and degree of fibrosis (FI) and histological activity index (HAI) as it decreases with increasing degree of fibrosis and HAI. Also, there was a statistically significant association between depression score and degree of fibrosis and HAI as it increases with increasing degree of fibrosis and HAI (Table 3).

There was a statistically significant difference between children with depressive symptoms (38 cases) and non-depressive symptoms (22 cases) regarding the level of serum 25-OH-vitamin D as it was lower in children with depressive symptoms [median (range) 17 (5–40), 27.5 (8–52, p = 0.04) respectively]. There were statistically significant differences between both normal and different degrees of depression regarding the serum level of 25-OH-vitamin D as it decreased with increasing severity of depression (Table 4).

There was a statistically significant negative correlation between 25-OH-vitamin D and ALT, AST, FI, HAI, and depression score, but there were no statistically significant correlations between 25-OH-vitamin D and other clinical and laboratory measures (Table 5).

There was a statistically significant positive correlation between the degree of depression score and ALT, AST, FI, and HAI, while there was a statistically significant

Table 1 Laboratory and histological characteristics of the hepatic group

Variables		Hepatic group (n = 60)
Hb (g/dL)	Mean ± SD (range)	10.7 ± 1.5 (7.4–13)
Platelets (× 10^3/mm^3)	Mean ± SD (range)	223 ± 119 (50–400)
WBC (× 10^3/mm^3)	Mean ± SD (range)	7.4 ± 3.1 (3.3–17)
ALT (U/L)	Mean ± SD (range)	115 ± 93 (75–483)
AST (U/L)	Mean ± SD (range)	143 ± 136 (88–769)
Total bilirubin (mg/dL)	Median (range)	3.11 (0.6–22.6)
Direct bilirubin (mg/dL)	Median (range)	1.85 (0.1–13.3)
Albumin (g/dL)	Mean ± SD (range)	3.9 ± 0.5 (2.3–5)
PT (s)	Mean ± SD (range)	14.5 ± 2.6 (11–25)
PTT (s)	Mean ± SD (range)	40.6 ± 6.4 (29.4–66)
INR	Mean ± SD (range)	1.33 ± 0.31 (1–2.9)
ALP (IU/L)	Mean ± SD (range)	371.47 ± 218.52 (91–1022)
Histological activity index (HAI)	(0–3/18) minimal	20 (33.3%)
	(4–8/18) mild	28 (46.7%)
	(9–12/18) moderate	9 (15%)
	(13–18/18) severe	3 (5%)
Degree of fibrosis (FI)	(F0/6) no fibrosis	3 (5%)
	(F1–2/6) mild fibrosis	27 (45%)
	(F3–4/6) moderate fibrosis	20 (33.3%)
	(F5–6/6) severe fibrosis	10 (16.7%)

Hb hemoglobin, *WBC* white blood cells, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *PT* prothrombin time, *PTT* partial thromboplastin time, *INR* international normalized ratio, *ALP* alkaline phosphatase

