Med. J. Cairo Univ., Vol. 86, No. 6, September: 3031-3035, 2018
www.medicaljournalofcairouniversity.net

Relation between Serum 25-Hydroxy Vitamin D Level in Blood and Liver Dysfunction in Chronic Hepatitis C Patients

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Abstract

Background: Vitamin D regulates the expression of over 200 different genes and it has also effect in treatment of asthma, type-1 diabetes mellitus and cardiovascular diseases also decrease the risk of developing multiple sclerosis and cancers. Hepatitis C is a major global public health problem, it is an infectious disease affecting primarily the liver, this infection is often asymptomatic but chronic infection leads to scaring of the liver, liver failure and liver cancer or life threatening esophageal and gastric varices. The prevalence of Vitamin D insufficiency has been estimated to range from a minimum of about 50% to a maximum of perhaps 75% or greater. The aim of this study is to assess the relation between serum 25-hydroxy Vitamin D level and liver dysfunction in chronic hepatitis c patients.

Patients and Methods: This cross sectional case controlled study was conducted on 90 patients who recruited from outpatient clinic and ICU patients from February 2016 to June 2016. Patients were divided into 3 groups according to Child Pugh Score: (30) Patients with Child score (A). (30) Patients with Child score (B). (30) Patients with Child score (C).

Results: The Vitamin D level was significantly decreased as the Child classification increasing from A to C. Also the vitamin D level in patients with Child A-C was significantly decreased when compared to healthy individuals (p-value= 0.001 *).

Conclusion: Vitamin D deficiency is present in patients with chronic liver disease, in view of the increasingly recognized beneficial effects of adequate levels of Vitamin D, measurement of 25OH Vitamin D levels and treatment of it may be considered as part of the overall management of patients with HCV cirrhotic patients.

Key Words: *Vitamin D – Hepatitis C patients – Vitamin D insufficiency.*

Introduction

VITAMIN D is a fat soluble vitamin that is naturally present in few foods as fatty fish species, eggs, beef liver, fish, mushrooms, yeast and also available as a dietary supplement [1].

The prevalence of Vitamin D insufficiency has been estimated to range from a minimum of about 50% to a maximum of perhaps 75% or greater [2].

Hepatitis C is a major global public health problem, it is an infectious disease affecting primarily the liver, this infection is often asymptomatic but chronic infection leads to scaring of the liver, liver failure and liver cancer or life threatening esophageal and gastric varices [3].

Egypt has a very high prevalence of HCV and a high morbidity from chronic liver disease, cirrhosis, hepatocellular carcinoma. Approximately 20% of Egyptian blood donors are HCV Ab positive [4,5].

The strong homogeneity okf HCV subtypes found in Egypt (mostly genotype A4), suggest an epidemic spread of HCV [6].

There is a relationship between Vitamin D and other liver diseases, as in review of bile acid dependent uptake of Vitamin D and its hepatic metabolism to expect an association between Vitamin D status and cirrhotic patients [7,8].

Patients and Methods

Patients were recruited from outpatient clinic and ICU patients, admitted to Internal Medicine Department at Tanta University Hospital from February 2016 to June 2016. Patients divided into 3groups each child score has 30 patients and 10 patients as normal healthy control patients.

All participants in this study were subjected to: Full history taking and full clinical examination regarding age, sex, residence, job, medical history,

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history of previous antiviral therapy, history of renal disease, duration of sun exposure, history of Vitamin D or calcium supplement during last 3 months, and timing diet history, and history of hepatic encephalopathy.

Sampling and all laboratory investigations were done in Clinical Pathology Department, Tanta University Hospitals. The kit uses a double antibody sandwich Enzyme Linked Immune Sorbent Assay (ELISA) to assay the level of human (25-OH-D) in the sample of human serum.

The liver dysfunction was classified according to Child Pugh scoring as illustrated in the following table.

Child-Pugh classification of severity of liver disease	Points assigned		
	1	2	3
Bilirubin (mg/dl)	≤2	2-3	>3
Albumin (g/dl)	>3.5	2.8-3.5	<2.8
Prothrombin time prolonged (second)	1-3	4-6	>6
Ascites	None	Slight	Moderate
Encephalopathy	None	Grade 1-2	Grade 3-4

Class A: 5-6 points. Class B: 7-9 points. Class C: 10-15 points.

