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Vitamin D Deficiency in HCV Antiviral Treatment Responders versus Non-Responders

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ABSTRACT

Background: Hepatitis C virus (HCV) is a major cause of chronic liver disease (CLD). Pakistan has a high burden of infectious diseases, including HCV. Its prevalence varies according to geographic regions in the country from about 2·4% to 6·5%. The objective of the study was to compare the frequency of vitamin D deficiency in responders and non-responders of antiviral treatment for chronic hepatitis C.

Material and Methods: This comparative cross-sectional study was conducted in Hepatitis Clinic, Jinnah hospital, Lahore from 20th May to 20th November 2013. After ethical approval, participants were selected by using purposive non-probability sampling, 52 responder patients i.e. who were labeled negative for HCV RNA by PCR after 12 weeks of antiviral treatment and 52 non-responder patients were included in this study. Data was collected by using pretested structured questionnaire. Vitamin D3 levels were measured by ELISA and a cut-off value of below 30ng/ml was labeled as Vitamin D deficiency. SPSS version 21 was used to analyze data with *p* value less than 0.05 taken as statistically significant.

Results: Out of 104 patients (mean age 35±8.1 years), 61.5% were males and 38.5 % were females. There was a significant difference in frequency of vitamin D deficiency in treatment responder group when compared to non-responders ($p = 0.016$). Mean level of vitamin D was 21.8±10.8ng/ml in responders whereas it was 15.6±7.5 in non-responders with a statistically significant difference ($p = 0.001$).

Conclusion: This study concludes that there is a significant vitamin D deficiency among treatment non-responders as compared to treatment responders in patients with chronic hepatitis C.

Key words: Vitamin D, Vitamin D deficiency, Viral Response

Authors' Contribution:
[1-3] Conception, synthesis, planning of research and manuscript writing Interpretation, discussion, [4-6] Data analysis, interpretation and manuscript writing, Active participation in data collection.

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Introduction

Hepatitis C virus (HCV) is a major cause of chronic liver disease (CLD). It is a global dilemma and an alarming health issue with global incidence of 200 million (3.3%).[1] Pakistan also has a high burden of infectious disease including HCV[2,3]. Its prevalence varies according to geographic regions from about 2·4% to 6·5%.[4,5] However, very low rate of HCV is reported from developed nations like Canada 0.8%, France 1.1%, Germany 0.6%, and Australia 1.1%. Similarly, prevalence rate of HCV lower than Pakistan have also been reported from Italy (2.2%) USA (1.8%), Japan (12.3%) and China (3.2%) respectively.[6-10] Whereas, Africa and Asia have the highest burden of HCV infection. Egypt alone with an estimated population of almost 73 million[11] has a high

seroprevalence rate of about 22%.[12] Liver is a vital organ for the metabolism of Vitamin D. It hydrolyzes vitamin D from skin and diet into 25-hydroxyvitamin D [25(OH)D] which can be estimated by ELISA[13]. Therefore, liver disease affect the metabolism of Vitamin D leading to disturbance in calcium and bone metabolism.[14] Deficiency of vitamin D is associated with osteopenia, osteoporosis, osteomalacia and muscle weakness, resulting in higher chances of bone fractures.[15] Moreover, Vitamin D deficiency is associated with multiple types of malignancies (e.g., prostate, colon, breast), as well as autoimmune inflammatory metabolic disorders. Vitamin D also plays a major role in calcium metabolism and in differentiation, proliferation and immunomodulation of cells.[16] Similarly, Vitamin D deficiency resists fibroblastic proliferation and augments the production of collagen. HCV infection leads to Chronic Liver Disease (CLD)[17] and eventually to hepatic fibrosis.[18] It is therefore essential to understand the role of vitamin D deficiency in the treatment of chronic hepatitis C, so that these patients may be screened and treated before starting the antiviral therapy.

