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Role of Vitamin D Receptor Polymorphism in Hepatic Fibrosis Progression in A Cohort of Hcv Egyptian Patients

El Emary Ahmed Taha Marouf[1], Mohamed Salah Abdelbary[1], Yasmin Saad [1], Ahmed Mohamed Khairy[1], Sherif Mofeed Ekladious[2]

[1]Department of Endemic Medicine, Faculty of Medicine, Cairo University

[2]Department of Clinical and Chemical Pathology, Faculty of Medicine, Cairo University

Corresponding author: El Emary Ahmed Taha Marouf

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Abstract:

Introduction: Several studies explored the association between vitamin D status and liver fibrosis with contradictory results.

Aim of the work: to investigate the potential role of VDR genetic variants in hepatic fibrosis progression in patients with chronic hepatitis C infection

Patients and Methods: It was a prospective study that included fifty patients with chronic HCV infection fulfilled the inclusion and exclusion criteria and who were divided according to their fibrosis stage measured by transient elastography (fibroscan) into the mild-moderate stage of fibrosis (<F2) (25 patients group II) and advanced fibrosis (>F2) (25 patients group III) in addition to fifty normal individuals who served as a control (group I). All participants were subjected to full history and clinical examination, routine laboratory investigations, abdominal ultrasound and liver stiffness assessment by fibroscan. In addition to serum analysis of vitamin D and DNA for VDR polymorphism.

Results: Normal control group had moderate vitamin D deficiency while HCV patients had significant severe vitamin D deficiency, moreover; a lower level was noted among patients with the advance of fibrosis. There was no significant difference among the three groups (control, mild to moderate fibrosis and severe fibrosis) regarding the VDR polymorphism either the genotypes or alleles, VDR polymorphism SNP rs#7975232 showed statistically significant correlation with liver stiffness toward the T allele while other SNPs did not show any significance.

Conclusion: low vitamin D status is associated with advanced liver fibrosis in chronic HCV liver disease patients with no role of VDR genetic variation in liver fibrosis progression except in SNP rs#7975232.

Keywords:vitamin D polymorphism, liver fibrosis, hepatitis C virus infection.

1. Introduction

Chronic infection with the hepatitis C virus (HCV) is a leading indicator of liver disease. HCV infection is a major public health burden in Egypt, where it bears the highest prevalence rate in the world (1, 2). Egypt is one of the world countries with the highest prevalence of HCV infection. Over the past decade, Egypt has continued efforts to achieve HCV control and works towards the common goal, targeted by the WHO, of the elimination of viral hepatitis by 2030. The universal access to treatment with the introduction of DAAs has resulted in a paradigm shift in HCV management and declining mortality. A large Egyptian study showed a marked decrease in mortality in Egypt (3).

Chronic infection with HCV is the leading cause of end-stage liver disease, hepatocellular carcinoma (HCC) and liver-related death in Egypt. HCV causes chronic hepatitis in 60%–80% of the patients, and 10%–20% of those patients develop cirrhosis over 20–30 years of HCV infection. About 1%–5% of the patients with liver cirrhosis may develop liver cancer and 3%–6% may decompensate during the following 20–30 years. The risk of death in the following year after an episode of decompensation is between 15% and 20% (4).

In addition, HCV infection increases the risk of type 2 diabetes mellitus and is associated with several extra-hepatic manifestations (arthralgia, cryoglobulinemia, skin manifestations, sicca syndrome and thyroid disorders) and increases the risk for circulatory diseases, kidney diseases, renal failure, cancers of the esophagus, prostate and thyroid and all-cause mortality (5-8).

Overall, 15%–35% of patients with chronic HCV have circulating cryoglobulins, and 5%–25% of them will develop clinical consequences including mixed essential cryoglobulinemia, systemic vasculitis, peripheral neuropathy and membranoproliferative glomerulonephritis (9).

Vitamin D is a fat-soluble vitamin metabolized by the liver and is converted to 25 dihydroxy vitamin D3 (the active form) which has been found to have an immunological role principally via regulating T-cell function (10-12).

Vitamin D can directly or indirectly influence the differentiation and activity of CD4 T-cells. It is hypothesized that vitamin D has an important role in the innate immune response against HCV; in addition, some studies have shown that vitamin D inhibits HCV replication (13, 14).

Decreased 25-OH vitamin D levels have been described in various forms of chronic liver disease and associated with advanced fibrosis (15).

