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Role of Vitamin D as a Predictive Marker of Depression in Pediatrics Chronic Liver Diseases

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Abstract: Background: Generally, chronic liver disease (CLD) is a disorder procedure that leads to sever devastation and redevelopment of the liver parenchyma causing cirrhosis and fibrosis. Patients suffering from chronic liver diseases (CLD) frequently complaining from depression deficiency and in vitamin D. Vitamin D receptor is expressed in brain, and recently by meta-analysis it is established that depression has been inversely concomitant with vitamin D. **Aim of the study:** was to examine the relationship amide vitamin D status and depressive symptomsamong children with chronic liver diseases. **Subject and Methods:** Eighty children were participated in this investigation and classified randomly into 2groups: patients group (60 patients) and healthy control group (20 children). The children Depression Inventory (CDI) was used to assess depression. All patients have been analyzed for their clinical, biochemical features, histological profile and serum 25-hydroxyvitamin D levels were measured. **Results:** 25-Hydroxyvitamin D serum level was significantly lower in patient with CLD than healthy control group. Depression score was elevated significantly in the hepatic group versus control group patients. There were significant negative association amide 25-OH-vitamin D and ALT, AST, FI and HAI. There was statistical significant negative correlation between 25-Hydroxyvitamin D and depression score (r = -0.286 & P value = 0.027). There were statistically significant positive correlation between degree of depression score and (ALT, AST, FI and HAI). **Conclusion:** It is a novel work performed on Egyptian children suffering from chronic liver diseases (CLD) to evaluate role of vitamin D as a predictive marker of depression in pediatrics CLD. Our study showed that vitamin D levels correlated with CDI scores in children with CLD. This finding represents the first step to prove the pivotal role of 25-Hydroxyvitamin D as a marker of depression in CLD, which requires to be confirmed by many future investigations purposed for assessing 25-Hydroxyvitamin D in depressed children suffering from CLD.

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Keywords: children depression inventory; chronic liver diseases; 25-Hydroxyvitamin D.

1. Introduction

Chronic liver disease (CLD) is a disease process that leads to sever deterioration and regeneration of the liver parenchyma leading to cirrhosis and fibrosis. CLD refers to disorder of the hepatic tissues for at least 6 months. Three phases are notices in the pathogenesis of the disease comprising chronic inflammation, hepatic cirrhosis, and carcinoma of the hepatic cells. CLD represents a relatively rare disorder in children (**Abou-Taleb et al., 2019).**

Chronic liver disease (CLD) in children may cause a number of local and systemic complications and pathologies within other organs and systems. Some of these complications such as variceal bleeding or encephalopathy are life□threatening, whereas others are subclinical and may manifest in long□term period. **(Baygin et al., 2017).**

Vitamin D can be gained from foods or supplements, and is belonging to fat- soluble vitamin group, where it synthesized in the skin, after exposure of exposed to ultraviolet B photons. Where vitamin D either obtained from the diet or synthesized from the skin is non-active biologically and necessitates some enzymes to convert to the main circulating active form (25-hydroxyvitamin, and after that by the help of enzymes in the liver and kidney converted to 1, 25-dihydroxyvitamin D **(Kraus et al.,2018).**

According to the Diagnostic and Statistical Manual of Mental Disorder, (DSM-5, 2013) Clinical depression, is defined as low self-esteem, the loss of interest in pleasure, fatigue, diminished ability to think or concentrate and disturbed sleep or appetite. These symptoms frequently turned to chronicity and repeated, and can lead to suicide at the worst. Depression has ranked as the 4th leading etiology of disability globally (WHO), and by the year 2020 will be the second leading cause **(AH et al., 2018).**

So the target from the present work was to investigate the association among vitamin D status and

depressive state among children with chronic liver diseases.

2. Subject and methods

This cross-sectional case controlled study was conducted on 60cases diagnosed with chronic liver diseases from the attendance of pediatric hepatology clinic in Benha University Hospitals and the study period from October 2018 to july2019, twenty age and sex matched healthy children were selected from general population as a control group.

They were divided as following:-

Group (1) Study group: it will include 60 patients with chronic liver diseases with mean±SD age (12±3) years ranged from 7-17 year, 55% were males and 45% were females.

Group (2) Control group: it will include20 apparently healthy children mean±SD age was 12±4 ranged from 7-17 years.

