

# World Journal of *Hepatology*

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*WJH* covers topics concerning liver biology/pathology, cirrhosis and its complications, liver fibrosis, liver failure, portal hypertension, hepatitis B and C and inflammatory disorders, steatohepatitis and metabolic liver disease, hepatocellular carcinoma, biliary tract disease, autoimmune disease, cholestatic and biliary disease, transplantation, genetics, epidemiology, microbiology, molecular and cell biology, nutrition, geriatric and pediatric hepatology, diagnosis and screening, endoscopy, imaging, and advanced technology. Priority publication will be given to articles concerning diagnosis and treatment of hepatology diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

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Retrospective Study

## Serum 25-hydroxyvitamin D deficiency and hepatic encephalopathy in chronic liver disease

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### Abstract

#### AIM

To investigate the relationship between 25-hydroxyvitamin D (25-OHD) deficiency and hepatic encephalopathy (HE) in patients with chronic liver disease (CLD).

#### METHODS

A retrospective analysis of the results of 392 adult patients with chronic liver disease who were assessed for liver transplantation between 2006 and 2010 was undertaken. HE, severity of CLD, nutritional status and 25-OHD were analysed in patients assessed for liver transplantation between 2006 and 2010. Patients who presented with acute, fulminant or subacute disease, with a primary diagnosis of liver cancer, were assessed for re-transplantation or who did not have a 25-OHD

measurement were excluded from the analysis.

## RESULTS

One hundred and sixty-five patients were included in this analysis. The mean age of all patients was  $53 \pm 8$  years. Moderate to severe 25-OHD deficiency was identified in 49 patients of whom 36 had grade 2-3 HE compared with 13 patients who were not encephalopathic ( $P \leq 0.0001$ ). Mild 25-OHD deficiency was not associated with HE. There was a significant correlation between the severity of 25-OHD deficiency and the severity of liver disease ( $r = 0.39$ ,  $P \leq 0.0001$ ) and disease severity and the presence of HE ( $P \leq 0.0001$ ). Importantly, individuals with 25-OHD deficiency were more likely to have a diagnosis of overt HE (OHE) at a significantly lower model for end stage liver disease (MELD) score than individuals without OHE ( $P \leq 0.0001$ ). This significant difference was observed with MELD scores from 10 to 38.

## CONCLUSION

25-OHD deficiency was observed in the majority of patients with CLD and for the first time was found to be significantly worse in patients with OHE.

**Key words:** Vitamin D; Chronic liver disease; Hepatic encephalopathy; Model For End Stage Liver Disease; Dementia; Malnutrition; Cognitive function

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**Core tip:** A strong association between vitamin D deficiency and deteriorating liver disease is identified in this investigation which supports previous reported findings. The novel finding in this investigation is the relationship between vitamin D deficiency and overt hepatic encephalopathy (OHE) in patients with chronic liver disease (CLD) which is independent of renal impairment and nutritional status. As repeated episodes of OHE may result in some residual neuropsychiatric alterations, maintenance of vitamin D levels within normal range in patients with CLD should be considered in clinical management. These results provide a strong rationale for future intervention studies in this group.

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## INTRODUCTION

Hepatic encephalopathy (HE) describes a complex collection of neuropsychiatric symptoms ranging from sub-clinical neuropsychiatric changes to coma<sup>[1]</sup> and has been identified in up to 55% of patients with chronic liver disease<sup>[2]</sup>. Symptoms include impaired cognition

and motor function and reduced energy levels<sup>[3]</sup> HE can be classified as covert or overt HE (OHE)<sup>[4]</sup>. Features of HE can be likened to symptoms seen in patients with dementia<sup>[4]</sup>.

The aetiology of HE is complex and multifactorial, and includes abnormal ammonia metabolism, dysbiosis which promotes inflammation in the gut and liver<sup>[5]</sup>, low levels of circulating branched chain amino acids<sup>[6]</sup>, electrolyte abnormalities<sup>[7]</sup> and alterations in zinc and manganese levels<sup>[8]</sup>. Importantly, the features of HE can often be significantly reversed following treatment consistent with a largely functional not a structural cause of cognitive impairment<sup>[9]</sup>.

