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Original Article

Serum and Urine Level of IP-10 in Patients with HCV infection Based on Clinical and Virological Markers

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Abstract

Background and Aims: IP-10 molecule is a new biomarker to predict response to treatment in chronic HCV infection. Also urine IP-10 has been suggested as a biomarker in other infections. But already, it has low data in urine as well as serum level of IP-10 for HCV infection. The aim of this study was to assess urine and serum level of IP-10 in patients with type 1 and 3a HCV infection.

Materials and Methods: In this case-control study, 105 patients with HCV infection were involved in three 35 people groups. Blood and urine sample of all patients was collected to determine IP-10 level. Finally, data analysis was reported using SPSS, mean statistics analysis and T test.

Results: The age mean was 41.6±11.2 ranging 21-68. Urine and serum level of IP-10 in patient group was significantly higher than control (p=0.001). Serum level of IP-10 based on HCV genotype was higher significantly in genotype 1a than 3a (p=0.001) but there was no significant difference of urine IP-10 level between genotypes 1a and 3a.

Conclusions: The results show IP-10 is a proper marker to determine the prognosis of fibrosis and progress liver inflammation and on the other hand, the prediction of response to treatment differs in various genotypes of HCV infection.

Keywords: Hepatitis C, IP-10, serum and urine, genotype 3a and 1a

Introduction

Hepatitis C virus (HCV) is an etiologic agent of liver diseases affecting about 3% of people worldwide (1). Standard therapy strategy is PEG-IFN and ribavirin resulting in chronic taking treatment in most people differing in response to treatment in various genotypes (2-4). Several viral and host factors including immune cytokines and chemokines are affecting on the HCV infection outcome and consequence of infection is determined by virus-host immune response interaction (5). Therefore, the features and response of host immune in different stages of disease and various types of virus genotypes responding to therapy differently is important (6). Several factors including age, race, viral load, virus genotype, Interleukin 28 (IL-28) gene polymorphism, NS5b genetic variation and host immunity can affect the HCV infection outcome in people hence; it is possible to use prognostic markers (7-9). Recent studies have used several prognostic immunogenetic markers such as IL-28 gene polymorphism (rs12979860) related to deletion resulted from therapy or immune response

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(10). Other factors involve chemokines and cytokines that their abnormal level can affect the response to treatment (11). For example, IL-18, IL-12 cytokines and IL-10 affect the response to therapy of genotype 1 (12). Other chemokine biomarker is IP-10 (CXCL10), a biomarker related to fibrosis (13). This small protein inducing IFN-gamma is secreted from monocytes, lymphocytes and hepatocytes in response to IFN-gamma (14). Different studies have shown that serum and tissue level of this chemokine is elevated in various disease including liver, autoimmune and cryoglobulinemia disorders (15, 16). This protein has two forms that entire form plays role in T-lymphocyte migration whereas defective form to result in defect to recruit T-lymphocytes to liver in HCV infection is antagonist of entire form (17, 18). The latter also play an important role in initiation and progression of liver fibrosis by recruiting active CXCR3-T cell to necrosis region of liver (19). It has been already shown that this chemokine is associated with liver inflammation, viral hepatitis and fibrosis. For instance, elevated level of IP-10 results in decreased sensitivity of IFN to virus particle and as a result lead to no responding to IFN and ribavirin in Patients with HCV infection (20). The studies showing elevated level of IP-10 in patients with HCV infection are associated with increased inflammation and fibrosis (21). In some studies, reduced level of IP-10 before treatment of in HCV-infected patients has led to finally no responding to IFN and ribavirin. Also defective form of IP-10 has elevated in these patients in opposite of entire form (22, 23). Other cases of serum and urine IP-10 level increase in patients with Mycobacterium tuberculosis are determined (24). Considering the importance of IP-10 level in infections causing disorder liver especially HCV infection, therefore determining the level of this chemokine in fluids such as urine and serum in various virus genotypes varying in term of disease intensity is considerably useful to evaluate disease prognosis and response to treatment. The aim of this study was to determine serum and urine level of IP-10 in patients with HCV infection based on clinical and virological markers.