2.1. Methods:

All children subjected to the following: **(1) Full history taking. (2) Physical examination**: *General examination. *Anthropometric measurements: including weight, height, BMI and *Abdominal examination. **(3) Laboratory Investigations:** Complete blood count (CBC), Serum transaminases (AST- ALT), alkaline phosphatase, serum bilirubin, serum albumin, PT, PTT, INR, total serum IgG levels, serum auto antibodies which include: ANA, ASMA titre, anti-LKM-1, hepatitis markers (HAV, HBV & HCV), liver biopsy and Serum 25-Hydroxyvitamin D level by ELISA**. (4) Aquestionaire** for assessment of depression by using CDI (children depression inventory) **(kovacs, 1985)** with using arabic translated form by **Gharib Abd El-fattah Gharib (1987),** Alazhar university, Egypt.

Statistical Analysis

Data management and statistical analysis were done using SPSS vs.25. (IBM, Armonk, New York, United states). Numerical data was summarized as means and standard deviations or medians and ranges. Categorical data was summarized as numbers and percentages. Comparisons between both groups were done using Mann Whitney U test for numerical data. Categorical data was compared using Chi-square test or Fisher's exact test if appropriate. Correlation analysis was done between 25-OH-vitamin D and other study measures and correlation analysis was done between depression score and other study measures using Spearman's correlation. "r" is the correlation coefficient. It ranges from -1 to +1. -1 indicates strong negative correlation. +1 indicates strong positive correlation while 0 indicates no correlation. Multiple linear regression analysis model, Enter method, was run to detect the significant predictors of vitamin D level. $R^2$is the regression coefficient = % of variation in the level of 25-Hydroxy vitamin D due to its relation with the model. Adjusted R^2= (the adjusted value was used as unadjusted R2 usually overestimate the association). SEE= standard error of the estimate. b_0= constant**,** b= slope of the regression line. 95% CI of b= 95% CI of the slope, if includes 0 = non significant (no slope = no line). The accepted level of significance in this work was stated at 0.05 (P <0.05 was considered significant).

3. Results

Demographic characteristics of the studied groups showed in Table (1). There was no statistically significant differences between studied groups regarding age, sex and consanguinity. Regarding to diagnosis of chronic liver disease group, 36.5%had metabolic and genetic liver diseases (3.3% Dubin Johnson syndrome, 5% congenital hepatic fibrosis, 15% glycogen storage disease, 6.6% Non alcoholic fatty liver disease and 6.6% Wilson disease) 21.6% had infective hepatitis (18. 3% HCV and 3. 3% HBV), 20% had autoimmune liver diseases, 10% had cholestatic liver disease (5% Alagille syndrome, 5% progressive familial intrahepatic cholestatis), 10% had chronic hepatitis for differential diagnosis and 1.7% had buddchiari syndrome (table 2).

4. Discussion

The present investigation was carried out on 80 children, 60 chronic hepatitis patients (group 1) who fulfilled the criteria for diagnosis of chronic hepatitis with mean±SD age (12±3) years ranged from 7-17 year, 55% were males and 45% were females with 35% had positive consanguinity. Control group (group2): comprised 20 apparently healthy children, their ages and sex were harmonized with group 1, the mean age was averaged 12±4 (range 7-17 years). There was no statistical significant difference between both group as regard age, gender and consanguinity. Regarding to diagnosis of chronic liver disease group, 36.5%had metabolic and genetic liver diseases (3. 3% Dubin Johnson syndrome, 5% congenital hepatic fibrosis, 15% glycogen storage disease, 6.6% Non alcoholic fatty liver disease and 6.6% Wilson disease) 21.6% had infective hepatitis (18. 3% HCV and 3. 3% HBV), 20% had autoimmune liver diseases, 10% had cholestatic liver disease (5% Alagille syndrome, 5% progressive familial intrahepatic cholestatis), 10% had chronic hepatitis for differential diagnosis and 1.7% had buddchiari syndrome.

Table (1) Demographic characteristics of the studied groups

Variables		Hepatic group (n = 60)	Control group (n = 20)	test	P value
Age (years)	Mean ±SD Range	12 ±3 7-17	12 ±4 7-17	Z= 0.408	0.683
Sex	Males n (%)	33 (55.0)	10 (50.0)	X2= 0.15	0.698
	Females n (%)	27 (45.0)	10 (50.0)		
Consanguinity	positive n (%)	21 (35.0)	4 (20.0)	X2= 1.750	0.21

Z: Mann Whitney U test was used for age. X2: Chi-square test was used for gender and consanguinity

Table (2) Diagnosis of hepatic group.