Irrespective of the underlying disease, serum concentrations of 1, 25-(OH) 2 vitamin D are decreased in patients with cirrhosis vs non-cirrhotic patients and a gradual decline has been observed in cirrhotic patients according to increasing Child-Pugh class and clinical decompensation (16).

Significant inverse correlations of 25-OH vitamin D with stages of fibrosis and severity of necro-inflammatory activity were observed in different populations with chronic hepatitis C (17, 18).

Vitamin D Receptor (VDR) is expressed in virtually every type of cell involved in immunity (12).

VDR serves as the physiological target to mediate vitamin D defects. Common genetic variations of the vitamin D receptor (NR1I1) gene such as the bat-haplotype consisting of rs1544410 (formerly BsmI), rs7975232 (ApaI) and rs731236 (TaqI) have been described (19-21).

VDR (NR1I1) gene variants modulate the biological effects of vitamin D without influencing vitamin D plasma levels (19).

Genetic variations in the VDR (NR1I1) gene have been described as an important modulator of multiple diseases including hepatic disorders such as primary biliary cirrhosis and autoimmune hepatitis (19).

Aim of the work:

To investigate the potential role of VDR genetic variants in hepatic fibrosis progression in patients with chronic hepatitis C infection.

Patients and Methods:

Design: it was a prospective study.

Patients: It included 50 HCV patients recruited from Cairo University center for Hepatic Fibrosis, Endemic Medicine Department, Kasr Al Aini Hospital from the period of 7 / 2015 to 7/ 2016 according to inclusion and exclusion criteria in addition to 50 normal volunteers who served as a control group

Inclusion criteria:

1. Adult patient (18-60 years).
2. Chronic HCV infection (more than 6 months).
3. Positive HCV Ab and HCV RNA by PCR

Exclusion criteria:

1. Co-infection with HBV, alcohol consumption or morbid obesity (BMI > 40 kg/m2).
2. Hepatocellular carcinoma.
3. Autoimmune hepatitis.
4. Presence of periportal fibrosis (grade II and III) by abdominal ultrasound.
5. Treated HCV patients.
6. Massive ascites preventing fibroscan.
7. Patients who refused to sign study consent.
8. Recent blood transfusion.
9. Hypersplenism
10. Leucopenia.
11. Drugs abusers

Methods: All Patients and control subjects were subjected to full history taking, general and local examination and routine investigations as complete blood count, Liver Profile (serum alanine aminotransferase (ALT), serum aspartate aminotransferase (AST), total and direct bilirubin, serum albumin, prothrombin time and concentration), fasting blood glucose, serum creatinine, serum vitamin D level, anti-schistosomal Ab and HCV PCR

Abdominal ultrasound examination: Using Toshiba Applio 400 (TUS-A400) with a 3.5 MHz convex transducer, all patients were examined to determine the size of the liver as well as the size of the spleen, texture and surface of the liver, presence of hepatic focal lesions or ascites.

Liver stiffness measurement (LSM): Using Fibroscan, the probe consists of a single-element ultrasound transducer with a central frequency of 3.5 MHz (frequency conventionally used for ultrasound abdomen imaging).

Interpretation of results of Fibroscan:

1-Up to ten successful acquisitions were performed on each patient. The success rate was calculated as the ratio of the number of successful acquisitions over the total number of acquisitions.

2-The median value of successful measurements was kept as representative of the liver stiffness

and spcinel stiffness

3-Only LSM obtained with 10 successful acquisitions and a success rate of at least 60% was considered reliable

Statistical analysis:

- Statistical package for social sciences (IBM-SPSS), version 24 IBM- Chicago, USA (May 2016) was used for statistical data analysis.
  - Data expressed as mean, standard deviation (SD), number and percentage. Mean and standard deviation were used as the descriptive value for quantitative data, while numbers and percentages were used to describe qualitative data.
  - Student t-test was used to compare the means between two groups, and a one-way analysis of variance (ANOVA) test was used to compare the means of more than two groups. Mann-Whitney test was used instead of the Student t-test in the case of non-parametric data.
  - Pearson Chi-square was used to compare percentages of qualitative data, and Fisher's Exact test was used for non-parametric data.
  - Univariate logistic regression analysis for prediction of fibrosis in HCV-infected patients as regards demographic, laboratory, liver stiffness and VDR polymorphism data
  - For all these tests, the level of significance (P-value) can be explained as:
    - No significance $P > 0.05$
    - Significance $P < 0.05$
    - High significance $P < 0.001$.