25-hydroxy Vitamin D levels were assessed prior to all patients with Enzyme Linked Immune Sorbent Assay (ELISA); concentrations were recorded in ng/mL. The following definitions for baseline Vitamin D levels were used: Severe deficiency, Vitamin D level <10ng/mL; deficiency, Vitamin D level ≥ 10ng/mL and <20ng/mL; and insufficiency, Vitamin D level ≥20ng/mL and <30 ng/mL.

Statistical analysis of the data:

Data were fed to the computer and analyzed using IBM SPSS software package Version 20.0. Quantitative data were described using range (minimum and maximum), mean, standard deviation and median. The distributions of quantitative variables were tested for normality using Kolmogorov-Smirnov test, Shapiro-Wilk test and D'Agstino test. If it reveals normal data distribution, parametric tests was applied. If the data were abnormally distributed, non-parametric tests were used. For normally distributed data, comparisons between more than two populations were analyzed F-test (ANOVA) to be used and Post Hoc test (LSD). For abnormally distributed data, Kruskal Wallis test was used to compare between different groups and pair wise comparison was assessed using Mann-Whitney test. Significance of the obtained results was judged at the p-value <0.05.

Subjects were informed about the purpose and procedure of the study and benefits of sharing in it. Ethical considerations of the study were carried out according to that of declaration of Helsinki.

Results

• *Age:*

Table (1): Comparison between patients and control groups as regard age.

Age	Child A	Child B	Child C	Control
Range	30-87	46-87	39-80	44-70
Mean ± SD	53.00±11.09	59.93±10.51	57.90±9.88	56.90±8.90
F-test	2.364			
p-value	0.076			

• *Sex:*

Table (2): Comparison between patients and control groups as regard sex.

Sex	Child A	Child B	Child C	Control	Total
Male:					
N	13	17	18	6	54
%	43.3%	56.7%	60.0%	60.0%	54.0%
Female:					
N	17	13	12	4	46
%	56.7%	43.3%	40.0%	40.0%	46.0%
Total:					
N	30	30	30	10	100
%	100.0%	100.0%	100.0%	100.0%	100.0%
Chi-square:					
χ^2	2.040				
p-value	0.564				

As regards the correlation between liver dysfunction and Vitamin D levels, we found that the Vitamin D levels in CHC patients with Child C were significantly decreased when compared to that in either Child A or Child B patients (p-value, 0.001). At the same time, the Vitamin D levels in CHC patients with Child B were significantly decreased when compared to that in Child A patients (p-value, 0.001).

These showed that Vitamin D levels were significantly decreased along with the deterioration of liver function from Child A to Child C.

Table (3): Comparison between patients and control groups as regard Vitamin D level.

Vitamin D level	Child A	Child B	Child C	Control
Range	23-53.9	22.8-30.8	1.9-31	33-42
Mean ± SD	35.29±6.92	26.76±2.21	19.37±5.84	36.70±2.58
F-test		55.801		
p-value		0.00 1 *		

p_1	p_2	p_3	p_4	p_5	p_6
0.00 1*	0.00 1*	0.459	0.001*	0.001*	0.00 1*

p1: Comparison between child A and child B.
p2: Comparison between child A and child C.
p3: Comparison between child A and control group.
p4: Comparison between child B and child C.
p5: Comparison between child B and control group.
p6: Comparison between child C and control group.

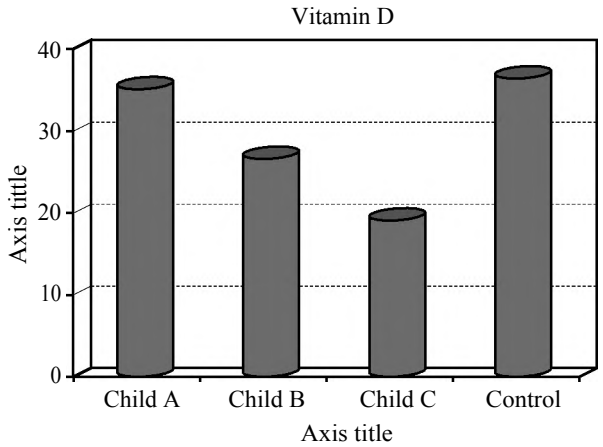

Fig. (1): Comparison between patients and control groups as regard Vitamin D.