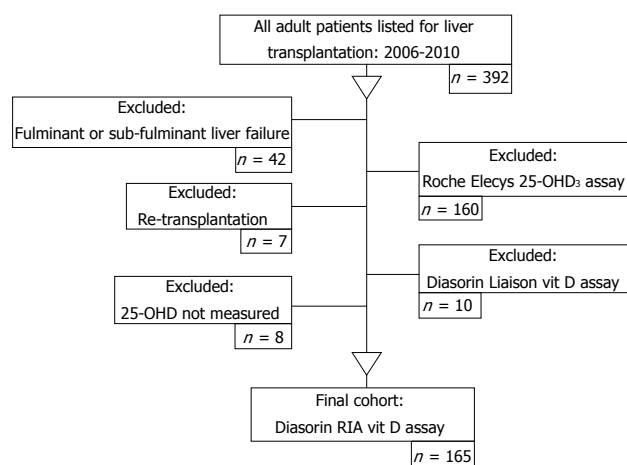
The development of HE presents significant challenges to patients and their carers<sup>[10]</sup>. Until recently, lactulose was the major cornerstone in the management of HE and continues to be used as a first line management for the control of the symptoms of chronic HE and for the reversal of the symptoms of acute episodes of HE<sup>[11]</sup>. The introduction of Rifaximin has reduced the rate of OHE and the frequency of hospital admissions due to OHE and improved the quality of life for the patient and their carers<sup>[12]</sup>.

Patients who experience repeated episodes of OHE can have persistent and cumulative deficits in working memory, response inhibition and learning<sup>[13]</sup>. There is growing evidence that some deficit in cognitive function remains in liver transplant recipients who were severely encephalopathic or who experienced multiple episodes of OHE prior to liver transplantation<sup>[9]</sup>. Therefore, the prevention of OHE is paramount to the preservation of mental integrity in patients with cirrhosis.

Vitamin D is a multifunctional steroid hormone with diverse actions that are only partially understood. It is increasingly apparent that vitamin D is not just involved in calcium homeostasis and bone metabolism but has multiple biological targets mediated by vitamin D receptors (VDR)<sup>[14]</sup> which are present in more than 30 tissues<sup>[15]</sup> including the brain, kidneys, intestine, parathyroid gland, pituitary, prostate, mammary glands, cardiac and skeletal muscle, non-parenchymal liver cells, endothelial cells and the immune system<sup>[16-20]</sup>.

Vitamin D is obtained from dietary sources and ultraviolet light exposure. The first step in the activation of vitamin D is the hydroxylation of cholecalciferol to the active metabolite 25-hydroxyvitamin D (25-OHD) which occurs in the liver<sup>[21]</sup>. This is the major circulating metabolite of vitamin D, bound to the carrier protein vitamin D binding protein (DBP) with a half-life of 15-21 d<sup>[21,22]</sup>. The second activation process to 1,25 dihydroxy vitamin D occurs predominantly in the kidney<sup>[21]</sup> and to a lesser extent in a range of other tissues including bone, breast, brain, monocytes, parathyroid gland and placenta<sup>[21]</sup>. This active metabolite has a shorter half-life of 10-20 h<sup>[22]</sup>. Consequently, vitamin D status is commonly assessed by measuring circulating levels of 25-OHD<sup>[22]</sup>.

Vitamin D has been identified as an immune modulator and anti-infective agent<sup>[23]</sup> and an association



**Figure 1 Study design.** The selection and application of inclusion/exclusion criteria for inclusion in the final analysis. 25-OHD: 25-hydroxyvitamin D; RIA: Radioimmunoassay.

between vitamin D deficiency and the progression of liver disease has been identified in hepatitis C virus (HCV)<sup>[24]</sup>, alcoholic liver disease (ALD)<sup>[25]</sup> and non-alcoholic fatty liver disease (NAFLD)<sup>[24]</sup>.

There is growing evidence of clinical associations between vitamin D status and global and specific areas of cognitive function<sup>[26]</sup> and that vitamin D deficiency may be associated with both depression and schizophrenia<sup>[27]</sup>. Further, vitamin D deficiency is associated with low mood and impairment in some areas of cognitive functioning without any impairment in physical performance<sup>[28]</sup> and with an accelerated decline in cognitive function<sup>[29]</sup>.