Diagnosis	Hepatic group (N=60)	No.	%
Autoimmune liver diseases	Autoimmune hepatitis	10	16.70%
	Autoimmune sclerosing cholangitis	2	3.30%
Infective hepatitis	Chronic hepatitis B	2	3.30%
	Chronic hepatitis C	11	18.30%
Metabolic and genetic liver diseases	Dubin Johnson syndrome	2	3.30%
	Congenital hepatic fibrosis	3	5.00%
	Glycogen storage disease	9	15.00%
	Non alcoholic fatty liver disease	4	6.6%
	Wilson disease	4	6.60%
Cholastatic liver diseases	Alagile syndrome	3	5.00%
	Progressive familial intrahepatic cholestasis	3	5.00%
Vascular liver diseases	Budd chiari syndrome	1	1.70%
Cryptogenic liver diseases	Cryptogenic cirrhosis	6	10.00%

These results run in accordance with **Mahmud et al., (2016)** who reported in their study on 60 children of liver diseases (53% males), by using the percutaenous liver biopsy as a diagnostic tool for pediatric liver diseases. The most common histological features was 23.3% neonatal hepatitis, 16.7% biliary atresia, 10.0% glycogen storage disease, 10.0% chronic hepatitis, 6.7% hepatoblastoma, lipid storage disease, intra-hepatic bile duct paucity and 6.7% cirrhosis and 3.3% congenital hepatic fibrosis. Chronic hepatitis (10.0%) & cirrhosis (6.6%) were the most common disorders in the older children (>5 years), whereas, in children at 1-5 year age group, glycogen storage disease and hepatoblastoma and non-specific changes were the most common signs. In addition, at ≤1 year age group both biliary atresia and neonatal hepatitis were common symptoms. 30% of the hepatic group complaining from consanguinity especially in neonatal hepatitis, storage disease intra-hepatic bile duct paucity and congenital hepatic fibrosis. Also, **(Abou-Taleb et al., 2019)** studied the clinicopathological pattern of pediatric chronic liver diseases on 151 children with diffuse liver diseases. In the current study, 63.5% were boys and 36.5% were girls. Their ages were averaged 20.4 ±27.6 (range 0.5 to 144 months) and 9 months was the median value. In pediatric department admission, consanguinity between patients was found in 47% of children and found that pediatric CLD comprised 1.6% of total cases. The leading etiology of chronic liver disease as reported in the current study was 35.1% metabolic liver disease (MLD) and 41.05% neonatal cholestasis disease (NCD). NCD included 25.1% neonatal hepatitis, 13.2% extra hepatic biliary atresia and 2.7% paucity of interlobular bile ducts. MLD comprised 26.5% glycogen storage disease, 5.3% undetermined inborn error of metabolism, 2.0% Gaucher' s disease and 1.3% Niemann Pick disease. Further etiologies of CLD such as congenital hepatic fibrosis (5.9%), autoimmune hepatitis (8.6%), chronic hepatitis C infection (2.7%), non-alcoholic fatty liver disease (4.0%), and the lowest incidence was Budd Chiari disease (0.6%).

Hashmi et al., (2017) who studied spectrum of histopathological diagnosis in paediatric liver disorders confirmed by liver biopsy on 74 children at the median age of 6.9 years, of the total, 23(31%) were girls and 51(69%) were boys. They stated that metabolic disorders were present in 36.5% of pediatric liver disease patients, whereas, glycogen storage disease was the more prevalence metabolic disease in (16.2%) of children, chronic hepatitis was (12.2%), biliary atresia was (5.4%), and vanishing bile duct syndrome was (1.3%).

In addition, **Sathe, (2016)** recorded that metabolic liver disease founded in 41.2 % of CLD patients including Wilson disease (15.4%). Also, **Cheema et al. (2015)** described that metabolic

diseases represented 36 % of pediatric liver disorder with glycogen storage disorder reached 13.7% of examined cases by using histological tools.