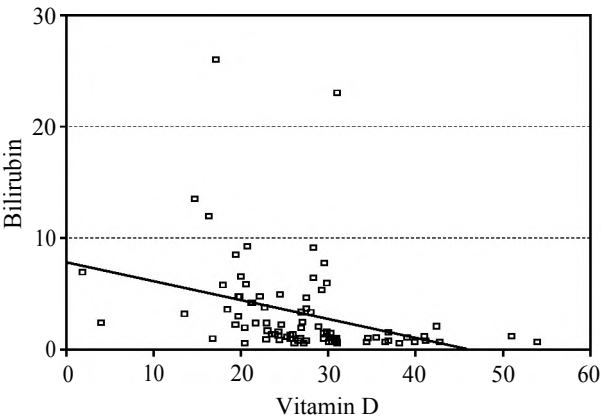

Fig. (2): Correlation between Vitamin D level and bilirubin level.

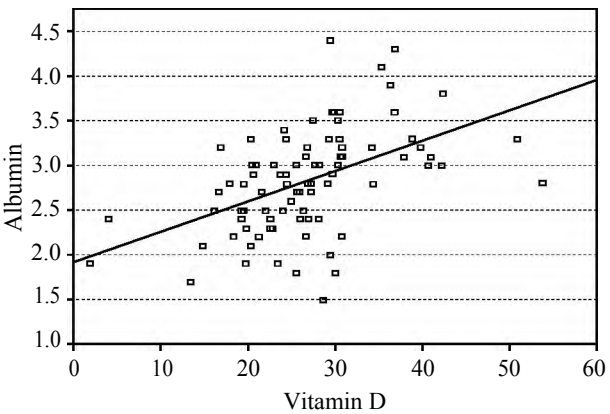

Fig. (3): Correlation between Vitamin D level and albumin level.

Discussion

The National Health and Nutrition Examination Survey 2005 to 2006 data were analyzed for Vitamin D levels in adult participants (N=4495). Vitamin D deficiency was defined as a serum 25-hydroxyvitamin D concentrations <20ng/mL (50 nmol/L). The overall prevalence rate of Vitamin D deficiency was 41.6% [9].

The role of Vitamin D in chronic liver disease has received much attention due to high prevalence of Vitamin D deficiency in patient group. Evidence is also beginning to unravel possible direct therapeutic benefits of Vitamin D therapy [10].

In the case of liver diseases, lower 25(OH)D levels have been associated with greater histologic severity in chronic hepatitis C, greater degree of hepatic dysfunction, and higher risk of non-alcoholic fatty liver disease, hepatic osteodystrophy and hepatocellular carcinoma [11].

Fisher et al., is also agreed to that the prevalence of Vitamin D levels <20ng/ml in CLD has been reported to range from 64% to 92% and is commonly inversely related to disease progression [8].

Moreover, a significantly higher prevalence of Vitamin D deficiency in patients with cirrhosis (86%) compared with those without cirrhosis (49%) was observed by, Chen et al., that there is an inverse association between Vitamin D status (assessed by 25(OH)D levels) and disease severity (assessed by the Child-Pugh score), patients in Child-Pugh class C had significantly lower mean 25(OH)D concentrations than patients in class A, also found 75% of patients with cirrhosis to have 25(OH)D levels <20ng/ml [12].

As would be expected, liver transplant patients exert a different pattern. Dicecco et al., found that 96% of these patients had inadequate Vitamin D stores pre-transplant but post-transplant, Vitamin D deficiency was uncommon, having a normal Vitamin D levels [13].

Arteh and his colleagues found Vitamin D <32 ng/ml in 92% of 118 patients with CLD, also the biochemical tests for liver dysfunction such as serum albumin, bilirubin, and International Normalized Ratio (INR) did not correlate with severe deficiency of Vitamin D [14].

