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Research Article

The importance of vitamin D status in liver histological progression and response to antiviral therapy

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Abstract. Objective: to evaluate the importance of vitamin D status in chronic viral C liver disease. Material and method: 91 patients with chronic HCV infection were included in the study. Subgroups were defined on the basis of age, gender, menopausal status, alcohol intake, hormonal therapy, Metavir score, and serum viral load. Bone mineral density at the level of lumbar spine was evaluated using DEXA equipment: the WHO classification of osteoporosis was used. Diagnosis of chronic HCV liver disease was based on clinical, laboratory, imaging and invasive (liver biopsy) evidence. Results: 55 (60.43%) were investigated referring to the baseline level of vitamin D, a low level was found in 29 patients (52.72%). 77.8% of patients with low vitamin D level had osteoporosis. A high activity grade (mean rank: 23.25 vs 13.58; p=0.002) and a more severe fibrosis (mean rank: 24.47 vs 12.55; p<0,001) were found in patients with Vitamin D deficiency. A higher probability to obtain SVR was found in patients with normal vitamin D level vs the ones with low vitamin D level (73.68% vs 21.43%; p=0.03). Conclusion: our results suggest that in patients with chronic viral C liver disease, a vitamin D deficiency was correlated with a high activity grade and stage of liver fibrosis. This was also found to be a risk factor for not achieving SVR in patients treated with peginterferon plus ribavirin.

Key Words: vitamin D, fibrosis, virusological response

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Introduction

Globally 130–150 million people are chronically infected with the hepatitis C virus (HCV) (World Health Organization 2014). Until recently, the standard of care for chronic HCV infection was pegylated interferon plus ribavirin for 24–48 weeks, depending upon HCV genotype (Kitson et al 2014). The first step next was to introduce in therapy telaprevir or boceprevir. Treatment has further progressed rapidly with the development of potent direct-acting antiviral (DAA) agents and the promise of interferon-free treatment regimens of 12 weeks or less with. However PEG-IFN plus RBV combination therapy will continue to play an important role in treatment due to the high costs associated with these new agents.

Vitamin D is a secosteroid hormone with pleiotropic effects that include the regulation of transcription of over 200 genes involved in cell proliferation and differentiation, immunomodulation, inflammation and fibrogenesis. Low serum concentrations of 25-hydroxyvitamin D (25[OH]D) have been associated with many non-skeletal disorders (Autier et al 2014). In the last decade, these non-classical roles have become increasingly recognized and may be relevant to patients with chronic liver disease (Kitson et al 2012). The hepatic effects of vitamin D shown in different studies refer to: vitamin D inhibits in vitro HCV replication in a dose-dependent manner (Gal-Tanamy et al 2011; Matsumura et al 2011) and supplementation may improve SVR rate in HCV (Abu-Mouch et al 2011; Nimer et al 2012); moreover vitamin D-binding protein is one of 3 metaproteins associated with SVR in HCV (Patel et al 2011). Regarding the effects on liver histology it was shown that vitamin D supplementation prevents liver fibrosis in preclinical studies (Reif et al 2011) and also improves liver histology in preclinical studies of NAFLD (Nakano et al 2011). However, recent reviews have doubts on any link between vitamin D deficiency and non-skeletal health outcomes, suggesting that vitamin D is not a factor implicated in the pathogenesis of disease (Autier et al 2014). In chronic HCV infected patients there are some discordant results in terms of the baseline vitamin D level and the response rate to PEG-IFN plus RBV antiviral therapy (Petta et al 2010; Grammatikos et al 2014).

Knowing all these published studies we wanted to evaluate the importance of vitamin D status in chronic viral C liver disease.

Material and methods

Our study, approved by the Ethics Commission of "Iuliu Hatieganu" University of Medicine and Pharmacy, included 91 patients with chronic HCV infection (a positive test for anti-HCV antibody for at least 6 months and HCV-RNA detectable in the serum), informed about the purpose of the study and who have agreed to be part of it. Histological evaluation was performed in all patients: liver biopsy to 77 of the 91 patients (84.7%), other tests (Fibroscan, Fibrotest and Fibromax) in 14 patients (15.3%). Activity and fibrosis were evaluated according

to the METAVIR scoring system. Diagnosis of chronic HCV liver disease was based on clinical, laboratory, imaging and morphopatological evidence.
WHO classification was used to express the changes in bone mineral density measured by dual energy absorptiometry technique (DEXA).
None of the subjects included in the study had another pathology or treatment that could influence Vitamin D serum level.
All variables, except the viral load were normally distributed, normality criteria being evaluated in relation to descriptive statistics, graphical inspection of the histogram and graphs of distribution. A Student t-test or Mann-Whitney test was used to compare two quantitative variables. A Bonferroni correction was used when comparing 2 subgroups. The significance level was the proportion between 0.05 and the number of comparisons. We used for calculating statistical test power G-Power, v.3.1.2 software.