As regarding to liver biopsy in our study, regards histological Activity Index, 33.3% had minimal activity, 46.7% had mild activity, 15% had moderate activity, 5% had sever activity. Regards Fibrosis Index, 5% had no fibrosis, 45% had mild fibrosis, 33.3% had moderate fibrosis, 16.7% had sever fibrosis. Regards Interface hepatitis, 80.0% had no Interface hepatitis, 6.6% had minimal degree, 8.4% had mild degree, 5% had moderate degree. According to type of prominent cells, 16.7% had plasma cell, 5% had eosinophils, 56.6% had lymphocytes, 5% had giant cells and 16.6% had Nonspecific inflammatory cells. These results were in agreement with **Pokorska-Spiewak et al., (2017)** who studied new serum biomarkers improved by BMI, z-score for the recognition of steatosis and liver fibrosis in children suffering from chronic hepatitis C on 30 children aged 9.4± 3.7 (14 males and 16 females) with chronic hepatitis C underwent liver biopsy showed that 8/30 (27%) patients presented with F0 and 15/30 (50%) of patients with F1, 7/30 (23%) with F2, no cases of cirrhosis was detected, hepatitis activity index was minimal in (4/30), mild in (14/30), moderate in (8/30) (27%) and severe in (4/30) (13%) patients. Also **Behairy et al., (2016)** who tried to predicting fibrosis in pediatric chronic liver disease by using transient elastography matched with hepatic sample and morphometry on children with chronic HCV, they reported that minimal activity (80%) and no/mild fibrosis (72%) was observed in the majority of HCV group, whereas, the maximum of autoimmune hepatitis group was showing moderate to severe fibrosis (95%) and mild to moderate activity (70%) and in addition, all Wilson's disease group had moderate to severe fibrosis (100%) and mild to moderate activity (100%).

Majethia et al. (2016) studied histo-pathalogical pattern in 118 cases of chronic liver disease with cirrhosis and found that 43 cases (36%) showed inflammatory infiltrate like lymphocytes and plasma cells (cases of HCV, HBV and autoimmune hepatitis respectively). Mononuclear infiltrate and bile duct proliferation was seen in 51.6% cases (cases of cholestasis due to extra hepatic biliary atresia). They found lympho-plasmacytic infiltrate and bile duct proliferation in cases of Wilson's disease with special stain for copper like Orcein showed reddish brown cytoplasmic granules. 2 cases (1.6%) showed hemosiderin deposition (cases of hemosidrosis), 2cases showed features of malignancy and three cases showed fatty change and necrosis (cases of non-alcoholic fatty liver disease).

In the current study, there was statistical significant difference between the studied regards level of serum 25-OH-Vitamin D as it was dropped in hepatic group. 75% of control group had sufficient vitamin D, 25% had insufficiency of 25-OH-vitamin D. While in hepatic group, 38.3% had sufficient 25-OH-vitamin D, 41.7% insufficiency and 20% had deficient 25-OH-vitamin D.

These findings run in accordance with **Lee et al., (2019)** who studied the vitamin D concentration in children in a tropical country complaining from CLD, they found that Vitamin D deficiency or insufficiency (28%) was predominant in children with CLD in spite of supplementation with vitamin D. Also**, Jamil et al. (2018)** who found in their study about vitamin D deficiency and its relationship with child-pugh class on 125 chronic liver disease patients 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 vitamin D levels (patients: 12% vs. controls: 47%).

Likewise, **Arteh et al., (2010)** reported that the incidence of vitamin D deficiency (25 hydroxy-vitamin D) was 20-100% in the general population in all age groups. In CLD patients, the occurrence of vitamin D levels <20 ng/ml has been estimated to 64% to 92%, which associated inversely to disease development.

An inverse relationship between severity of liver disease and decreasing vitamin D level can be attributed to various possible causative agents. The mechanism of action is generally multifactorial and expected to differ between various liver pathologists. Essential probable mode of action to deliberate are (1) decreased external supplements of patients with various sources of vitamin D (e.g. sunlight, foods); endogenous decrease in the production of Vit. D and albumin in the liver, deficiency of bile salts which are required for gastrointestinal absorption of vitamin D which impair GIT function particularly in the presence of cirrhosis; augmented catabolic removal of 25(OH)D and impaired hepatic hydroxylation of vitamin D to 25(OH) D **(Stokes et al., 2013)**

In the present work, significant difference reported between the studied groups regards depression score as 30% of control group had mild depression while 36% of hepatic group had mild depression, 16.7% had moderate depression and 10% had severe depression. These findings were in covenant with **Akram et al., (2017)** who studied anxiety and depression in 750 CLD patients (59% males) through appluing Hamilton anxiety rating scale (HARS) and the Hamilton depressing rating scale (HDRS). They reported that patients suffering from depression was 59.3%, anxiety was 17.4%, and both anxiety and depression were 30.7%. Also, **Behairy**

(2016) reported that and depression scores were elevated significantly in children with chronic hepatitis C with treatment (17.57± 5.12) and without treatment (13.87±6.54) more than the control group (.65 ±5.2). Also, **Kerkar et al. (2013)** established that children with non-alcoholic fatty liver disease (NAFLD) have higher levels of depression than obese control. While **Arslan et al. (2003)** found that there was non-significant variation in the scores of mean depression and anxiety among the studied groups.