Vitamin D deficiency was thought to be predominantly found in cholestatic liver disorders because of impaired intestinal absorption commonly observed in such patients. Accumulating evidence supports its widespread presence in CLD regardless of etiology [15].

Fisher and his colleagues, analyzed 100 outpatients with noncholestatic CLD and showed that

91% of these subjects had Vitamin D deficiency inadequate 25(OH)D levels (<32ng/ml) in 91% of patients with non-cholestatic CLD, and the majority (68%) were Vitamin D-deficient (<20ng/ml) **[8]**.

Another study made by Bikle et al., conclude that 25OHD, like 1, 25-dihydroxyvitamin D, is transported in blood bound primarily to DBP and albumin. Changes in the concentrations of DBP and albumin affected the total and free fractions of 25OHD in serum **[16]**.

Considering only noninvasive parameters, the AUC of the model that includes Vitamin D levels to predict severe fibrosis remains good. This suggests the potential use of serum 25(OH) D levels as a noninvasive marker of liver fibrosis, a use that needs to be tested and validated in large prospective cohort studies in patients with CHC of all genotypes, and in chronic liver disease of other origins **[17]**.

Studies have found that low serum levels of 25(OH) D are also associated with low Sustained Virological Response (SVR) to Peg-IFN/ribavirin therapy **[18]**.

Furthermore, Vitamin D supplementation improves Early Virological Response (EVR) (94% vs 48%) and SVR (86% vs. 42%) in HCV treated with Peg-IFN/ribavirin. Therefore, hypovitaminosis D in our HCV population has clinical implication both for liver fibrosis progression and for treatment efficacy. Ensuring adequate Vitamin D levels in this population is important **[18]**.

Conclusion:

Vitamin D deficiency is present in patients with CLD, in view of the increasingly beneficial effects of adequate levels of Vitamin D, measurement of 25OH Vitamin D levels and treatment may be considered as a part of management of patients with CLD.

Recommendations:

Our findings raise the question whether testing for and treating Vitamin D deficiency may improve liver function and outcome in cirrhotic patients. This should be urgently evaluated in randomized controlled trials among cirrhotic patients for which our study provides a good rationale.

Vitamin D levels relates to degree of fibrosis remain good. This suggests the potential use of serum 25OH Vitamin D level as a noninvasive marker of liver fibrosis, a use that needs to be tested and validated in large prospective cohort studies.

Acknowledgements:

We would like to thank all participants who helped during this study.

Conflict of interest: None declared.

References

1- Institute of Medicine Food and nutrition Board. Dietary reference intake for calcium and Vitamin D. Washington, DC: National Academy Press 2010.

2- GORDEN C.M., FELDMAN L., SINCLAIR L., et al.: Prevalance of Vitamin D. Defeciency among healthy infant and tiddlers. Arch. Pediatr. Adolesc. Med. June, 162 (6): 505-12, 2008.

3- RYAN K.J., RAY C.G. (editors) ed. Sherries Medical Microbiology. (4th ed) Mc Graw Hill, pp. 551-2. ISBN 0838585299, 2004.

4- EL-ZEYADI A.R., BADRAN H.M., BARAKAT, et al.: Hepatocellular carcinoma in Egypt asingle center over adecade. World J. Gastroenteral., 11: 5193-8, 2005.

5- STRICK LAND G.T, ELHEFNI H., SALAMON T., et al.: Role of Hepatitis C infection in chronic liver disease in Egypt. Am. J. Trop. Med., H9967, 436-42, 2002.

6- ROSEN H.R.: Clinical practice, chronic hepatitis C infection the new England Journal of Medicine, 364 (25): 2429-38, 2011.

7- SOUTHERN P., EL-SAYED P., FENTON L., et al.: Influence of vitamin D supplementation on outcome in the treatment of chronic hepatitis C, Gut., 59: A41, 2010.

8- FISHER L. and FISHER A.: Vitamin D and parathyroid hormone in outpatients with non cholestatic chronic liver disease. Clinical Gastroenterology Hepatology, 5: 013-520, 2007.

