ORIGINAL ARTICLE

CONTENTS

The significant impact of T-cell immunoglobulin and mucin domain 3(Tim-3) gene polymorphism on HCV infection and viral load

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ABSTRACT

Aim: To evaluate the role of -574 locus gene polymorphism in promotor region of TIM-3 gene in HCV infection and viral load.

Materials and Methods: The current study executed on 100 subjects (50 patients with HCV and 50 obviously healthy objects as control). Blood sample compiled from all participants. All samples underwent to diagnosis for HCV confirm by viral load measurement by real time-polymerase chain reaction (RT-PCR). Extraction the Genomic DNA performed from blood. The gene fragment corresponding the-574 locus (rs10515746) in TIM-3 gene was amplified and genotyping by allele specific - polymerase chain reaction (AS-PCR).

Results: In recessive model, in patients the frequency of GT-TT genotype was significantly higher than controls (86% vs. 62%) with a highly important variation (OR=3.76, 95% CI=1.41-10.05, p=0.008 at allelic level, T allele was more continual in patients than controls (60% contra 42%) with a considerable variation (OR=2.07, 95%CI=1.18-3.64, p= 0.015). About 42% of patients carrying TT genotype had viral load ≥200000 IU/ml compared with 15.38% GT carriers and 0% GG carries with such a viral load with a significant difference. At allelic level, T allele was more continual in patients than controls (60% contra 42%) with a significant variation (OR=2.07, 95%CI=1.18-3.64, p= 0.015.

Conclusions: T allele of rs10515746 considered a risk factor for HCV infection as well as for higher hepatitis C viral load in those patients, and it could predict treatment failure. However, with more aggressive antiviral therapies, viral cure could be achieved.

KEY WORDS: Hepatitis C virus, T-cell immunoglobulin and mucin domain 3, single nucleotide polymorphism

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INTRODUCTION

Hepatitis C infection is contagious disease happened due to hepatitis C virus (HCV), Which a positive single stranded RNA virus with lipoprotein envelope offers a spherical structure of approximately 55 nm in diameter and classify of the family *Flaviviridae* located within the genus Hepacivirus [1]. Susceptibility to acute HCV infection mediated by received unsafe medical procedures, used injection drugs, and lived with human immunodeficiency virus [2]. HCV main reason for acute hepatitis infection and these evolve to chronic hepatitis C. A huge number of patients disregard to reply to antiviral treatment, thus lasting risk for illness advancement. HCV progressed mechanism to avoid immune elimination in the greater number of infected persons. The consequences chronic HCV infection induces a chronic inflammatory disease process lead to liver cirrhosis, hepatocellular carcinoma and death [3-5]. The features of HCV-specific T-cell responses from both CD4+T-helper lymphocytes (Th) and CD8+ cytotoxic lymphocytes(CTLs) in patients with HCV infection play key role in development of liver injury and viral rescue [6]. Genetic series implicated in mission and organization of T lymphocytes further confirm the task of the acquired immune response that intent the history of HCV by factors have critical action in T-cell concerning genes. In addition, several genes implicated in innate NK cell response established the complicated interaction between elements of immune apparatus needful for effective response to infection [7]. T cell immunoglobulin and mucin-domain-containing molecule-3 (Tim-3) is a type I transmembrane protein, and implied important role in innate and adaptive immunity further a diverse of metabolic and immunomodulatory pathways. As a form of T cell surface restrained molecule, does as a negative regulator of Thelper1 and Tcytotoxic1 cell task by induce planning

cell death via interactivity with Galectin-9 ligand, and promote peripheral tolerance. This negative activity of TIM-3 has immediately developed to comprise its participation in promotion status of impairment T cell function or "attrition" noticed in persist viral diseases [8-9]. On addition, immune cells express TIM-3 also on their surface such as dendritic cells, macrophages and natural killer cells and the overexpression of Tim-3 on these cells lead to harm immune action of aforementioned immunocytes [10]. In human, three genes encode for members of the TIM belongings (HAVCR1, HAVCR2 and TIMD4, encoding TIM1, TIM3 and TIM4, respectively) [11]. The TIM-3polymorphism explained to modify the interplay between TIM-3 and its ligand, just like that simulating the pathway that outcome in definite immune disease [12-13] and effectively contributed in the tumors pathogenesis [14]. Polymorphism in both coding and non-coding region of HAVCR2 in humans linked with autoimmune and allergic diseases [15]. HAVCR2 have three major Polymorphism has linked with diverse certain situations:

Number of polymorphism comprises +4259T/G (rs1036199) in the coding region and −1516G/T (rs10053538) and −574G/T (rs10515746) in the promoter area related with rhinitis and of the gastrointestinal cancer [16-17], pancreatic cancer and renal cell carcinoma [18-19], non-small-cell lung cancer. Additionally, HIV-1 infection common related with γ-chain (γc) cytokines that prompt Tim-3 expression in an antigen-independent manner in HIV-1 patients, with non-Hodgkin lymphoma [20]. One report declared that the certain kind of SNP interconnection to elevation the TIM-3 expression that include PD1 (+8669AA (rs10204525) and HAVCR2 (−1516G/T) via liver-infiltrating lymphocytes in patients who have HBV infection and suffer from hepatocellular carcinoma [21]. Further the patients with osteoarthritis carrying the HAVCR2 +4259T/G allele, was found direct relation between T cell task and polymorphism of HAVCR2, who viewed elevation levels of IFNγ output by their CD4+ T cells [22]. Another study announced the expression of TIM-3 protein level was revealed by immunohistochemistry in women with breast cancer, subsequently was reported rs10053538 had a strikingly elevated risk of BC, contrasting with the wild-type genotype [23]. The polymorphism of TIM-3 is clinical significance that intervention in prediction of HBV-concerning liver disease [24]. As expected, Tim-3 was intended to serve as a significant barrier to prevent the T cells from performing their duties, In a northern Chinese Han population with myasthenia gravis (MG), the -574 site variant was examined and a significant difference was found between the GT+TT genotype and the frequency of the T allele on the Tim-3 promoter [25].

AIM

The aim of our report was to investigate the diversity of the Tim-3 gene promoter region and the association with viral infection and load.

MATERIALS AND METHODS

THE STUDY POPULATION

Hundred subjects enrolled in the control study, including 50 HCV patients and 50 healthy controls. The study carried out at Gastroenterology and liver Hospital-Medical City (Baghdad, Iraq) during period from March 2024 to August 2024. Documentary consent acquired from all groups before involvement in the study. The diagnosis HCV was performance by laboratory tests including Anti-HCV antibodies identified with enzyme-linked immunosorbent assays (ELISAs) (CAMP, Romania) and confirms these tests by viral load measurement by real time-PCR completed in laboratory of aforementioned hospital. Ethical approval to perform the research acquired from College of Medicine, University of Diyala.

DATA AND SAMPLE COLLECTION

Demographic characteristics including age, sex, body mass index (BMI) was calculated, residence, family history of HCV and comorbidities collected through direct interview with all participants in a preformed form. Clinical characteristics of patients including type of infection, treatment, almost 5 mL of venous blood obtained from each entrant, storage the blood samples at −80 °C until be used.

MOLECULAR ASSAY

DNA extraction from the genome was accomplished using a commercially available kit (GsyncTM DNA extraction kit, Geneaid, Taiwan) It follows the protocol documented at the time of its creation. The concentration of DNA extracted from the samples was measured at 260 nm/280 nm (A260/A280) using a Biospec nanospectrophotometer. Allele-specific PCR (AS-PCR) was used to examine the -574 locus (rs10515746). To achieve this, three different primers were used.

