

Effect of Sustained Viral Response of Chronic Hepatitis C on Serum Vitamin D Level

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Abstract

Background: The aim of the study was to investigate the change in serum vitamin D levels in patients who achieved sustained viral response by treatment with DAA.

Material and Method: Between June 2016 and June 2018, 107 patients with chronic hepatitis C treated with direct-acting antivirals were included in this study. Pre-treatment, post-treatment and control groups were analyzed for serum vitamin D levels. The effect of sustained viral response of Chronic Hepatitis C on vitamin D levels was evaluated.

Results: The prevalence of vitamin D insufficiency (20 - 30 ng/mL) and deficiency (< 20 ng/mL) were 13% and 60.7% in patients with Chronic Hepatitis C, respectively. Considering patients with low serum vitamin D, the mean serum vitamin D level before treatment was 22.9 ± 19.9 ng/dl, whereas the mean serum vitamin D level after treatment was 25.3 ± 17.7 ng/dl and was statistically significant increased (p < 0.001).

Conclusion: The prevalence of vitamin D deficiency is high in patients with Chronic Hepatitis C. Vitamin D levels may increase with direct-acting antiviral treatment, particularly in patients with Vitamin D deficiency and insufficiency.

Keywords: Chronic Hepatitis C; Vitamin D; Direct Acting Antivirals

Introduction

Vitamin D is an essential hormone for calcium homeostasis [1]. Vitamin D is synthesized on the skin exposure to ultraviolet B radiation endogenously (vitamin D₃, cholecalciferol) or ingested vitamin D (Vitamin D₂, ergocalciferol). These types of Vitamin D are inactive and converted to 25-hydroxyvitamin D by hepatic microsomal vitamin D hydroxylases. subsequently, the majority of 25-hydroxyvitamin D is converted to its active form, calcitriol, in the kidney. The effects of 1,25-dihydroxy vitamin D mediate its binding to vitamin D receptors in related cells [2]. Renal production of 1,25-dihydroxy vitamin D is regulated by parathyroid hormone levels, serum calcium and phosphorus levels, and phosphaturic hormone fibroblast growth factor-23 [3]. 25-hydroxyvitamin D level is the best measure of real serum vitamin D level. However, there is no clear consensus regarding optimal vitamin D level [1,3-5]. The Endocrine Society Clinical Practice Guidelines define serum levels < 30 ng/mL as insufficiency and levels < 20 ng/mL as deficiency [4].

Until recently, in other words, until treatment era with direct acting antivirals (DAA) was initiated the level of serum vitamin D on Chronic Hepatitis C (CHC) therapy has been an interesting research topic. Further *in vitro* investigation has identified a synergistic effect of calcitriol supplementation with interferon-alpha to suppress HCV viral replication [5,6]. Furthermore, vitamin D may play a role in viral

suppression independently [7]. However, recently, interest in this subject has decreased due to the high ratio of success achieved with DAA, anymore.

Today, interesting subject is effect of sustained viral response of CHC on Serum Vitamin D. There are studies showed that an inverse relation between serum vitamin D level and chronic liver disease but studies analyzing the change of serum vitamin D levels with treatment are not sufficient [8-10]. Especially, there is just one study has evaluated the change in serum vitamin D levels by treatment with DAA [11].

Aim of the Study

The aim of the study was investigated the change in serum vitamin D levels in patients who achieved sustained viral response by treatment with DAA.

Materials and Methods

One hundred and seven patients with chronic hepatitis C who completed DAA therapy and achieved sustained viral response between June 2016 and June 2018 were consecutively enrolled in this study. Data of the patients were collected via Enlil system by retrospectively. All patients had been treated with ledipasvir + sofosbuvir or daclatasvir + ombitasvir, paritaprevir and ritonavir and a sustained viral response was obtained. Patients over 18 years old and without comorbid chronic liver disease were included in the study.

