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

MOHAMED E. SHERIF, M.Sc.*; ABDALLAH A. EL-SAWY, M.D.*; EKHLAS H. EL-SHEIKH, M.D.** and MERVAT A. EL-KHATEB, M.D.*

The Departments of Internal Medicine* and Clinical Pathology**, Faculty of Medicine, Tanta University, Egypt

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 scarring 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 scarring 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 3 groups 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,
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.

<table>
<thead>
<tr>
<th>Child-Pugh classification of severity of liver disease</th>
<th>Points assigned</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilirubin (mg/dl)</td>
<td>1</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>≤2</td>
</tr>
<tr>
<td>Prothrombin time prolonged (second)</td>
<td>1-3</td>
</tr>
<tr>
<td>Ascites</td>
<td>None</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>None</td>
</tr>
</tbody>
</table>

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>
<thead>
<tr>
<th>Age</th>
<th>Child A</th>
<th>Child B</th>
<th>Child C</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SD</td>
<td>30.87 ± 11.09</td>
<td>59.93 ± 10.51</td>
<td>39.80 ± 9.88</td>
<td>57.90 ± 9.88</td>
</tr>
<tr>
<td>F-test</td>
<td>2.364</td>
<td></td>
<td></td>
<td>0.076</td>
</tr>
</tbody>
</table>

• Sex:

<table>
<thead>
<tr>
<th>Sex</th>
<th>Child A</th>
<th>Child B</th>
<th>Child C</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male: N %</td>
<td>13 %</td>
<td>17 %</td>
<td>18 %</td>
<td>6 %</td>
</tr>
<tr>
<td>Female: N %</td>
<td>17 %</td>
<td>13 %</td>
<td>12 %</td>
<td>4 %</td>
</tr>
<tr>
<td>Total: N %</td>
<td>30 %</td>
<td>30 %</td>
<td>30 %</td>
<td>10 %</td>
</tr>
<tr>
<td>Chi square</td>
<td>2.040</td>
<td></td>
<td></td>
<td>0.564</td>
</tr>
</tbody>
</table>

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>
<thead>
<tr>
<th>Vitamin D level</th>
<th>Child A</th>
<th>Child B</th>
<th>Child C</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SD</td>
<td>35.29 ± 6.92</td>
<td>22.8 ± 10.8</td>
<td>19.37 ± 5.84</td>
<td>26.76 ± 2.21</td>
</tr>
<tr>
<td>F-test p-value</td>
<td>55.801</td>
<td>0.001 *</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P_1 P_2 P_3 P_4 P_5 P_6</td>
<td>0.001*</td>
<td>0.001*</td>
<td>0.459</td>
<td>0.001*</td>
</tr>
</tbody>
</table>

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.
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 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.

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Conflict of interest: None declared.

References


العلاقة بين مستويات 25-هيدروكسي فيتامين D في مصل الدم والقصور الكبدي في مرضى الالتهاب الكبدى المزمن سي

وقد خلصت هذه الدراسة إلى إنخفاض مستوى فيتامين (D) بشكل ملحوظ مع زيادة تصفيف تضليل من A إلى C. كما انخفض مستوى فيتامين (D) في المرضى الذين يعانون من تشديد A-C بشكل ملحوظ بالمقارنة مع الآخرين. ونستنتج من ذلك وجود علاقة عكسية بين مستويات فيتامين (D) في مصل الدم ودرجة التشمع الكبدي الناتج عن الإلتهاب الكبدى الفيروسي سي بحيث أن مع زيادة درجة التشمع تنخفض مستويات فيتامين (D).