Results

It was prospective that the study included 50 patients with chronic HCV infection who fulfilled the inclusion and exclusion criteria and who were divided according to their fibrosis stage measured by transient elastography (fibroscan) into the mild-moderate stage of fibrosis (<F2) (25 patients group II) and advanced fibrosis (>F2) (25 patients group III) in addition to 50 normal individuals who served as a control (group I).

Regarding the basic demographic features of the studied groups, we found that age was significantly higher in HCV patients regardless of the stage of fibrosis than the normal control group, male predominance among studied groups was noted with no statistical significance.

As regard the laboratory parameters; ALT, AST, prothrombin time, creatinine, and fasting blood sugar were significantly higher among HCV patients compared to controls.

On the assessment of vitamin D level, it was noted that the normal control group had moderate Vit. D deficiency while HCV patients had severe vitamin D deficiency with a significant difference, moreover; a lower level was noted among patients with advanced of fibrosis as shown in Table (1).

Liver stiffness measurements by fibroscan of the studied groups increased steadily from group I (4.49±0.74) to group II (4.89±1.45) to group III (5.12±1.87) with a significant difference (p-value = 0.009).

There was no significant difference among studied groups regarding the VDR polymorphism the genotypes or alleles (table 2).

On studying the correlation between different SNPs of VDR polymorphism and demographic, laboratory & liver stiffness measurement, no significant correlation was found except in rs#7975232 which shows a statistically significant correlation with liver stiffness toward the T allele.

Univariate logistic regression analysis for prediction of fibrosis in HCV-infected patients as regards demographic, laboratory, liver stiffness and VDR polymorphism data. As none of these parameters showed significant relation in the univariate regression analysis model, there was no need to perform multivariate regression analysis and none of the above factors was proved as a possible risk factor for hepatic fibrosis, based on our data and number of cases (Table 3).

Table 1. Laboratory parameters of the studied patients.

	Group I	Group II	Group III	*P-value
Total bilirubin (mg/dL)	0.74±0.18	0.89±0.24	0.97±0.58	0.564
ALT (U/L)	7.46 ±1.09	37.32 ±15.61	40.08 ±17.88	<0.001
AST (U/L)	7.52 ±1.78	35.08 ±12.10	45.32 ±21.91	<0.001
AST/ALT ratio	1.03±0.28	1.00±0.22	1.18±0.35	0.051
Serum Albumin (g/dL)	4.14±0.44	3.65±1.23	3.22±1.09	0.089
Prothrombin conc. (%)	14.40±0.38	16.89±2.56	18.32±3.76	0.008
HCV PCR (IU/ml)	0	1672073 ±4432873	1586867 ±2373701	<0.001
Creatinine (mg/ml)	0.74±0.11	0.87±0.15	0.86±0.18	0.045
FBG (mg/ml)	78.38±11.71	96.12±23.65	99.11±16.33	0.008
Vitamin D level	13.01±13.88	7.93±8.2	5.63±6.79	<0.001

Table 2: Prevalence of studied 3 SNPs in VDR polymorphism among the studied groups

SNP	Variable		Group I N=50 N (%)	Group II N=25 N (%)	Group III N= 25 N (%)	p-Value
rs# 1544410	Genotypes	AA	0	0	1(4%)	0.482
		AG	32(64%)	14(56%)	16(64%)	
		GG	18(36%)	11(44%)	8(32%)	
	Alleles	A alleles	32(32%)	14(28%)	18(36%)	0.692
		G alleles	68(68%)	36(72%)	32(64%)	
rs# 731236	Genotypes	CC	10(20%)	4(16%)	8(32%)	0.587
		CT	25(50%)	14(56%)	9(36%)	
		TT	15(30%)	7(28%)	8(32%)	
	Alleles	C alleles	45(45%)	22(44%)	25(50%)	0.801
		T alleles	55(55%)	28(56%)	25(50%)	
rs# 7975232	Genotypes	GG	6(12%)	3(12%)	5(20%)	0.579
		GT	19(38%)	13(52%)	8(32%)	

		TT	25(50%)	9(36%)	12(48%)	
	Alleles	G alleles	31(31%)	19(38%)	18(36%)	0.655
		T alleles	69(69%)	31(62%)	32(64%)	