Methods

Patients and study design. This case-control study was performed by recruitment of 105 patients with chronic HCV infection referring to Shahid Sadoughi Hospital in Yazd between 2014-2015 years. All studied patients had level of viremia and diagnosis of chronic HCV infection based on positive HCV antibody was confirmed by third generation Kit and positive RT-PCR. The people participating in this study were categorized to three groups based on liver ALT enzyme level: The first, the patients with HCV infection and high level of ALT, the second, the patients with HCV infection and more than five years normal level of ALT and the third, the people with undetectable level of viremia and normal ALT level entitled as recovered people. The group having viremia was categorized in two groups: the one lacking taking treatment and another patient with no responding to standard therapy (PEG-IFN and Ribavirin). The recovered group had no viral RNA after 6-24 months since end of therapy. All people were negative in term of HIV antibody and HBS Antigen in onset of treatment. 35 people were as control group lacking liver disorders resulted from viral hepatitis types and were also HCV antibody negative. Clinical and demographic features of both two groups are shown in Table 1.

Virological and biochemical tests. 6cc blood and 1cc urine were collected from every patient and these samples were centrifuged at 3500 rpm separately so that serum and urine supernatant were taken and stored at -20 Celsius freezer. Plasma levels of viral RNA in people and virus genotypes were determined using the approaches described previously (25). Serum and urine level of IP-10 were measured by R & D system ELISA kit.

Data analysis. All these data were recorded in previously designed form and analyzed by statistic software SPSS 20. Chi-squared test for descriptive and demographic information and T-test, Spearman's correlation coefficient and Mann–Whitney test to compare among groups

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were used. The level of statistical significance was considered as 0.05.

Results

Patients. 105 patients with hepatitis (35 recovered people, 35 people with high level of enzyme and 35 people with normal level enzyme) and 35 people as control group were entered in this study being 96 people male and 44 people female. The age mean of people was 41.6±11.2 years old ranging 21-68. Information based on three patient groups and genotype types are shown in table 1. Difference in genotype distribution among patient groups was not significant.

Serum and urine level of IP-10 in two various genotypes of HCV. Serum and urine level of IP-10 in two groups of genotype 1a and 3a were determined. The mean of serum and urine level of IP-10 is shown in Table 2. Serum level of IP-10 in patients with genotype 1a was upper than patients with genotype 3a and this difference was significant (p=0.001).

Comparison of serum and urine level of IP-10 in three groups with HCV infection based on virus genotype of the healthy group. Serum level of IP-10 in genotype 1a was significantly upper than 3a but the difference of urine level of IP-10 between genotype 1a and 3a was not significant. Serum and urine levels of IP-10 based on genotype are shown in Table 3.

Comparison of serum and urine levels of IP-0 between patient and healthy groups. Serum and urine levels of IP-10 were compared between patient and control groups. In patient group, serum and urine levels of IP 10 were significantly upper than the control group. These results are shown in Table 4.

Serum and urine levels of IP-10 among groups with HCV infection. Serum and urine levels of IP-10 in three groups with HCV infection (with high and normal level of liver enzyme and recovered people) were determined (Table 5). Serum level of IP-10 was upper than urine one in all patients. Serum and urine levels of IP-10 in patient group with high level of liver enzyme was significantly upper than one in patients with normal level of liver enzyme (p=0.001). Serum and urine levels of IP-10 in patient groups with high level of liver enzyme were significantly upper than recovered people. Serum and urine levels of IP-10 also in patient groups with normal level of liver

Table 1: Information of patients with HCV infection and control.

Variable	Studied groups	Virus genotype frequency HCV (%)			P value
		3a	1a	Total	
Studied group	HCV infection with high level of liver enzyme	22(62.9)	13(37.1)	35(100)	0.687
	HCV infection with normal level of liver enzyme	24(68.6)	11(31.4)	35(100)	
	Recovered HCV infection (Negative PCR)	19(54.3)	16(45.7)	35(100)	
	Healthy subjects	21(60)	14(40)	35(100)	
	Total	86(61.4)	54(38.6)	140(100)	
Sex	Male	54(56.3)	42(43.8)	96(100)	0.092
	Female	32(72.7)	12(27.3)	44(100)	
Age	Less than 30 years old	45(63.4)	26(36.6)	71(100)	0.103
	30-39 years old	37(64.9)	20(35.1)	57(100)	
	40-49 years old	4(44.4)	5(55.6)	9(100)	
	More than 50 years old	0(0)	3(100)	3(100)	

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Table 2: Serum and urine level of IP-10 in tow genotypic groups.