VDR protein is present in most neurons and the glia in the human brain<sup>[30]</sup>. The hypothalamus and the cortex of the human brain are key areas in cognition<sup>[31]</sup>. The presence of both VDR protein and vitamin D metabolites in these areas of the brain are an indication that the vitamin D system is involved in the normal functioning of the human brain<sup>[32]</sup>.

As the first step in the hydroxylation of vitamin D occurs within the liver 25-OHD, levels decrease with progressive liver dysfunction. Vitamin D deficiency has been reported in up to 92% of patients with chronic liver disease and at least one third of these have severe 25-OHD deficiency<sup>[33]</sup>. 25-OHD deficiency is associated with increasing Child-Pugh classification rather disease aetiology<sup>[34]</sup> and is more prevalent in patients with cirrhosis than those who are not cirrhotic<sup>[33]</sup>. Increased all-cause mortality is associated with 25-OHD deficiency and specifically with increased mortality in patients with cirrhosis<sup>[35]</sup>. To date, an association between 25-OHD deficiency and HE has not been described. Therefore, we aimed to investigate the relationship between 25-OHD, cirrhosis and HE.

## MATERIALS AND METHODS

### Patient selection

All patients who present for assessment for liver trans-

plantation routinely undergo a comprehensive series of tests and examinations prior to consideration of suitability for transplantation. A retrospective analysis of the results of 392 adult patients with chronic liver disease who were assessed for liver transplantation between 2006 and 2010 was undertaken. Approval to access medical records was granted by the Sydney Local Health District Ethics Review Committee (RPAH X15-0209).

### Data collection

Data collated included primary diagnosis, demographic information, standard biochemical markers of liver function, disease severity scores model for end stage liver disease (MELD)<sup>[36]</sup> and Child Turcotte Pugh (CTP)<sup>[37]</sup>, subjective nutritional assessment (SGA) scores<sup>[38]</sup>, 25-OHD levels and the presence of HE assessed using the West Haven criteria<sup>[39]</sup>. Patients who presented with acute, fulminant or subacute disease were excluded from the analysis due to the acute nature of their illness. Patients with a primary diagnosis of liver cancer or who were undergoing assessment for re-transplantation or who did not have a 25-OHD measurement were also excluded from the analysis.

25-OH vitamin D status was defined as sufficient (> 75 nmol/L), insufficient (50-75 nmol/L), mild deficiency (25-50 nmol/L), moderate deficiency (12.5-25 nmol/L) and severe deficiency (< 12.5 nmol/L)<sup>[40,41]</sup>.

During the study period, three different 25-OH D assay methods were used: (1) radioimmunoassay (RIA), referred to as the Diasorin-RIA<sup>®</sup> assay; (2) the electrochemiluminescence immunoassay, referred to as the Roche Elecys<sup>®</sup> vitamin D<sub>3</sub> assay; and (3) the Liaison total automated direct competitive chemiluminescence immunoassay, referred to as the Diasorin Liaison<sup>®</sup> 25-OH vitamin D assay. 25-OHD levels are frequently overestimated with greater intra-assay variation when assessed by more recent methodologies<sup>[42]</sup>. As the Diasorin RIA<sup>®</sup> assay was regarded as the most accurate measure of 25-OHD<sup>[43]</sup> at the time of this investigation, the final analysis included only patients with 25-OHD levels measured using the Diasorin RIA<sup>®</sup> assay technique (Figure 1).

### Statistical analysis

Results were analysed using Prism 6 for Mac (GraphPad Software Inc, La Jolla, CA, United States). Categorical values were analysed using  $\chi^2$  and quantitative continuous results were compared using the Mann-Whitney *U* test. Relationships between quantitative variables were assessed using Spearman correlation analysis. Multiple comparisons were made using One-way ANOVA, Kruskal-Wallis test and Dunn's multiple comparison test. The threshold for statistical significance is  $P < 0.05$ .