Table 3: Univariate logistic regression analysis for prediction of fibrosis in HCV-infected patients as regards demographic, laboratory, liver stiffness and VDR polymorphism data

Variables		P-Value	OR	95% C.I. for OR	
				Lower	Upper
Age		0.355	1.033	0.964	1.108
BMI		0.506	0.866	0.565	1.325
AST		0.068	1.041	0.997	1.088
ALT		0.556	1.010	0.976	1.045
Total bilirubin		0.233	1.045	0.965	1.187
Albumin		0.089	0.674	0.561	1.345
PC		0.122	1.099	0.931	1.110
HCV viral load		0.931	1.000	0.998	1.002
VD		0.232	0.949	0.871	1.034
Liver stiffness		0.629	1.108	0.921	1.282
rs#1544410	AA	1.000	-	-	-
	AG	0.564	1.397	0.449	4.350
	GG	0.384	0.599	0.189	1.898
rs#731236	CC	0.192	2.471	0.634	9.625
	CT	0.159	0.442	0.142	1.376
	TT	0.758	1.210	0.360	4.065
rs#7975232	GG	0.445	1.833	0.387	8.674
	GT	0.155	0.434	0.138	1.371
	TT	0.391	1.641	0.529	5.093

Discussion:

The anti-inflammatory and anti-fibrotic roles of vitamin D have the potential to reduce HCV-mediated liver disease and, perhaps, to positively contribute to treatment outcomes (22, 23).

Regarding the present study, age was significantly higher among HCV patients specifically in patients with advanced fibrosis which could be related to higher vulnerability to environmentalfactors (especially oxidative stress), or reduction in blood flow, mitochondria capacity or immune capacities (24).

Male predominance in our study was noted but with no statistically significant difference. Males have 10 times more rapid progression to cirrhosis than females, regardless of age (25-27).

The level of vitamin D, on the other hand, was significantly lower among HCV patients compared to controls and even less with advanced fibrosis. An early study demonstrated that low serum 25(OH) D was associated with the severity of liver fibrosis in HIV/ HCV co-infected patients (28). Other studies showed that low serum 25(OH)D status was associated with hepatic dysfunction (29).

Common genetic variations of the vitamin D receptor (NR1I1) gene such as the bat-haplotype consisting of rs1544410 (formerly BsmI), rs7975232 (ApaI) and rs731236 (TaqI) have been described. VDR (NR1I1) gene variants modulate the biological effects of vitamin D without influencing vitamin D plasma levels (30, 31).

Genetic variations in the VDR (NR1I1) gene have been described as an important modulator of multiple diseases including hepatic disorders such as primary biliary cirrhosis and autoimmune hepatitis (32).

Fan et al. in their study of patients with liver cirrhosis of viral (HBV or HCV) and alcoholic origin, did not demonstrate any differences in the allele and genotype frequencies of the VDR polymorphisms between the patients and controls (33). Also, Suneetha et al. did not demonstrate differences in VDR polymorphism allele frequencies between controls and patients with chronic viral hepatitis due to HCV (34).

In the study done by Hung et al., they investigated the possible association between VDR gene polymorphisms and HCC in a Chinese population with chronic HCV infection. Their data showed that patients with HCC had a higher frequency of ApaI CC genotype and bAt [CCA]-haplotype as compared to control subjects (35).

Falleti et al. have demonstrated that VDR genetic polymorphisms were significantly associated with the occurrence of HCC in cirrhotic patients who underwent liver transplantation. However, this relationship was more specific for patients with an alcoholic etiology, but not for those with cirrhosis of viral origin. This discrepancy is explained by the small size of the studied cohort with virus-cirrhotic subjects (36). Another study reported that genetic variations in CYP2R1, GC, and DHCR7 are associated with progression to HCC in patients with chronic hepatitis C, according to four heterogeneous independent cohorts (37).

It was noted that vitamin D level was lower in normal healthy individuals in our studied group which was also documented by Mansoor et al. who made a study of the prevalence and significance of vitamin D deficiency and insufficiency among apparently healthy adults. They found a high prevalence of 25(OH) vitamin D deficiency 90% had low serum 25(OH)D levels (69.9% were deficient and 21.1% had insufficient levels of 25(OH)D among apparently healthy adults, hospital staff and health care professionals (38).

Conclusion:

Our study concluded that vitamin D was significantly lower among patients with liver fibrosis and advanced fibrosis. However, VDR polymorphism has not been to be significantly related to liver fibrosis.

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