Forward 1 (F1)
5′-GGCTTATGCTGGGAGTTGCT-3′
Forward 2 (F2)
5′-GGCTTATGCTGGGAGTTGCG-3′
Reverse for the F1 and F2 (R) series.
5′-GGT GTCTGATTGCCAGTGATTC-3′[25]

The F1 and R primers were employed to amplify the T alleles, while the F2 and R primers were employed to

Table 1. Demographic features of the study population

Variables	Patients (n=50)	Controls (n=50)	p-value
Age, years			
Mean±SD	41.26±15.22	44.98±9.5	0.146
Range	9.0-73	17-62	
Gender			
Male	27(54%)	22(44%)	0.317
Female	23(46%)	28(56%)	
BMI, kg/m^2			
Mean±SD	25.94±3.56	25.26±3.6	0.225
Range	17.75-33.2	21.67-28.73	
Residence			
Rural	38(76%)	41(82%)	0.641
Urban	12(24%)	9(18%)	
Family history			
No	39(78%)	47(94%)	0.041
Yes	11(22%)	3(6%)	
Comorbidity			
No	27(54%)	36(72%)	0.062
DM	6(12%)	5(10%)	0.727
Hypertension	7(14%)	5(10%)	0.538
Renal failure	8(16%)	0(0%)	0.006
Others	4(8%)	6(12%)	0.505

SD: standard deviation, BMI: body mass index, DM: diabetes mellitus.

amplify the G alleles. Overall, the samples were subpar to AS-PCR with F1/R and F2/R, all of the expatiate fragments have a total of 539bp. Overall, the segments that were magnified were 539 bp in length, each sample had to be optimized for AS-PCR by following several steps.

As a result, the following mixture of nucleotides on reactivity expansion was generated in the 25 µl final volume, which comprised 12.5 µl of master mix (Promega, USA), 2 µl of primers (1.0 µl from the forward side and 1.0 from the reverse side) and 1.0 µl of DNA template, all of which were achieved by double distilled water. Touchdown PCR method used to amplify the target sequence, during heating applied:

A thermal cycler was used for this purpose under the following conditions; 94°C for 5 min; 94°C for 30 s; annealing temperature 60°C for 30 s; extension at 72°C for 30 s; then cycle at 72°C for 30 s for 30 s; the final extension was performed at 72°C for 7 min. For gel electrophoresis, the amplified product exposed to 1.5 g agarose in 100 ml 10x Tris-borate-EDTA (TBE) (Promega, USA) and developed with ethidium bromide to identify the product.

STATISTICAL ANALYSIS

The statistical software SPSS 25.0 (SPSS, Chicago) used to conduct the analyses. The mean and standard deviation of continuous data displayed, and the Student t-test utilized for analysis. The Chi-square test utilized to assess categorical variables, which reported as numbers and percentages. The relationship between HCV infection and rs10515746 in the TIM-3 gene's promoter region was assessed applying binary logistic regression. The odds ratio (OR) and associated 95% confidence interval (CI) were computed from this test. Any change that deemed statistically significant had a p-value of less than 0.05.

Table 2. Clinical features of the patients

Variables	Values
Type of infection	
Acute	31(62%)
Chronic	19(38%)
Treatment	
No	29(58%)
Yes	21(42%)
Viral load, IU/ml	
<200000	39(78%)
≥200000	11(22%)

RESULTS

DEMOGRAPHIC FEATURES OF THE PATIENTS

The mean age of the patients was 41.26±15.22 years (range 9.0-73 years) compared with 44.98±9.5 29 years (range 17-62 years) for controls with no significant variation. Although females were less frequent in patients than controls (46% vs. 56%), the difference was not significant. Likewise, the two groups were comparable