Results

Out of 91 patients 55 (60.43%) were investigated referring to the baseline level of vitamin D.

Tabel 1: Baseline characteristics of patients.

Variables	Patients with HCV infection (n=91)
Gender (male/female)	25/66
Ages (years)	23-71
Grade of inflammation	
A1	18
A2	55
A3	18
Stage of liver fibrosis	
F1	28
F2	36
F3	17
F4	10
SVR	32
Vit D serum level	
Not evaluated	36
Normal level (40-70 ng/l)	26 (47.27%)
Low level (<40 ng/l)	29 (52.72%)

A higher frequency of osteoporosis (T score less than -2.5) was observed in patients with low vitamin D level vs. patients with normal vitamin D level (77.8% vs 25%; p<0.001), as it was previously shown in other studies (Bischoff-Ferrari 2004). No differences were described in the frequency of osteopenia (T score between -1.5 and -2.5) (p=0.18).
When investigating the correlations between METAVIR score and vitamin D level we observed that vitamin D deficiency was more prevalent in patients with high activity grade (mean rank: 23.25 vs 13.58; p=0.002).
Moreover the patients with low vitamin D level have had a more severe fibrosis vs patients with normal vitamin D level (mean rank: 24.47 vs 12.55; p<0.001).

Figure 1. Correlations between activity grade (A - score Metavir) and vitamin D levels

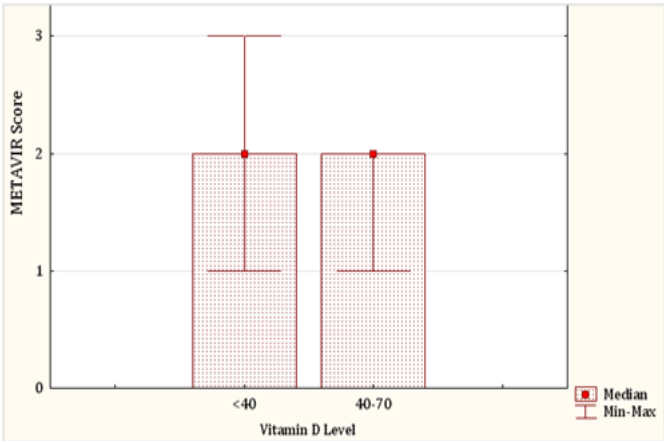


Figure 2. Correlations between score F and vitamin D levels

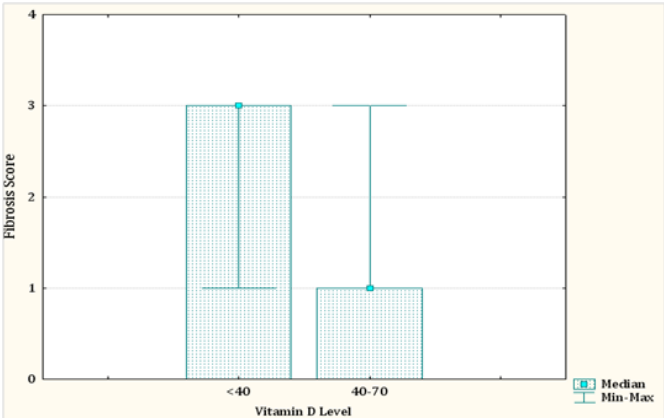
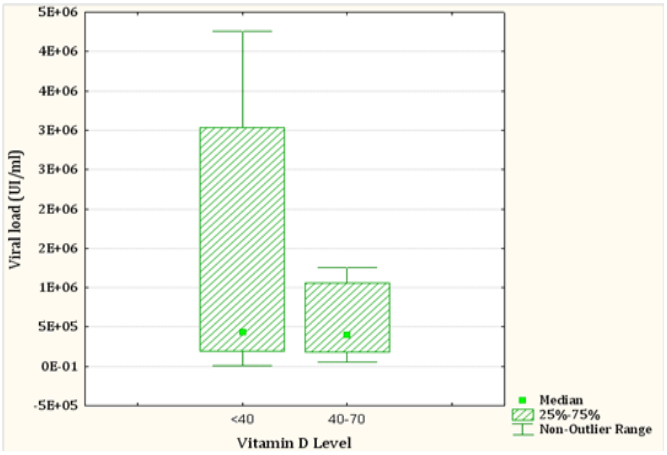