Material and Methods

This comparative cross-sectional study was `conducted in Hepatitis Clinic, Jinnah hospital, Lahore from 20th May to 20th November, 2013 after obtaining approval from the institutional ethics committee. Non-probability purposive sampling technique was used for sample collection. Patients of either sex of age 20-60 years, coming for follow up in hepatitis clinic of Jinnah Hospital Lahore were enrolled in this study. All patients had received 12-week treatment for chronic hepatitis C i.e. conventional interferon injection and ribavirin tablets. Patient taking calcium/ Vitamin D supplementation, having advanced impaired liver and /or renal functions were excluded from the study.

After informed consent, 52 responders and 52 non-responder patients were segregated into 2 groups. Data was collected using pretested structured questionnaire. Blood samples were collected using aseptic technique and vitamin D3 levels were assessed by Enzyme-Linked Immunosorbent Assay (ELISA). Genotype of HCV was also recorded to cater for effect modification. Data was entered and analyzed in SPSS version 21. Frequencies and percentages were calculated for qualitative variables while mean and standard deviation were computed for quantitative variables. Vitamin D deficiency was compared in both groups i.e. responders and non-responders using chi square test of homogeneity as a test of significance, with p value less than or equal to 0.05. Data was cross tabulated to determine the effect of age, sex and genotyping on treatment response and Vitamin D deficiency. Independent sample t test and Chi square were used to rule out effect of these confounders. Vitamin D deficient patients were divided into two classes i.e. severe deficiency, if Vit D level less was than 15 ng/ml and deficiency, if levels were between 15 and 30ng/ml. The difference in responders and non-responders was cross tabulated again.

Results

Out of 104 patients i.e. 52 responders and 52 non-responders, patients with mean age of 35.3 $\pm$ 8.1 years were included. Mean vitamin D level came out to be 18.8 ng/ml $\pm$ 9.7 (range 7.7 to 44 ng/ml). There were 61.5% (n=64) males and 38.4% (n=40) females, respectively. Genotype distribution showed 79 patients (76%) with genotype 3, 19 Patients (18%) had type 1 and only 6 patients (5.8%) had type 2 genotype of hepatitis C virus. Out of 104 patients 82 individuals (79%) were vitamin D deficient. Mean level of vitamin D was 21.8 $\pm$ 10.8 ng/ml in responders while it was 15.6$\pm$7.5 ng/ml in non-responders. Cross tabulation of vitamin D deficiency categories and treatment response groups among Hepatitis C patients, showed significant difference of Vitamin D Deficiency among treatment responders as compared to non-responders (p= 0.016) (Table I). Response to antiviral treatment is also significantly associated with genotype of Hepatitis C (p = 0.05). To rule out the effect of age and gender, we cross tabulated age groups of patients in both groups i.e. > 30 years and <30 years and gender with treatment response, which showed that younger patients have a better response to treatment than older groups. There was no correlation of gender with treatment response (p=0.314) (Table II).

Table I: Cross tabulation of Vit D deficiency and HCV genotypes with responder and non-responders					
		Groups			
		Responders	Non-Responders	Total	*P* Value
Vitamin D level	Normal	16	6	22	Pearson Chi square 0.016
	Deficient	36	46	82	
Genotypes	Gen 3	45	34	79	Fisher's Exact 0.05
	Gen 2	2	4	6	
	Gen 1a or 1b	5	14	19	

Table II: Cross tabulation of Vit D deficiency and HCV genotypes with responder and non-responders					
		Groups			
		Responders	Non-Responders	Total	P Value
Gender	Male	29	35	64	Pearson Chi square 0.314
	Female	23	17	40	
Age group	>30 years	22	48	70	Fisher's Exact <0.001
	<30 years	30	4	34	