Demographic characteristics were assessed prior to the initiation of treatment and included age, sex and genotype. Serum vitamin D levels were assessed prior to the start of therapy and at twenty-four weeks after the end of the treatment, with chemiluminescence immunoassay; concentrations were recorded in ng/mL.

The following operational definitions for baseline vitamin D levels were employed: deficiency, ≥ 10 ng/mL and < 20 ng/mL; and insufficiency, ≥ 20 ng/mL and < 30 ng/mL.

Vitamin D deficiency is defined as a 25(OH)D below 20 ng/ml, and vitamin D insufficiency as a 25(OH)D of 21 - 29 ng/ml according to The Endocrine Society Clinical Practice guideline.

Mean serum vitamin D levels before treatment were compared with control group and vitamin D levels after treatment. Changing of the number of patients with vitamin D deficiency and vitamin D insufficiency by treatment were analyzed.

Statistical analysis

Data were analyzed using PASW Statistics version 18.0 SPSS (Chicago, IL, USA). Descriptive statistics, including frequencies, chi-square and t-tests, were used for the baseline demographics and serum vitamin D levels. Results were presented as percentage for categorical variables and as mean \pm standard deviation or median for continuous variables. T-test and Chi-square test were used for baseline demographic data and frequency. T-test and Chi-square test were used for basic demographic data and frequency. Binary logistic regression analysis was used for changes in serum vitamin D levels by treatment. $p < 0.05$ was considered as significant.

Results

A total of 107 CHC patients were included in the study. The mean age was 65 ± 9 years, most of the patients were female (67%), mean D vitamin level was 23 ± 19 ng/ml. The mean age was 60 ± 11 years, most of the patients were female (60%), mean D vitamin level was $22,9 \pm 11$ ng/ml. There was no significant difference between the control group and the group of patients with chronic hepatitis C in terms of age, gender distribution and serum vitamin D level (Table 1).

	Age	Sex (female)	Mean vitamin D level
CHC group	65 ± 9	67%	23 ± 19 ng/ml
Control group	60 ± 11	60%	22,9 ± 11 ng/ml
p	p > 0.05	p > 0.05	p > 0.05

Table 1: Baseline demographics and mean Vitamin D levels.

Overall, 60.7% (n = 65) of subjects were found to have vitamin D deficiency (vitamin D < 20 ng/mL) and 13% (n = 14) were found to have insufficiency (vitamin D 20 - 30 ng/mL) before treatment. Serum vitamin D level was below 30 ng/ml in 79 (73.8%) of all patients before treatment, but 70 (65.4%) of all patients' level below 30 ng/ml after treatment. Fifty-two (48.5%) of subjects were found to have vitamin D deficiency (vitamin D < 20 ng/mL) and n = 18 (13%) were found to have insufficiency (vitamin D 20 - 30 ng/mL) after treatment. The number of patients with vitamin D sufficiency and insufficiency has decreased by DAA treatment (Table 2).

	Below 20 ng/mL	Between 20-30 ng/mL	Below 30 ng/mL	Above 30 ng/mL
Number of patients before treatment n (%)	65 (60,7%)	14 (13%)	79 (73,8%)	28 (26,2%)
Number of patients after treatment n (%)	52 (48,5%)	18 (16,8%)	70 (65,5%)	37 (34,6%)

Table 2: Presentation of the change of number of patients by treatment.

Considering to all vitamin D sufficiency group was analyzed, the mean serum vitamin D level before treatment was 22.9 ± 19.9 ng/ml, while the mean post-treatment serum vitamin D level was 25.3 ± 17.7 ng/ml and was statistically significantly increased (p < 0.001).

While, mean D vitamin level was increased in vitamin D deficiency group and insufficiency group, decreased in normal vitamin D group by treatment (p < 0.001) (Table 3).