## RESULTS

The patient selection process is outlined in Figure 1. After the exclusion criteria were applied 165 patients remained

Table 1 Population characteristics

	Total cohort (n)	Overt HE <sup>1</sup> (n)	No HE <sup>1</sup> (n)
Demographics	165	88	77
Gender			
Male	119	68	51
Female	46	20	26
Mean age (years ± SD)	53 ± 8	52 ± 7	54 ± 8
Primary indication for liver transplantation			
Viral hepatitis	91	52	39
Alcoholic cirrhosis	23	18	5
Cholestatic disease (PBC, PSC, autoimmune)	30	10	20
Non-alcoholic steatohepatitis	7	6	1
Other	14	2	12
Ethnicity			
Caucasian	130	75	55
Asian	22	6	16
Middle Eastern	8	4	4
Other	5	3	2
Clinical characteristics			
CTP score mean ± SD	9 ± 2.5	11 ± 1.7 <sup>a</sup>	7 ± 2 <sup>a</sup>
CTP stage			
A	41	0 <sup>a</sup>	41 <sup>a</sup>
B	47	22	25
C	77	66 <sup>a</sup>	11 <sup>a</sup>
Ascites			
None	51	7 <sup>a</sup>	44 <sup>a</sup>
Medically controlled	54	36 <sup>a</sup>	18 <sup>a</sup>
Poorly controlled	60	45 <sup>a</sup>	15 <sup>a</sup>
BMI (kg/m <sup>2</sup> ± SD)	27.4 ± 5.2	28.7 ± 5.4 <sup>a</sup>	25.7 ± 4.2 <sup>a</sup>
Nutritional status	104	65	39
SGA: A (well nourished)	12	9	3
SGA: B (moderately malnourished)	65	40	25
SGA: C (severely malnourished)	27	16	11
Biochemical characteristics			
25-OHD (vitamin D) (nmol/L) mean ± SD	36 ± 15	30 ± 13 <sup>a</sup>	42 ± 16 <sup>a</sup>
MELD score mean ± SD	17.1 ± 6.8	19.9 ± 6.5 <sup>a</sup>	13.9 ± 5.7 <sup>a</sup>
Bilirubin (μmol/L) mean ± SD	114 ± 152	141 ± 167 <sup>a</sup>	83 ± 128 <sup>a</sup>
Creatinine (μmol/L) mean ± SD	84 ± 50	85 ± 35 <sup>a</sup>	83 ± 63
Albumin (g/L) mean ± SD	33 ± 6	31 ± 5 <sup>a</sup>	35 ± 6 <sup>a</sup>
INR mean ± SD	1.6 ± 0.5	1.8 ± 0.6 <sup>a</sup>	1.3 ± 0.3 <sup>a</sup>
Sodium (mmol/L) mean ± SD	136 ± 5	135 ± 5 <sup>a</sup>	138 ± 4 <sup>a</sup>
Zinc (μmol/L) mean ± SD	8 ± 4	8 ± 3 <sup>a</sup>	10 ± 5 <sup>a</sup>

<sup>a</sup> $P < 0.05$ . <sup>1</sup>Unless otherwise indicated there is no significant difference between HE and no HE. 25-OHD: 25-hydroxyvitamin D; HE: Hepatic encephalopathy; CTP: Child Turcotte Pugh; BMI: Body mass index; SGA: Subjective nutritional assessment; MELD: Model for end stage liver disease; INR: International normalized ratio.

in the study. Table 1 identifies the primary disease aetiology for liver transplantation assessment and the patient physical and biochemical characteristics.

The group was predominantly male with a mean age of  $53.0 \pm 8$  years. Seventy nine percent of the group was Caucasian and there was no significant difference in 25-OHD levels identified across the different ethnic groups. The major cause of listing for liver transplantation was decompensated cirrhosis secondary to viral hepatitis. All patients had advanced disease as demonstrated by the CTP and MELD scores. OHE was present in 53% of patients. The majority of the cohort (69%) had ascites which was defined as grade 3-4 in 53% of patients<sup>[44]</sup>. Patients with OHE had a higher body mass index (BMI) ( $P < 0.001$ ) with an associated significantly increased incidence of medically controlled and poorly controlled ascites ( $P < 0.0001$ ) and significantly lower serum albumin levels ( $P < 0.0005$ ).