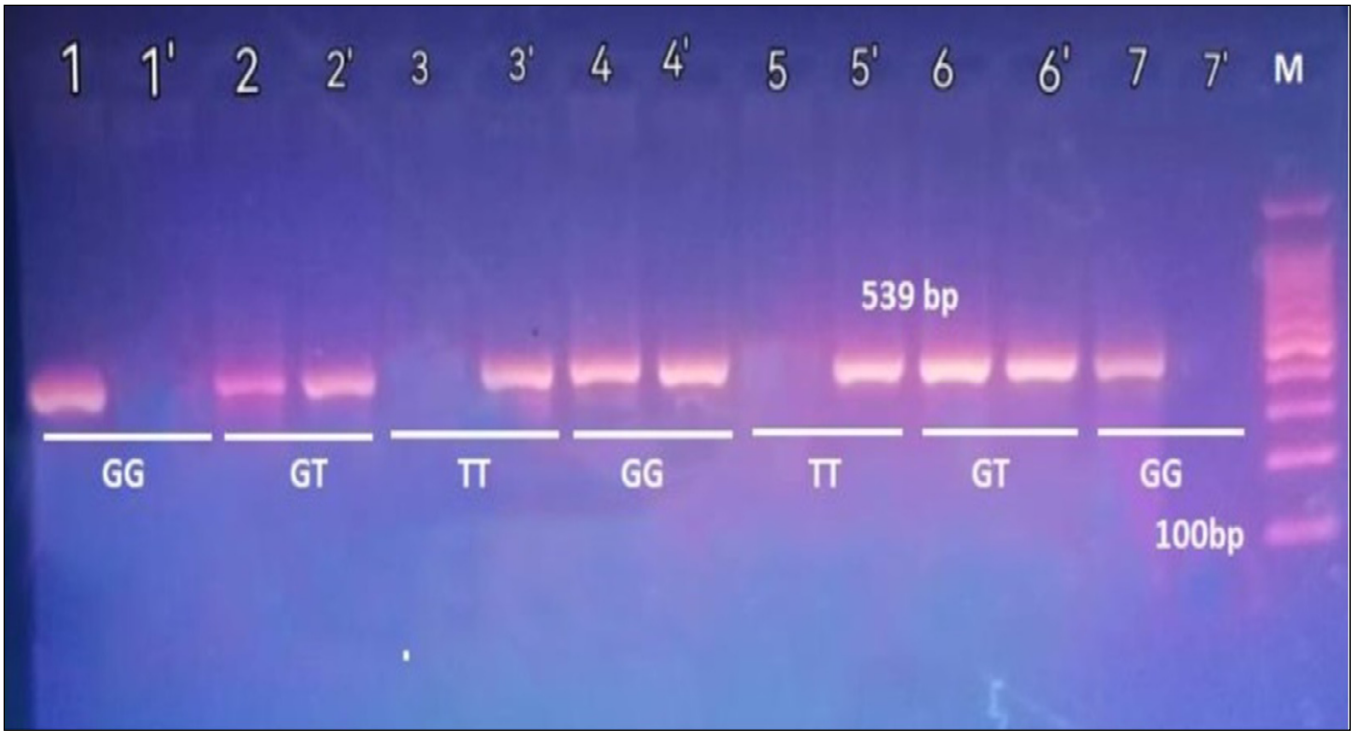

Fig. 1. Genotype patterns of rs10515746 in the promoter region of TIM-3 gene allele-PCR conceived under UV transluminator.
M: DNA marker, lanes 1, 4and 7: GG genotype, lanes 2 and 6: GT genotype, lanes 3 and 5; TT genotype.

in terms of BMI and residence with no significant variation. However, 22% of patients had a family history of HCV compared with only 6% of control with such a history, with significant difference. Furthermore, 16% of patients had renal failure comorbid disease versus none in controls with a highly significant difference, Table 1.

CLINICAL CHARACTERISTICS OF THE PATIENTS

Acute infection reported in 31 patients 62% while chronic infection found in 19 patients 38%. Only 42% of the patients were under specific treatment for HCV. Viral load was ≥200000 IU/ml in 11 patients 22% as viewed in table 2.

MOLECULAR ASSAY

In this study, the SNP rs10515746 in the promoter region of TIM-3 gene investigated in its association with HCV infection. Genotyping performed using allele specific-PCR. PCR products are shown in fig.1. The SNP appeared in three genotypes: GG, GT and TT. The distribution of these genotypes was in a good accordance with Hardy Weinberg equilibrium in patients and controls.