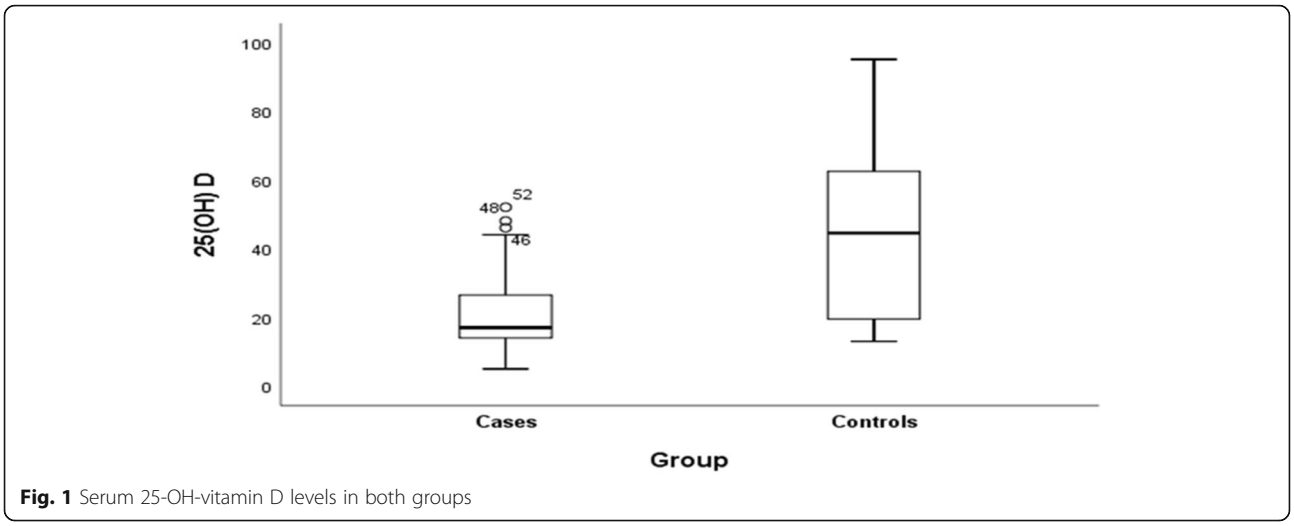

Fig. 1 Serum 25-OH-vitamin D levels in both groups

negative correlation between the degree of depression score and hemoglobin and albumin. There were no statistically significant differences between the degree of depression score and other variables (Table 5).

Discussion

The present study shows that there was a statistically significant difference between the studied groups as regards the level of serum 25-OH-vitamin D as it was statistically lower in the hepatic group. Seventy-five percent of the control group had sufficient, and 25% had insufficiency of 25-OH-vitamin D. While in the hepatic group, 38.3% had sufficient 25-OH-vitamin D, 41.7% insufficiency, and 20% had deficient 25-OH-vitamin D. Such findings are consistent with Lee et al. [15] who found that vitamin D deficiency was prevalent in children with CLD despite supplementation of vitamin D. Overall, 28% of the subjects were either vitamin D deficient or insufficient. Also, Jamil et al. [16] found that 88% had either insufficient (patients, 52.8% vs. controls, 27%) or deficient levels (patients, 34.4% vs. controls, 26%) of vitamin D, while only 12% had sufficient levels of vitamin D (patients, 12% vs. controls, 47%). Likewise, Arteh et al. [17] reported that the global prevalence of vitamin D deficiency (VDD) in the general population has been reported to effect all age groups ranging from 20 to 100% for serum 25(OH) vitamin D concentrations < 20 ng/ml. The prevalence of vitamin D levels < 20 ng/ml in CLD has been reported to range from 64 to 92% and is generally inversely linked to the progression of the disease.

There are many possible reasons for the reported inverse relationship between liver disease severity and falling vitamin D status. The underlying mechanisms are almost definitely multifactorial in nature and likely to vary between different liver pathologies. Important possible mechanisms to consider are as follows: reduced exogenous exposure of patients to vitamin D sources (e.g., dietary, sunlight), deficiency of bile salts needed for gastrointestinal absorption of vitamin D, reduced endogenous production of vitamin D and albumin which impaired by cirrhosis, impaired hepatic hydroxylation of vitamin D to 25(OH) D, and increased catabolic removal of 25(OH) D [18].

Table 2 Serum 25-OH-vitamin D and depression score among studied groups

Variables		Hepatic group (n = 60)		Control group (n = 20)		Test	p value
25-OH-vitamin D (ng/ml)	Median (range)	17 (5–52)		45 (13–95)		$Z = -3.804$	< 0.001
25-OH-vitamin D (ng/ml)	Deficiency(< 12 ng/ml)	12	20.00%	0	0.00%	$\chi^2 = 9.357$	0.009
	Insufficiency (12–20 ng/ml)	25	41.70%	5	25.00%		
	Sufficiency (20–100 ng/ml)	23	38.30%	15	75.00%		
Depression score	Normal, n (%)	22	36.6%	14	70.00%	$\chi^2 = 6.7$	0.009
	Mild, n (%)	22	36.7%	6	30.00%	$\chi^2 = 29$	0.049
	Moderate, n (%)	10	16.7%	0	0.00%	FET	0.021
	Severe, n (%)	6	10%	0	0.00%	FET	0.039

Table 3 Relation between both serum 25-OH-vitamin D and depression score and liver biopsy findings

Liver biopsy		Serum 25-OH-vitamin D (ng/ml)		*F* test	*p* value
		Mean ± SD	Range		
Degree of fibrosis (FI)	(F0/6) no fibrosis	24.74 ± 12.402	8–52	2.8	.045 (S)
	(F1–2/6) mild	20.80 ± 9.920	5–44		
	(F3–4/6) moderate	19.67 ± 18.475	9–41		
	(F5–6/6) sever	15.00 ± 9.119	6–39		
Histological activity index (HAI)	(0–3/18) minimal	26.30 ± 14.907	7–52	3.1	.032 (S)
	(4–8/18) mild	19.18 ± 8.87	6–44		
	(9–12/18) moderate	15.00 ± 8.88	5–29		
	(13–18/18) sever	12.33 ± 5.77	9–19		
Degree of fibrosis (FI)	Depression score			148	.001
		Mean ± SD	Range		
	(F0/6) no fibrosis	4.67 ± 0.57	4–5		
	(F1–2/6) mild	10.85 ± 4.11	5–19		
	(F3–4/6) moderate	13.05 ± 5.82	5–26		
	(F5–6/6) sever	16.80 ± 4.32	11–25		
Histological activity index (HAI)	(0–3/18) minimal	9.55 ± 4.49	4–19	5.1	.003
	(4–8/18) mild	12.50 ± 4.87	5–25		
	(9–12/18) moderate	17.11 ± 6.05	7–26		
	(13–18/18)sever	17.67 ± 2.52	11–26		