Marker level		Genotype		P value
		1a	3a	
UIP10*	Frequency	54	86	0.872
	Mean and Standard Deviation	58.85 ± 38.29	59.92 ± 38.08	
SIP10*	Frequency	54	86	
	Mean and Standard Deviation	438.94 ± 447.8	243.36 ± 243.8	0.001
	Mean and Standard Deviation	40.05 ± 15.17	41.86 ± 17.42	

UIP10*= Urine IP-10, SIP*-10= Serum IP-10

enzyme was upper than recovered people significantly (p=0.005).

Discussion

Interferon stimulated protein 10 (IP-10) is produced by various cells that one of the most important of them is hepatocyte. Because of high level of IP-10 in a large population with chronic HCV infection and also higher level of IP-10 in patients lacking sustained virologic response after therapy in comparison with the people clearing virus, IP-10 is considered as an appropriate predicting criteria in prior to therapy in patients with HCV infection. Therefore, defining the prognosis of SVR acquiring in acute infection or acquiring SVR after therapy is considerably important. In

Table 3: Comparison of serum and urine levels of IP-10 in three groups with HCV infection based on virus genotype of healthy group.

Genotype	Patients groups		SIP10*	UIP10*	ALT
3a	Hepatitis C with high level of liver enzyme	Frequency	22	22	22
		Mean	601.5 ± 217.7	36.2 ± 108	67.64 ± 14.48
	Hepatitis C with normal level of liver enzyme	Frequency	24	24	24
		Mean	176.5 ± 57.65	46.24 ± 11.89	31.87 ± 3.88
	Recovered Hepatitis C (Negative PCR)	Frequency	19	19	19
		Mean	111.8 ± 42.06	60.2 ± 21.7	37.72 ± 4.24
1a	Hepatitis C with high level of liver enzyme	Frequency	13	13	13
		Mean	1111.8 ± 319.7	111.9 ± 34.7	62.3 ± 14.9
	Hepatitis C with normal level of liver enzyme	Frequency	11	11	11
		Mean	450.7 ± 235.9	51.03 ± 13.07	33.3 ± 4
	Recovered Hepatitis C (Negative PCR)	Frequency	16	16	16
		Mean	192.5 ± 78.3	51.5 ± 20.2	35.2 ± 5.07
	P value		0.001	0.872	0.532

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Table 4: Comparison of serum and urine levels of IP-10 between patient and control group.

Marker level		Patient group	Control group	P value
UIP10	Mean	71.1 ± 37	24.5 ± 6.5	0.001
SIP10	Mean	401.4 ± 367.7	70.8 ± 24.2	0.001

Table 5: Serum and urine levels of IP-10 in three groups with HCV infection.

Patients groups		SIP10*	UIP10*
Hepatitis C with high level of liver enzyme	**Mean**	793 ± 359.7	109 ± 35.2
Hepatitis C with normal level of liver enzyme	**Mean**	262.7 ± 187.6	47.7 ± 12.3
Recovered hepatitis C (Negative PCR)	**Mean**	148.6 ± 72.8	56.2 ± 22.3
	P value	0.001	0.005

other hand, it has been shown IP-10 level in patients with chronic HCV infection is higher than normal people and even people with chronic HBV. These results show IP-10 plays a significant role in HCV infection pathogenesis. Several studies also have shown IP-10 correlate with liver inflammation and fibrosis progression severity and possibly have an important role in predicting liver disease progression. Therefore, in recent study, serum and urine levels of IP-10 in patients with HCV infection, recovered people and healthy people with different genotypes were determined.