ASSOCIATION OF RS10515746 WITH HCV INFECTION

The GG genotype of this polymorphism was less frequent in patients than controls (14% vs. 38%) with a significant difference (p= 0.028). In contrast, the heterozygous genotype (GT) was more frequent in patients than controls (52% vs. 40%) with a important variation (OR= 4.19, 95%CI=1.32-13.47, p=0.015). Similarly, the mutant homozygous genotype (TT) was more frequent in patients than (34% vs. 22%) although the difference was not significant. In recessive model, the frequency of GT-TT genotype was significantly higher in patients than controls (86% vs. 62%) with a highly significant variation (OR= 3.76, 95%CI= 1.41-10.05, p= 0.008). At allelic level, T allele was more frequent in patients than controls (60% vs. 42%) with a significant variation (OR=2.07, 95%CI=1.18-3.64, p= 0.015) as shown in table 3.

ASSOCIATION OF DIFFERENT GENOTYPES OF RS10515746 WITH THE CLINICAL CHARACTERISTICS OF THE PATIENTS

There was no significant impact of different genotypes of rs10515746 polymorphism on the development of infection into chronic status. However, 41.81% of patients carrying TT genotype had viral load ≥200000 IU/ml compared with 15.38% GT carriers and 0% GG carries with such a viral load with a significant difference, Table 4.

DISCUSSION

Hepatitis C-virus infection is critical public health issue worldwide. A study represented the predominance of HCV in Iraq and its geographic rating is significant to

Table 3. The frequency of different genotypes and allele of rs10515746 polymorphism in HCV patients and control

Rs10515746 Polymorphism	Patients (n=50)	Controls (n=50)	P-value	OR(95%CI)
Genotypes				
GG	7(14%)	19(38%)	0.028	1.0
GT	26(52%)	20(40%)	0.015	4.19(1.32-13.27)
TT	17(34%)	11(22%)	0.723	1.19(0.45-3.09)
HWE	0.556	0.206		
Dominant model				
GG+GT	33(66%)	39(78%)	0.184	1.0
TT	17(34%)	11(22%)		1.83(0.75-4.44)
Recessive model				
GG	7(14)	19(38%)	0.008	1.0
GT+TT	43(86%)	31(62%)		3.76(1.41-10.05)
Alleles				
G	40(40%)	58(58%)	0.011	1.0
T	60(60%)	42(42%)		2.07(1.18-3.64)

Table 4. Association of different genotypes of rs10515746 with the clinical characteristics of the patients

Variables	GG (n=7)	GT(n=26)	TT(n=17)	p-value
Type of infection				
Acute	5(71.43%)	14(53.85%)	12(70.59%)	0.465
Chronic	2(28.57%)	12(46.15%)	5(29.41%)	
Viral load, IU/ml				
<200000	7(100%)	22(84.62%)	10(58.82%)	0.041
≥200000	0(0%)	4(15.38%)	7(41.81%)	