Our results showed a strongly negative correlation between MELD score and 25-OHD levels ( $P < 0.0001$ ) in all patients (Figure 2). Patients with OHE had significantly worse liver disease with a MELD score of  $19.9 \pm 6.5$  whilst those who were not encephalopathic had significantly lower MELD score of  $13.9 \pm 5.7$  ( $P < 0.0001$ ) (Figure 3A). 25-OHD levels were lower in patients with OHE ( $P < 0.0001$ ) (Figure 3B).

SGA of nutritional status was available for 104 patients. The majority of patients were either moderately or significantly malnourished (88%) and there was no significant correlation between nutritional status and 25-OHD levels (Figure 4). There is trend towards a higher incidence and increased severity of malnutrition in patients with OHE but this did not reach statistical significance. The correlation between RIA 25-OHD and the biochemical and physical parameters of the group are further outlined in Table 2.

**Table 2 25-hydroxyvitamin D categories in patients assessed for liver transplantation**

	25-OHD (nmol/L)	Total number	Overt HE <sup>1</sup> (n = 88)	No overt HE <sup>1</sup> (n = 77)
Sufficient	> 75	2	0	2
Insufficient	50-75	27	6	21
Mildly deficient	25-50	87	46	41
Moderately deficient	12.5-25	42	30 <sup>a</sup>	12 <sup>a</sup>
Severely deficient	< 12.5	7	6	1

<sup>a</sup>P < 0.05. <sup>1</sup>Unless otherwise indicated there were no significant differences between the overt HE and no-overt HE groups. 25-OHD: 25-hydroxyvitamin D; HE: Hepatic encephalopathy.

**Table 3 Univariate 25-hydroxyvitamin D correlations with physical and biochemical markers determined by Spearman correlation**

	Spearman r	P value	Significance
Age	0.1110	0.16	ns
Total bilirubin	-0.3493	< 0.0001	f
Albumin	0.3153	< 0.0001	f
ALP	0.0203	0.80	ns
GGT	0.2055	0.0081	b
ALT	0.0246	0.75	ns
AST	-0.1741	0.0253	a
Creatinine	-0.0687	0.38	ns
Na <sup>+</sup>	0.2666	0.0005	e
Zn <sup>+</sup>	0.2790	0.0004	e
RBP	0.2913	0.0002	e
Transferrin	0.3568	< 0.0001	f
INR	-0.4232	< 0.0001	f
Ca <sup>2+</sup>	0.2370	0.0022	b
Ca <sup>2+</sup> corrected	-0.1531	0.08	ns
PTH	-0.1824	0.0205	a
BMI	-0.2244	0.0055	b

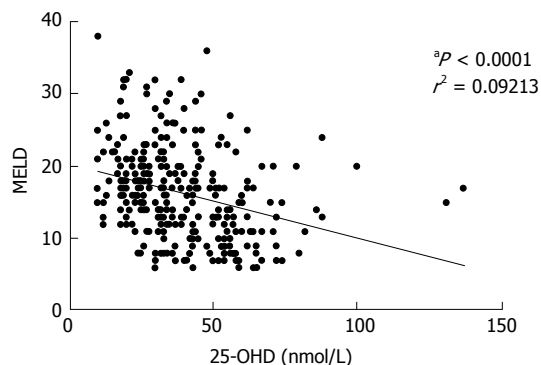
<sup>a</sup>P < 0.05; <sup>b</sup>P < 0.01; <sup>c</sup>P < 0.001; <sup>f</sup>P < 0.0001. ns: Not significant; ALP: Alkalinephosphatase; GGT: Glutamyl transpeptidase; ALT: Alanine transaminase; AST: Aspartate transaminase; RBP: Retinol binding protein; INR: International normalized ratio; PTH: Parathyroid hormone; BMI: Body mass index.

Mild 25-OHD deficiency was not associated with an increase in OHE (Table 3). However, moderate and severe 25-OHD deficiency was significantly associated with the development of OHE (P < 0.0001). The relationship between 25-OHD vitamin D and OHE is outlined in Figure 3B.