	Vitamin D deficiency	Vitamin D insufficiency	Normal Vitamin D
Levels of vitamin D before treatment	12,9 ± 7,4	22,9 ± 19,9	51,10 ± 16
Levels of vitamin D after treatment	20,11 ± 14,6	25,3 ± 17,7	42,5 ± 20
	p < 0.001	p < 0.001	p < 0.001

Table 3: Presentation of the change of levels of vitamin D by treatment.

Discussion

Besides being the main hormone in calcium homeostasis, vitamin D has an important role in many metabolic activities. The effects of vitamin D on cardiovascular system functions, pancreatic functions, endocrine cells, immune system, muscle and adipose tissue functions have been described [12-14]. In addition, vitamin D is a prognostic factor in chronic liver disease; low serum levels of vitamin D have been associated with increased hepatic encephalopathy and reduced survival [15].

As mentioned earlier, the optimum range of serum vitamin D has not been clearly determined yet, discussions on this topic are continued. The Endocrine Society Clinical Practice guideline recommends a serum vitamin D level above 30 ng/mL [4]. Suboptimal vitamin D level is common worldwide [16]. The main causes of the low serum levels of vitamin D are insufficient sun exposure, decreased dietary intake, obesity and advanced age [17]. Vitamin D deficiency in hepatitis C-related liver cirrhosis is probably due to decrease of activation and hydrolysis of 25 (OH) D or a reduced absorption of vitamin D due to portal hypertension. In our study, vitamin D deficiency

was found to be quite high in both study and control group. The study was conducted in north of the country and it is likely possible that low serum vitamin D levels in the control group was related to low sun exposure.

Previous studies have shown that most of patients with CHC have vitamin D deficiency or insufficiency [18]. In our study, the mean serum level of vitamin D in the patient and control groups was 23.0 ± 19 ng/ml and 22.9 ± 11 ng/ml, respectively, and contrary to the literature, comparing the vitamin D level there was no significant difference between the groups. In addition, the mean vitamin D level in the control group was lower than expected, based on meta-analysis [9]. This can be considered as one of the limitations of the study.

Although there have been many studies evaluating vitamin D level in interferon-based treatment groups, there have not been enough studies in patients with CHC used direct-acting antivirals (DAA) due to these are relatively new drugs. In the first study on this subject, Gayam, *et al.* showed that pre-treatment vitamin D level had not effect on sustained virologic response (SVR) [19]. The data of our study also supports that study. Backstedt, *et al.* showed that the serum vitamin D level of patients with CHC treated with DAA increased slightly, although not statistically significant [11]. In our study, a statistically significant increase in serum D vitamin level was seen in both patients with vitamin D deficiency and insufficiency by the DAA treatment. In addition, the number of patients with vitamin D sufficiency and insufficiency has decreased by DAA treatment.

Limitation of the Study

There is some limitation in our study. The first of these, as mentioned earlier, is that our study is single-centered and the serum vitamin D of the people who live in the north of the country is low. However, the primary purpose of this study is to show the serum vitamin D change after the treatment. Although the serum vitamin D level of patients with CHC was not differ at the beginning compared to the control group, it was shown that the serum vitamin D level increased in patients with CHC after the treatment. Another limitation is that the time taken for control of serum vitamin D is short. To reach SVR in DAA treatment is requires between 24 and 36 weeks and this may not be enough for liver function to improve and serum vitamin D level to change. Despite this limitation, this study showed that achieving by DAA treatment increased D vitamin level in patients with CHC.

This study proves that serum vitamin D deficiency and insufficiency are common in patients with CHC and that serum vitamin D level may increase with DAA treatment. Vitamin D supplements are recommended in patients with deficiency to prevent the progression of liver disease and reduce the risk of complications. However, recovery in liver function with the treatment of CHC also improves serum vitamin D level. Although, our study supporting this proposition, further studies which are larger sample size and have longer follow-up are needed.

Conclusion

The prevalence of vitamin D deficiency is high in patients with Chronic Hepatitis C. Vitamin D levels may increase with direct-acting antiviral treatment, particularly in patients with Vitamin D deficiency and insufficiency.

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