According to the several researches concerning the predominant of depression among patients with CLD, systematic investigations of depression have been scarce. Usually, the chief explanations comprise the following probabilities: (i) The disease itself: the pain for long-period due to disease and therapies, and sensation of fault, and anxiety from advancement of disease, etc. (ii) Social and economic stress, comprising necessary requirements for living, working and studying, social judgment and elevated the treatment costs. Emerging evidence supported reduced differences of serotonin and dopamine transporter binding in chronic hepatitis patients with cognitive impairment, which might be linked with depression **(Huang et al., 2017).**

The current study showed that, there were statistically significant differences between serum level of 25-OH-vitamin D and Fibrosis index (FI) and histological activity index (HAI) as it decrease with increase fibrosis index and hepatitis activity index. There was statistical significant negative correlations between 25-OH-vitamin D and ALT, AST, FI and HAI. However there was no statistical significant connection among serum level of 25-OH vitamin D and other clinical and laboratory measures.

These findings are supported by **Skaaby et al., (2014)** who studied the association between vitamin D status and liver enzymes on a total of 2,649 individuals (45% males) and reported a significant inverse relationship amide incident liver disease and vitamin D level with a hazard ratio = 0.88 per 10 nmol/l higher vitamin D status at baseline (adjusted for season, gender, education, smoking, alcohol consumption, dietary habits, physical activity, ALT and BMI). In patients with lower vitamin D concentration, there are a risk of having a high concentration of AST, ALT, or GGT, in spite of a anon-significant differences were recorded. In this universal population investigation, vitamin D level was inversely related with happening of liver disorder. Also, **Peng et al., (2019)** vitamin D status are inversely correlated with severity of liver fibrosis in post Kasai's portoenterostomy biliary atresia (PKBA) patients with native control liver. Also, **Nobili et al. (2014)** who studied the association between vitamin D levels and liver histological alterations in 73 children (64% males) aged 8–18 years with nonalcoholic fatty liver disease and found that vitamin D concentration are inversely correlated in children with NAFLD with non-alcoholic steato-hepatitis and fibrosis.

While **Yodoshi et al., (2019)** found that the majority of cases were either vitamin D insufficient (50%) or deficient (32%) within 3 months of their liver biopsy and reported that there was no correlation was found amide serum 25(OH)-vitamin D levels and serum aminotransferases or histologic scores. Whereas, the percentage of individuals with significant fibrosis (stage ≥ 2) was higher significantly among those who were vitamin D insufficient (29%), this association didn't found between those who were lacking in 25(OH)-D (15%) or when supplemented patients were excepted from the statistical analyses, proposing that a pathophysiologic association is not clear.

C. Putz-Bankuti et al. (2012) found a significant relationship between 25(OH) vitamin D level with the severity of liver failure and propose that low 25(OH)D status may forecast hepatic decompensation and death in patients suffering from chronic liver dysfunction.

Concerning the influence of vit. D and its impacts on liver fibrosis, vitamin D holds an anti-fibrotic impact on hepatic stellate cells through vitamin D receptor-mediated specific signal transduction pathways, which subsequently suppress the expression of pro-fibrogenic genes. Moreover, many researches established a significant relationship amide low vitamin D status and an elevated risk of liver fibrosis. Furthermore, elevate an incidence of vitamin D deficiency was observed in patients with liver fibrosis, proposing the practice of vitamin D levels as a biochemical marker reflecting the development of liver fibrosis **(Udomsinprasert and Jittikoon 2019).**

Rode et al. (2010) established a negative association among 25(OH) vitamin D and albumin in addition to bilirubin levels in serum of patients with chronic liver disease.