Using  $\chi^2$  analysis lower 25-OHD levels were associated with a significant trend towards increasing levels of OHE (P < 0.0001). A significant difference between 25-OHD levels in patients with OHE and those without OHE was identified (P < 0.0001) and is demonstrated in Figure 5. Furthermore, there was a significant correlation between increasing OHE in patients with lower 25-OHD levels at the same level of disease severity as measured by the MELD scores.

## DISCUSSION

Our results demonstrate that at the same level of disease severity patients with OHE have significantly lower 25-OHD levels than those who do not have OHE. This is the first description of this association.



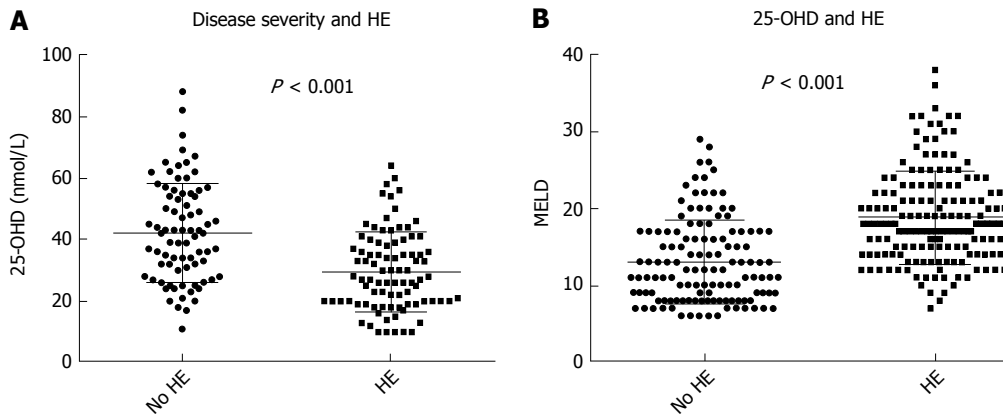
**Figure 2 Vitamin D and severity of liver disease.** 25-OHD levels fall with worsening liver disease. 25-OHD: 25-hydroxyvitamin D; MELD: Model for end stage liver disease.

When stratified into patients who have OHE and those who do not, our results show that, in patients assessed for liver transplantation, there is a statistically significant relationship between low 25-OHD levels and OHE. Importantly, a significantly higher incidence of OHE was observed in individuals with low 25-OHD levels at similar levels of disease severity. This association raises the possibility that vitamin D deficiency has an effect on the manifestation of HE or is associated with other unrecognised factors. Importantly, OHE rarely occurred with normal Vitamin D levels but individuals could have low vitamin D and not have OHE. This is a similar relationship to the association of elevated serum ammonia with the development of OHE<sup>[45]</sup>. Consequently, the presence of moderate to severe 25-OHD deficiency means OHE is more likely in patients with ESLD.

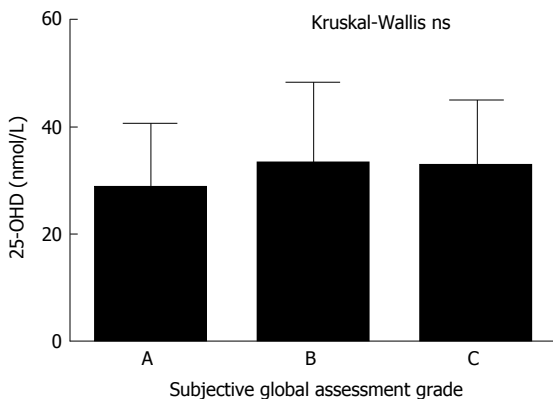
It was beyond the scope of this investigation to explore the relationship between covert HE and 25-OHD deficiency. A large proportion of patients with insufficient (78%) or mild 25-OHD deficiency (47%) were not diagnosed with OHE. It possible that in a proportion of patients with insufficient or mild 25-OHD deficiency reduced levels of 25-OHD could be associated with the development or presence of covert HE. This is analogous to ammonia levels in ESLD which are elevated in HE but elevation does imply the presence of HE either OHE or covert HE.