In the current study, there was a statistically significant difference between the studied groups as regards depression score as 30% of the control group had mild depression, while 36% of the hepatic group had mild depression, 16.7% had moderate depression, and 10% had severe depression. Such results follow Akram et al. [19] who recorded that patients suffering from depression were 59.3%, anxiety was 17.4%, and both anxiety and depression were 30.7%. Also, Kerkar et al. [20] found that children with NAFLD have higher levels of depression than those with obese controls, while Arslan et al. [21] found that the mean depression and anxiety scores between children with chronic hepatitis B and control group were not significantly different ($p > 0.05$).

Relative to many studies of depression prevalence in CLD patients, mechanistic depression research was incomplete. Generally, the main reasons for this include the following aspects: (i) the disease itself: the long-term discomfort caused by illness and treatment, feeling of guilt, and anxiety about the progression of the disease, etc. and (ii) social and economic strain, including basic research and working conditions, social discrimination, and high medical treatment costs. Emerging evidence supported reduced serotonin and dopamine transporter binding in chronic hepatitis patients with cognitive impairment, which could be associated with depression [1].

In the present study, there was statistically significant positive correlation between the degree of depression score and ALT, AST, FI, and HAI; there are many studies run in line with our results and reported that depression was associated with more severe fibrosis and HAI [22–24].

In this study, there were statistically significant differences between both normal and different degrees of depression regarding serum level of 25-OH-vitamin D as it decreased with increasing severity of depression; also, there was a statistically significant negative correlation between 25-OH-vitamin D and ALT, AST, FI, HAI and

Table 4 Relation between serum 25-OH-vitamin D level and depression score

		Serum 25-OH-vitamin D (ng/ml)		*F* test	*p* value
		Mean ± SD	Range		
Depression score	Normal (22 cases)	27.52 ± 14.27	8–48	3.15	0.01 (S)
	Mild (22 cases)	24.04 ± 10.12	7–52		
	Moderate (10cases)	16.70 ± 6.3	9–33		
	Severe (6cases)	7.40 ± 3.2	5–13		

Table 5 Correlation between 25-OH-vitamin D and degree of depression score and clinical and laboratory measures

Variables	25-OH-vitamin D (ng/ml)		Depression score	
	r	*p*	*r*	*p*
Liver span (cm)	− .059	0.654	.108	.409
Spleen size (cm)	− .140	0.286	− .20	.879
Hemoglobin (g/dL)	− .056	0.669	− .263*	.042
Platelets (× 10^3/mm^3)	− .120	0.36	.098	.457
WBC (× 10^3/mm^3)	0.079	0.546	− .005	.972
ALT (U/L)	− .370**	0.004	.186*	< .05
AST (U/L)	− .399**	0.002	.174*	< .05
PT (s)	0.008	0.951	.165	.208
PTT (s)	− .060	0.647	.270	.077
INR	− .097	0.459	.152	.248
Total bilirubin (mg/dL)	− .058	0.658	.112	.395
Direct bilirubin (mg/dL)	− .057	0.666	.039	.767
Albumin (g/dL)	0.053	0.689	− .367**	.004
ALP (IU/L)	− .066	.618	− .058	.660
FI	− .444**	< 0.001	.507**	.000
HAI	− .293*	0.023	.442**	.000
Depression score	− .286*	0.027	–	–

Spearman's correlation was used
r correlation coefficient, *FI* degree of fibrosis, *HAI* histological activity index, *WBC* white blood cells, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *PT* prothrombin time, *PTT* partial thromboplastin time, *INR* international normalized ratio, *ALP* alkaline phosphatase, *IgG* immunoglobulin G
*Significant, **Highly significant

depression score. These findings are supported by Skaaby et al. [25] who reported a statistically significant inverse association between vitamin D status and incident liver disease with a hazard ratio = 0.88 (95% confidence interval 0.79–0.99) per 10 nmol/L higher vitamin D status at baseline. The risk of having a high level of ALT, AST, or GGT appeared to be higher for lower vitamin D levels, but not statistically significant, and they stated that vitamin D status was inversely related to incident liver disease. Also, many studies had reported an inverse association between vitamin D status and degree of liver fibrosis [26, 27], while Yodoshi et al. [28] found that the majority were either vitamin D insufficient (50%) or deficient (32%) within 3 months of their liver biopsy and recorded no association between serum 25(OH)-vitamin D concentrations and serum aminotransferases or histological scores, and they claimed that vitamin D deficiency and insufficiency are common in children with nonalcoholic fatty liver disease (NAFLD), but not consistently linked to severity of histological disease.