Table III: Vitamin D levels in HCV treatment Responders and Non-Responders and different HCV genotypes						
Variables		Groups			Total	*P* Value
		Severely deficient	Deficient	Normal		
Study groups	Responders	22	14	16	52	Pearson Chi square 0.026
	Non-responders	34	12	6	52	
HCV genotype	Gen 3	43	21	15	79	Fisher's Exact <0.865
	Gen 2	3	1	2	6	
	Gen 1a or 1b	10	4	5	19	

Table IV: Distribution of Vitamin D levels according to Gender and Age groups						
Variables		Groups			Total	*P* Value
		Severely deficient	Deficient	Normal		
Gender	Male	34	19	11	64	Pearson Chi square 0.257
	Female	22	7	11	40	
Age Grous	>30 years	43	18	9	70	Pearson Chi square 0.01
	< 30 years	13	8	13	34	

An inverse relationship of response to interferon therapy with Vitamin D deficiency was also reported (p=0.026). Severity of vitamin D deficiency is not related to genotype and gender but is affected by age (Tables III and IV).

Discussion

The mean age of patients in our study shows that hepatitis has affected our population in the most productive age group. Similarly, vitamin D deficiency is also very common involving almost 80% of our population. Genotype 3 is the main circulating viral genotype in our population, and is easily treatable. Our results also show higher frequency of Genotype 3 in treatment responders. Although previous studies showed that vitamin D levels are not associated with sustained virologic response (SVR) to antiviral therapy (PEG-IFN and RBV) in hepatitis C patients, but effect of Vitamin D supplementation on SVR was not clear.[19] However, our study showed that Vitamin D deficiency has significant negative correlation with response to hepatitis C treatment; but the causal relationship cannot be elicited due to the limitation of the study design. Kitson et al reported mean 25(OH)D level of 79.6 nmol/L, with 48% prevalence of 25(OH)D <75 nmol/L and 16% <50 nmol/L respectively in Chronic Hepatitis C genotype 1 patients. Their study showed no association of baseline 25(OH) level with SVR or fibrosis in HCV-1, but significant association with high activity grade.[20] Similarly, Ladero et

al also mentioned presence of vitamin D deficiency among Spanish chronic hepatitis C patients.[21] About 41 vitamin D deficient patients were treated with vitamin D supplements and later on re-evaluated. Vitamin D deficiency (<20ug/dl) was seen in 36.1% and suboptimal levels (20-30ug/dl) were observed in 40.9% patients.[21]

Our study findings are in agreement with Mohamed et al[22] who reported low vitamin D levels in HCV patients as compared to the healthy population. Higher levels of Vitamin D were observed among responders of ribavirin plus Pegylated interferon alpha 2a therapy while low levels were observed among non-responders. Therefore, it was concluded that vitamin D deficiency may contribute to delayed or unfavorable response of antiviral therapy in HCV infected patients.

Another study by Amanzada et al showed that lower pre-treatment 25(OH)D levels and higher serum ferritin levels were significantly associated with fibrotic alteration and inflammatory activity.[23] Yu et al also reported significantly lower concentration of 25(OH)D in liver cirrhosis group than the control group with the conclusion that vitamin D might function as a protective factor against development of cirrhosis.[24]

Similarly, Villar et al reported in a systematic review that out of 1575 Hepatitis C patients, 1117 (71%) were vitamin D deficient. With respect to treatment, this systemic review had included 8 studies of both HCV persons without previous treatment and pooled patients with sustained viral response. In patients with very high SVR, Vitamin D levels was >30 ng/dl which could be either supplemented or natural regardless of types of genotype. The results established high occurrence of vitamin D deficiency in Hepatitis C patients and SVR in persons with upper vitamin D levels or in patients getting vitamin D supplementation.[25]

Conclusion

There is a significant difference in vitamin D levels among treatment responders and non-responders in patients with chronic Hepatitis C, with a very low rate of vitamin D observed among non-responders. Severity of vitamin D deficiency is not related to genotype and gender but is affected by age. It is hereby recommended to screen every patient before the start of antiviral treatment for a better outcome of Hepatitis treatment.

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