There is a significant relationship between worsening liver function and 25-OHD deficiency. This is consistent with the growing awareness of the association between





**Figure 3** Disease severity, overt hepatic encephalopathy and vitamin D levels. A: Patients with overt HE have significantly higher MELD than patients without overt HE; B: 25-OHD levels measured by Diasorin-RIA and HE. Patients with overt HE have significantly lower 25-OHD levels than those without overt HE. 25-OHD: 25-hydroxyvitamin D; HE: Hepatic encephalopathy; MELD: Model for end stage liver disease.



**Figure 4** 25-hydroxyvitamin D and nutritional status. 25-OHD levels are independent of nutritional status. 25-OHD: 25-hydroxyvitamin D; ns: Not significant.

disease severity and reduced levels of 25-OHD in patients with cirrhosis<sup>[25]</sup>. Less than 2% of patients assessed for liver transplantation in this group had adequate levels of 25-OHD which is comparable to a previous study which identified vitamin D deficiency in 96% of patients waiting for liver transplantation<sup>[46]</sup>.

As liver disease progresses, patients become increasingly malnourished with an associated increase in HE<sup>[8]</sup>. Alterations in macronutrient requirements and reductions in oral intake are a feature of decompensated cirrhosis<sup>[8]</sup>. However, our results did not show a significant association between malnutrition and 25-OHD levels. This is consistent with changes in 25-OHD metabolism being a determinant of deficiency in CLD.

Vitamin D supplementation is now recognised as an important component of the management of patients with cirrhosis. Routine vitamin D supplementation for patients with chronic liver disease and insufficient levels of 25-OHD has become the standard of care in hepatology clinics to treat or prevent osteoporosis in CLD<sup>[47]</sup>. These results suggest a role for vitamin D supplementation in patients with CLD and reduced levels of 25-OHD.

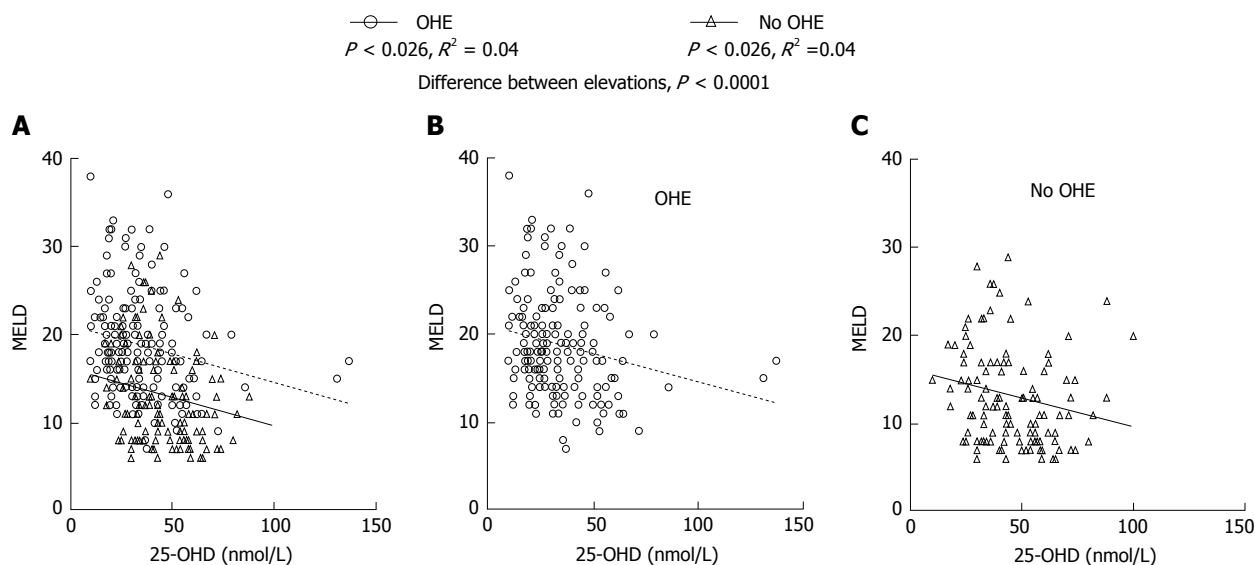
There is growing evidence for an association between

25-OHD deficiency and the development of all-cause dementia and a reduction in cognitive capacity<sup>[48]</sup> which is not confined to older populations. A linear relationship between 25-OHD deficiency and cognitive impairment has been identified in younger adults (30-60 years) as well as adults older than 60 years<sup>[49]</sup>. A systematic review of vitamin D and cognitive impairment concluded that "25-OHD insufficiency likely negatively affects specific cognitive functions, such as explicit episodic memory"<sup>[31]</sup> but there is a need for robust clinical investigation in this area.