Fisher and Fisher (2007) found that the determination of serum 25(OH) D levels < 10 ng/ml can be used as predictor for decreasing platelet count and serum albumin and serum bilirubin. Also **(Lee et al., 2019)** founded that The percentage of children with vitamin D deficiency (Deficiency/insufficiency) was significantly elevated in children with bilirubin level ≥34 µmol/L versus in children <34 µmol/L (47% vs. 19%).

In the current study, there were there were statistically significant differences between serum depression score and Fibrosis index (FI) and Histological activity index (HAI) as it increases with increase fibrosis index and Histological activity index.

However there was no statistical significant difference between depression score and type of cells. Also, there were statistically significant positive correlation between degree of depression score and (ALT, AST, FI and HAI), while there were statistically significant negative correlation between degree of depression score and (Hemoglobin, Albumin).

The present findings are in agreement with **Youssef et al., (2013)** who found the relationship between depression, anxiety with the degree of histological structures in patients with CLD on 567 patients with biopsyproven CLD (67% females) and reported that, depression was associated with more severe fibrosis and HAI.

Also, these results are consistent with **Tomeno et al., (2015)** who studied the clinical features of non‐alcoholic fatty liver disease (NAFLD) comorbid with clinical depression on 32 patient (56% males) and reported that clinical depression was associated with more severe histological liver pathology.

In addition **Russ et al., (2015)** reported that a significant increase in depression with increased severity of liver disease.

In the current study, there was statistical significant negative association among 25-OH-vitamin D and depression score (r = -0.286 & P value = 0.027). These data are in agreement with **Bahrami et al., (2018),** who investigated the impacts of supplementation with vitamin D on depression score among adolescent girls and reported that supplementation with a dose of 50,000 IU of vitamin D, once a week for 9 weeks can enhance the depression scores.

Smith et al., (2014) who studied the correlation amide the presence of depressive signs and 25(OH) vitamin D status in youths (7–17 years) with cystic fibrosis and found that serum 25(OH) vitamin D was correlated negatively with children depression inventory (CDI) scores (r = −0.55), and the group of subjects with insufficient 25(OH) vitamin D status, certainly found significantly more depressive signs.

Högberg et al., (2012) found a significant enhancement in depression score and well‐being with vitamin D supplementation indicates a correlation among vitamin D levels and depression.

Sarris et al., (2018). A meta-Analysis who studied the clinical trials using adjunctive nutrients for depression. They reported that vitamin D is recommended for use with antidepressant medications in effectively treating depression.

Some theories tries to explain the role of Vitamin D in stopping the time of depression via augmenting a number of procedures that are significant to keep normal healthy neurons. Vit.D arrives the nucleus of cells, then it links with the retinoid X receptor (RXR) and after that combines to Vit.D response element (VDRE), which is found on a great number of genes. It preserves Ca2+ homeostasis via persuading the expression of Na+/Ca2+ exchanger 1 (NCX1), the plasma membrane Ca2+-ATPase (PMCA) pump parvalbumin and calbindin. It furthermore controls Ca2+ by decreasing the expression of the CaV1.2 calcium channel. It also play a role in stimulation of an expression of several antioxidant genes like g-glutamyl transpeptidase (g-GT), the nuclear factor-erythroid-2-related factor 2 (NRF2), glutathione reductase (GR), glutathione peroxidase (Gpx) and glutamate cysteine ligase (GCLC). It manages the synthesis of serotonin via augmenting the concentration of tryptophan hydroxylase 2 (TPH2) but suppressing tryptophan hydroxylase1 (TPH1). It is suppressing the inflammatory processes through diminishing the expression of inflammatory cytokines. In addition, it controls the expression of various mitochondrial proteins that keep normal mitochondrial respiration. Lastly, it controls the epigenetic landscape by encouraging the expression of DNA demethylases like lysine-specific demethylase 1 and 2 (LSD1, LSD2) and Jumonji domain-containing protein 1A and 3 (JMJD1A, JMJD3) **(Berridge, 2017).**

Conclusion

It is a novel investigation carried out on Egyptian children with chronic liver diseases (CLD) to evaluate role of vitamin D as a predictive marker of depression in pediatrics CLD. Our study showed that vitamin D levels correlated with CDI scores in children with CLD. This finding represents the first step to prove the pivotal role of 25-Hydroxyvitamin D as a marker of depression in CLD, which necessities to be confirmed with extra studies assessing 25-Hydroxyvitamin D in serum in depressed children with CLD.

Conflict of interest:

No conflict of interest.

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