administer the increasing incidence of HCV [26]. For age, our study explained no impact variation between patients and controls. A previous study explained nearly two decades average of recent HCV infection has been declined contrast to other world range HCV epidemic, the fast evolution of this wide scale pandemic from the seventies during the nineties and the reality that it has been particularly affecting individuals in their twenties and thirties is amazing in Pakistan. By 2050, individuals older than 60 consider the age group with widest infection encumber, as the young infected cohort sensible and the incidence endure to decline HCV [27]. The history of prevalence of HCVAb and viral hepatitis in families appeared to be significant in regards to variation between groups. Previous research demonstrated the association between familial histories of viral hepatitis C and the investigation of clusters of situations within households and the documented elevated prevalence of disease in individuals with an infected family member in comparison to the general population [28-29]. Additionally, a cross sectional study of patients with HCV conducted in China demonstrated that those who had long term exposure to the disease were more likely to be infected with it [30]. A significant that a long-standing commitment to low-risk methods such as tooth brushes, accidental exposure to the infected blood of a razor, and the nail clipper could still lead to infection. However, a potential commentary that is specific to the same household could be vulnerable to the same external dangers. For instance, visiting family members to the same healthcare professional's office with a significant relationship to increase the risk of infection, such as the use of intravenous drugs, dangerous healthcare-related injections, or blood transfusions. [31]. One of most substantial outcome in our study was the significant related between renal failure and HCV infection. This result is compare with results of other local studies. Hemodialysis patients with diabetes mellitus and dental operation more expanded to hepatitis C infection [32]. Another study in 2023 considering relationship between HCV infection and transmission and dental patterns, no statistically significant difference was found between the hemodialysis patients who received a transfusion and those who did not receive any transfusion before and significantly differences showed between the hemodialysis patients who received dental treatment and did not receive any dental treatment before ($p>0.05$) [33]. This might relate to different degree of sanitation and disinfection of HD machines instruments and environmental surface to prevent nosocomial transmission [34]. Tim-3 is an effect on the immune system's regulatory functions, its location on chromosome 5q33.2 in humans is comprised of 301 amino acids that are involved in the initial structural domains, such as the cytometer domain of the phosphorylation site, the structural domain that is similar to mucin, the transmembrane area and the

signal domain. [35-37]. Two perpendicular β segments and a metal ion are involved as the ligand-binding site of Tim-3, in the immunoglobulin V domain of constant composition [38-39]. In current study, the heterozygous genotype (GT) was more frequent in patients than controls with a significant difference. Similarly, the mutant homozygous genotype (TT) was more frequent in patients. These finding specified as correlation between the -574 locus polymorphism and HCV infection in Iraq. Furthermore, patients bearing TT genotype had viral load ≥200000 IU/ml compared with 15.38% GT carriers and 0% GG carries with such a viral load with a significant difference, Table 4. Several studies have demonstrated that the immunoglobulin-and mucin domain-containing molecule-3 (Tim-3) is involved in the abnormal behavior and loss of function of CD8 + T cells in relation to hepatitis B and C. The expression of Tim-3 is increased in HBV/HCV-specific CD8 + T cells, this is of concern because of the loss of CD8 + T cells in patients with HBV/HCV infection [40-42]. Additionally, the association of Tim-3 with its ligand, galectin-9, can increase the expression of the Tim-3 protein during the stimulation of regulatory T cells (Treg), this increase in Tim-3 causes the death of helper T cells, and the decrease in Tim-3 is associated with a decrease in Th1 cells and an increase in Th2 cells. [43, 44]. Association of TIM3 SNPs with disease more predispositions in diverse autoimmune disease, such as type I diabetes and Ankylosing Spondylitis (AS) have been investigated [45]. Unfortunately, there is no previous study that addresses association between role of -574 locus genes with HCV infection. However, it can be deduced that the presence of substitution of thymine instead of guanine in -574 locus of the promoter region of TIM-3 gene could increase the transcription of this gene may be due to increase RNA polymerase to the promoter region. Upregulation of TIM-3 transcriptions with impede the T-cell activity and increase the HCV opportunity to replicate and initiate the infection, and therapeutic interventions that block or modulate TIM-3 could potentially restore effective T-cell responses and improve viral clearance. Chronic viral infections like HCV are often associated with T-cell exhaustion, partly mediated by TIM-3 overexpression. Targeting TIM-3 to reinvigorate exhausted T cells could enhance antiviral immunity.

CONCLUSIONS

T allele of rs10515746 considered a risk factor for HCV infection as well as for higher hepatitis C viral load in those patients. The association between the GT+TT genotype and higher viral loads suggests that patients with this genotype may benefit from closer monitoring and more aggressive antiviral therapies to achieve better disease control. Screening for the rs10515746 polymorphism could be useful in identifying patients at risk for higher viral loads, enabling personalized treatment approaches.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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