Concerning the effect of vitamin D on liver fibrosis, vitamin D has an anti-fibrotic effect on hepatic stellate cells through different signal transduction pathways mediated by receptor vitamin D, which in turn inhibits the expression of pro-fibrogenic genes. Also, some studies showed a significant correlation between low vitamin D levels and an increased risk of hepatic fibrosis. Additionally, the high prevalence of vitamin D deficiency was observed in patients with liver fibrosis, suggesting the use of vitamin D status as a biochemical marker that reflects the progression of liver fibrosis [29].

With regard to the inverse correlation between vitamin D and depression score, these results are consistent with Smith et al. [30] who found that serum 25(OH) vitamin D was negatively associated with Children Depression Inventory (CDI) scores ($r = -0.55$, $p < 0.001$), and the group of patients with insufficient level 25(OH) vitamin D levels did show significantly more depressive symptoms ($p < 0.001$). Also, many researchers who reported significant improvement in depression and well-being with vitamin D supplementation suggest a link between vitamin D status and depression [31, 32]. Likewise, Sarris et al. [33] have confirmed that vitamin D is recommended for use with antidepressant drugs in successful depression treatment.

Region-specific expression of vitamin D receptors (VDR) in the cingulate cortex, thalamus, cerebellum, substantia nigra, amygdala, and hippocampus suggests the possibility of a function of vitamin D in psychiatric disorders. Many of these regions also express 1α-hydroxylase enzymes capable of metabolizing 25(OH) D to 1, 25(OH)2D3, suggesting that vitamin D may play an autocrine or paracrine action in the brain [34]. Indeed, vitamin D may play a key role in the pathophysiology of depression and several studies have shown the existence of vitamin D, its receptors (VDR) and associated enzymes (CYP 24A1, CYP 27B1) in several brain regions, pointing to the importance of vitamin D as a neuroactive/neurosteroid hormone involved in key functions such as neuroprotection, neuroimmunomodulation, regular brain function, and brain development [34, 35]. Also, evidence of possible neuroprotective roles is emerging that vitamin D may play through its effects on inflammation. Certainly, increasing data suggest that the upregulation of proinflammatory cytokines in the brain can be linked with depression [36] and vitamin D may will be one of the modulators in the association between depression and inflammatory response by its impact on the immune system [37].

Strength and limitations

25-OH-vitamin D represents the first step to prove the pivotal role of 25-OH-vitamin D as a marker of depression in chronic liver diseases.

Limitations in our study

Include a small number of cases which make us unable to rebost regression model by sufficient number of predictors and this is from statistical point of view.

Conclusion Children with chronic liver disease who had depressive symptoms showed a significantly lower level of 25-OH-vitamin D when compared with those without depressive symptoms; also, 25-OH-vitamin D had an inverse correlation with depression score in these children.

Abbreviations
CLD: Chronic liver diseases; MDD: Major depressive disorder; FI: Degree of fibrosis; HAI: Histological activity index

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Authors' contributions
1- O B: contributed to the design and implementation of the research, aided in choosing the patients and helped shape the research, supervised the findings of this work, discussed the results, writing of the manuscript, and read and approved the final manuscript. 2- A A: contributed to the design and implementation of the research, contributed to the revision of the work and the acceptance of the final form of the manuscript, and read and approved the final manuscript. 3- A M: contributed to the design and implementation of the research, performed the laboratory work, and read and approved the final manuscript. 4- K M: contributed to the design and implementation of the research, contributed in the collection of the data and in performing the statistical part of the work, and read and approved the final manuscript.

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Availability of data and materials
All data and materials are available.

Ethics approval and consent to participate
The study was performed according to the ethical guidelines of the 1975 Declaration of Helsinki. The current study was approved by the Medical Research Ethical Committee of the Faculty of Medicine, Benha University. All subjects were informed about the procedures and the aim of the study, and informed written consent was obtained from the parents or caregivers of enrolled children. The committee's reference number is not applicable and/or not available.

Consent for publication
Not applicable

Competing interests
None of the authors have any conflicts of interest or financial disclosures related to this work.

Author details
[1]Pediatrics Department, Faculty of Medicine, Benha University, Benha, Qualiopia, Egypt. [2]Clinical Pathology Department, Faculty of Medicine, Benha University, Benha, Egypt.

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