9- FORREST K.Y. and STUHLDREHER W.L.: Prevalence and correlates of Vitamin D deficiency in US adults. Nutrition Research, 31 (1): 48-54, 2011.

10- McKINNEY T.J., PATEL J.J., BENNS M.V., et al.: Vitamin D status and supplementation in the critically ill. Current Gastroenterology Reports, 18 (4): 18, 2016.

11- SILVA M.C., SILVA T.E. and ALENTAR M.L.: Factors associated with 25-hydroxyvitamin D levels in patients with liver cirrhosis. Annals of Hepatology, 14 (1): 99-107, 2015.

12- CHEN C.C., WANG S.S., JENG F.S., et al.: Metabolic bone disease of liver cirrhosis: Is it parallel to the clinical severity of cirrhosis? J. Gastroenterol. Hepatol., 11: 417-21, 1996.

13- DICECCO S.R., WIENERS E.J., WIESNER R.H., et al.: Assessment of nutritional status of patients with end-stage liver disease undergoing liver transplantation. In Mayo Clinic kProceedings 1989, January, Vol. 64, No. 1, pp. 95-102. Elsevier.

14- ARTEH, JIHAD, SRILAKSHMI NARRA & SATHEESH NAIR: " Prevalence of Vitamin D deficiency in chronic liver disease." Digestive Diseases and Sciences, 55 (9): 2624-8, 2010.

15- COLLIER J.D., NINKOVIC M. and COMPSTON J.E.: Guidelines on the management of osteoporosis associated with chronic liver disease. Gut., 50 (Suppl 1), i1-i9, 2002.

16- BIKLE D.D., GEE E., HALLORAN B., et al.: Assessment of the free fraction of 25-hydroxyvitamin D in serum and its regulation by albumin and the vitamin D-binding protein. The Journal of Clinical Endocrinology & Metabolism, 63 (4): 954-9, 1986.

17- PETTA S., CAMMA C., SCAZZONE C., et al.: Low Vitamin D serum level is related to severe fibrosis and low responsiveness to interferon-based therapy in genotype 1 chronic hepatitis C. Hepatology, 51 (4): 1158-67, 2010.

18- MANDORFER M., REIBERGER T., PAYER B.A., et al.: Low Vitamin D levels are associated with impaired virologic response to PEGIFN + RBV therapy in HIV-hepatitis C virus coinfected patients. AIDS, 27: 227-32, 2013.

العلاقة بين مستوى ٢٥-هيدروكسى فيتامين د فى مصل الدم والقصور الكبدى فى مرضى الإلتهاب الكبدى المزمن سى

أجرى هذا البحث على ٩٠ شخصا ممن يترددون على العيادات الخارجية والمرضى المحجوزين فى عنابر قسم الباطنة بجامعة طنطا. ويتم البحث فى الفترة من بداية فبراير ٢٠١٦ حتى نهاية يونيو ٢٠١٦، وتم أخذ التاريخ المرضى للمرضى وإخضاعهم للفحص الإكلينيكى الشامل وفحوصات معملية مثل ٢٥ هيدروكسى فيتامين د ودلالات فيروسات كبدية ووظائف كبد كاملة و نسبة اليومين بمصل الدم ومستوى الصفرا بمصل الدم وزمن ونشاط بروثرمبين ونسبة بولينا بالدم وكرياتنين بمصل الدم وتحليل بول كامل وبروتينات ٢٤ ساعة بول وموجات فوق صوتية على الكبد للحالات بعد الحصول على الموافقة اللازمة.

وقد خلصت هذه الدراسة إلى إنخفاض مستوى فيتامين (د) بشكل ملحوظ مع زيادة تصنيف تشيلد من A إلى C. كما إنخفض مستوى فيتامين (د) فى المرضى الذين يعانون من تشيلد A-C بشكل ملحوظ بالمقارنة مع الأفراد الأصحاء.

ونستنتج من ذلك وجود علاقة عكسية بين مستوى فيتامين (د) فى مصل الدم ودرجة التشمع الكبدى الناتج عن الإلتهاب الكبدى الفيروسى سى بحيث أن مع زيادة درجة التشمع تنخفض مستويات فيتامين (د).