Although it is plausible that 25-OHD deficiency could impact on cognitive function in CLD, neither a causative relationship nor a mechanism for this has been demonstrated. The level at which 25-OHD deficiency adversely affects brain function is unknown. 25-OHD is associated with verbal fluency, a marker of executive function and therefore a marker of cognitive function. Individuals with supratherapeutic 25-OHD levels of > 100 nmol/L scored significantly higher on verbal fluency tasks than those with inadequate 25-OHD levels<sup>[50]</sup> further supporting the role of vitamin D in the development of cognitive decline.

Neurobehavioral abnormalities are the major clinical component of HE and have shown to be associated with increased levels of inflammatory cytokines<sup>[51]</sup>. Systemic inflammation and changes in hepatic metabolism (*i.e.*, increased ammonia levels) are increasingly recognised as a precipitants of HE and worsen existing HE<sup>[52]</sup>. Vitamin D has been shown to have anti-inflammatory properties<sup>[52]</sup>. It can be postulated that vitamin D deficiency is associated with an increase in systemic inflammation thereby giving rise to the development of HE.

It is unclear whether there is a steady decline in brain function as 25-OHD levels drop or whether there is a threshold from which point there is a significant reduction in brain function in patients with cirrhosis. To show a causative relationship of the vitamin D with HE it is now necessary to examine the effects of vitamin D supplementation on encephalopathy symptoms in



**Figure 5 Overt hepatic encephalopathy, disease severity and 25-hydroxyvitamin D.** Patients were stratified into those who had overt HE and those who did not. The combined data is presented in (A) and the sub groups of patients with OHE (B) and those without OHE (C). Vitamin D deficiency correlates with MELD score in both patients with and without OHE. Across the range of MELD scores from 10-30 patients with OHE (B) had significantly lower levels of 25-OHD than those who did not (C). 25-OHD: 25-hydroxyvitamin D; OHE: Overt hepatic encephalopathy; MELD: Model for end stage liver disease.

patients with CLD.

To date, the literature suggests association not causality. There is sufficient association between cognitive and behavioral changes associated with 25-OHD deficiency to suggest a role for vitamin D deficiency in the development of HE in patients with chronic liver disease. Further studies are required to investigate the relationship between 25-OHD levels and the development of HE in patients with CLD.

## COMMENTS

### Background

Hepatic encephalopathy (HE) describes a complex range of neuropsychiatric symptoms and is associated with the development and progression of hepatic cirrhosis. HE has been described as a form of dementia which is largely reversible. Low vitamin D levels [25-hydroxyvitamin D (25-OHD)] are associated with dementia and impaired cognition in the general population. The association between low 25-OHD levels and HE has not been previously investigated.

### Research frontiers

It is not known whether the association between low 25-OHD levels and HE is causative. The association described requires further investigation to determine the precise role of 25-OHD deficiency in the development of HE. Historically, the assays used to determine 25-OHD levels have varied significantly. Consistent assay methodology should be implemented to investigate this relationship further.

### Innovations and breakthroughs

It has been established that patients with chronic liver disease (CLD) have low levels of 25-OHD which are associated with overt HE. Monitoring of 25-OHD vitamin D levels and regular and appropriate vitamin D supplementation in patients with cirrhosis may help prevent the development of HE.

### Applications

Monitoring 25-OHD levels and replacement therapy is an important aspect of the overall management of patients with CLD.

### Terminology

Automated immunoassays are used for routine analysis of serum 25-OHD levels

and there is wide variation between the different assay techniques. At the time of this investigation, the Diasorin RIA assay was identified as the most reliable method of measuring serum 25-OHD levels.

### Peer-review

This is very interesting paper about the relationship between 25-OH deficiency and HE. Author concluded that there is a significant association between low-25-OHD levels and the development of HE.

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