Serum and urine levels of IP-10 in people with HCV infection was upper than healthy people and IP-10 level in serum was upper than urine one according to previous studies (26, 27). Consistent with this, in one study done by Petrone in 2014 in Italy, it was shown serum level of IP-10 being higher than urine level and also serum and urine levels of IP-10 in people with HCV infection was significantly higher than healthy (28). Also in Johansson study in 2015 in USA, it was shown that serum level of IP-10 was higher than healthy people (29). Our result based on higher level of IP-10 in patients with HCV infection in comparison with healthy people also has agreed to Chan study in 2011 (30). It has been shown that IP-10 level correlate with HCV-induced fibrosis being as an HCV related liver disease activity criteria (31). Therefore IP-10 level is considered as negative predicting marker of therapy efficacy. To highlight the role of IP-10 in HCV infection pathogenesis

Serum level of IP-10 in patient group with high level of liver enzyme, was upper than people with normal level of liver enzyme and if the fibrosis level was considered, we had found stronger correlation between IP-10 and fibrosis level. These results were according to Petron study showing the correlation of IP-10 level with fibrosis as well as liver cytolysis (28). Reiberger showed also in 2008 in Australia that IP-10 level correlate with liver enzyme level such that serum level of IP-10 in patient group with high level enzyme was higher than people with normal level of liver enzyme in consistent with our study (32). Hence, these results show that serum level of IP-10 can be an appropriate predicting of response to therapy and an HCV related fibrosis marker in agreement with previous studies (30)

Our study also showed that serum and urine levels of IP-10 in patient group with high level of liver enzyme were higher recovered people acquiring SVR. Serum and urine levels of IP-10 also in patient group with normal level of liver enzyme were higher than recovered people significantly. This result also was seen

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in Petrone study. In other hand, Felds study in Australia showed no relationship between IP-10 level and rapid response to therapy while in our study IP-10 level in recovered people with SVR was lower than patients with HCV infection (33). These result diversities among various studies may be based on the other host agents also could affect in response to therapy sequel. One of these agents is interleukin-28 gene polymorphism predicted more also by IP-10 (34). The role of IL-28 has been shown as a predicting marker of rapid and definitive response to therapy (35)

This study also determined IP-10 level based on various HCV genotypes to understand the role of IP-10 in each one of them. Serum level of IP-10 in patients with genotype 1a was upper than one in genotype 3a significantly but the urine level difference of IP-10 between genotypes 1a and 3a was not significant. In other studies, IP-10 level in patients with various HCV genotypes and their association with acquiring response to therapy and fibrosis have been considered. In Carlins study in 2015, the role of IP-10 in predicting the response to therapy in HCV infection with genotype 3a was indicated, such that in these people having response to therapy, IP-10 level was upper (36). IP-10 level was also upper in people with genotype 2 having response to therapy than the people lacking response to therapy (37). So in recent studies, there is a reverse correlation between IP-10 level and the response to therapy (38). This suggest that people with lower level of IP-10 may produce more suitable response to therapy because interferon-based therapy increases the stimulation of a large network of interferon stimulated genes, all together inducing an appropriate response and virus clearance. This difference between IP-10 and prediction of response to therapy therefore require further studies with various genotypes.

It should be mentioned that serum level of IP-10 in patients with HCV genotype 1a and high or normal level of liver enzyme was upper than the same group with genotype 3a. This point indicates genotype 1a is more effective in inducing IP-10 in consistent with SVR and RVR acquisition rate in patients with HCV genotype 1a is lesser than 3a. Serum level of IP-10 factor therefore can be accounted a proper negative predicting no leading to sustained virologic response in genotype 1a, however, the other host factors such as IL-28 also can affect in this genotype according to polymorphism type of IL-28 as previous studies indicated (39). In Reibergers study also IP-10 level in people having SVR was lower than those lacking SVR in agreement with our study (32). In other study in 2013, it was shown that IP-10 level with SVR was stronger in genotype 1a requiring more samples. This result was in agreement with our study, such that IP-10 level in genotype 1a was upper than genotype 3a in turn indicating low rate of response to therapy in genotype 1a may be related to higher level of IP-10 (33).

Serum and urinary IP-10 in Iran and the world was higher than the control group. As well as IP-10 in HCV patients with different conditions (high and normal liver enzymes, treated with SVR), the results showed that serum and urinary IP-10 in patients with high liver enzymes, higher than the enzyme normal liver and had been treated. The serum IP-10 in patients with genotype 1a patients with genotype 3a is greater than the difference between genotypes 1a and 3a Urinary IP-10 levels are not significant and did not care. The results suggest that IP-10 is a prognostic marker for inflammation, fibrosis and liver disease progression and predict response to treatment will be determined on the other hand.

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