Fig 3. The level of viremia prior therapy in patients with normal and low vitamin D



No statistically differences were identified in terms of viral load in patients with low levels of vitamin D compared to those with normal levels (p=0.57).
Baseline vitamin D levels were compared between patients who achieved an SVR to PEG-IFN plus RBV antiviral therapy and those who did not. The patients with normal vitamin D level have a higher probability to obtain SVR vs the ones with low vitamin D level (73.68% vs 21.43%; p=0.03).

Discussion

The natural history of chronic hepatitis C is the development of fibrosis and ultimately of cirrhosis. The fibrosis progression

rate is variable, with some patients progressing to cirrhosis within a few years, while others may never progress even after decades from infection, depending on the presence and type of host, viral and environmental factors (Rüeger et al 2014). The only factor that can stop the progression is the antiviral treatment that leads to SVR (D'Ambrosio et al 2012). Any other drugs that have been tested have had discouraging results, and no one have been validated in the clinical setting (Schuppan et al 2012). A large number of studies have examined the relationship between the vitamin D status of patients with chronic hepatitis C and disease outcome and they found that HCV-positive patients had 25(OH)D levels below 30 ng/ml, in contrast to control subjects (Autier et al 2014), vitamin D deficiency is likely to exacerbate chronic inflammation in HCV-positive patients (Rahman et al 2013) and correlate with the liver fibrosis stage (Cholongitas et al 2012). Optimal vitamin D levels may increase the likelihood of successful antiviral treatment in HCV-positive patients treated with interferon and ribavirin, as evidenced by the fact that vitamin D and its metabolites can synergize with IFN treatment to directly inhibit HCV RNA replication in vitro (Gal-Tanamy et al 2011).

In our study, a significant association between vitamin D deficiency and high activity grade or liver fibrosis stage was found. These results are different from those published by Kitson and al. They showed existing associations only between 25(OH)D level and high activity grade (Kitson et al 2013). An independent association between low 25(OH)D level and increased hepatic necroinflammatory grade has been suggested by other studies (Petta et al 2010; Bitetto et al 2011). Petta et al also showed that low level of 25 (OH)D is independently associated with the presence of severe fibrosis (2011).

Our results, in spite of being obtained in an under-powered study due to the small number of patients, indicate that a low baseline vitamin D level is significantly associated with a low probability of obtaining SVR. Petta et al also concluded that a lower 25(OH)D serum levels were an independent negative risk factor for SVR (2011). However a meta-analysis published in 2014 found that the baseline 25(OH)D level has no impact on SVR with regard to therapy with PEG-IFN plus RBV (Autier et al 2014). Except for the larger number of patients, we observed there are some methodological differences between the current study and meta-analisys: there is a difference between the cut-off value: for the meta-analysis 30 ng/ml was used as the lower limit, with a level between 20–30 ng/ml labelled as "vitamin D insufficiency"; we used 40 ng/ml as the lower limit, as this was laboratory limit. The Institute of Medicine (Washington, DC) defines vitamin D deficiency as <20 ng/ml and recommends vitamin D supplementation in this population in view of a clear evidence of the detrimental effects on skeletal health in those with vitamin D deficiency (Institute of Medicine 2011).A panel from the Endocrine Society concluded that 32 ng/ml should be used as the threshold of 25(OH)D sufficiency in patients with various disease conditions (Holick et al 2011). Also there is a difference in measured parameters: we measured 1.25 (OH)2D but in the mentioned meta-analysis there was measured 25-hydroxyvitamin D, a precursor of the biologically active form of vitamin D. Moreover we did not include IL28B genotype data and we did not consider the vitamin D supplementation at the time of baseline blood sampling. We believe that it would be helpful because there are few randomized clinical trials that found that vitamin D3 supplementation improved SVR in CHC genotype 1, 2 and 3 infection treated with peginterferon plus ribavirin (Abu-Mouch et al 2011; Nimer et al 2012) and this could be the opportunity for a future study.

In conclusion in our patients with chronic viral C liver disease, a vitamin D deficiency was correlated with a high activity grade and stage of liver fibrosis. This was also found to be a risk factor for not achieving SVR in patients treated with peginterferon plus ribavirin.

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