The Role of Inflammatory Cytokines in Hepatitis C Hemodialysis and Non-uremic patients

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Abstract: There is a strong relationship between hepatitis C virus (HCV) and hemodialysis (HD). Therefore in end-stage renal disease (ESRD) patients, HCV remains a significant cause of morbidity and mortality.The aim of this study was to compare the biochemical characteristics of hepatitis C virus (HCV) in hemodialysis patients and in those with normal renal function. Sixty two HCV infected patients were selected for the study (Group I: included 28 with ESRD waiting for HD treatment and group II include 34 HCV infected patients with normal renal function, defined by creatinine<1 mg/dl) as well as 20 apparently healthy volunteers with matched age and sex with the patient group. They were subjected to full history and clinical examination, abdominal ultrasonogrphy. Laboratory investigations including: Liver and kidney function tests, complete blood count, hepatitis markers for HBV and HCV, HCV-RNA by quantitative PCR, C-reactive protein, IL-6 and hepatocyte growth factor (HGF). All investigations were done once for HCV patient (group II) and control group, the same investigations were done for ESRD (group I) three times (at start of the study, 6 and 12 months later after regular HD). The results of the study showed that, a significant increased in the levels of HGF, IL-6 and CRP among both group I and group II as compared to control group, while no significant difference was detected in their levels as comparing among group I and group II patients, while as regard viral load, no significant difference was detected between both patient groups. After 6 months of regular HD, the levels of ALT, AST, Alkaline phosphatase, total bilirubin, S. urea, S. creatinine, uric acid and S. potassium were significantly decreased as compared to before HD levels, and more decrease in their levels were detected after one year of regular HD. The S. albumin and creatinine clearance levels were significantly improved after HD. Moreover, HGF level was significantly increased in group I after 6 months of regular HD, and more significantly increased after one year of regular HD, while, the viral load was significantly decreased. In spite of decreasing levels of IL-6 and CRP, their levels were not reached statistical difference. The levels of HGF was significantly correlated to ALT, AST, total bilirubin, serum albumin, S. urea, S. creatinine, uric acid and viral load in group I patients. While IL-6 was only correlated to ALT and CRP was correlated to ALT and AST levels. In conclusion: The increasing serum levels of HGF in HCV infected patients regardless renal function and increasing its level after regular HD with improvement of liver and kidney suggesting its role as a protective against liver damage. Therefore, HGF agonist may be used to in these group of patients to ameliorate liver damage and disease progression.

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1. Introduction

Hepatitis C is the main cause of chronic liver disease in patients with end-stage renal disease (ESRD) (Fabrizi*et al.,* 2002). The natural history of chronic liver disease caused by HCV in hemodialysis (HD) patients remains unknown (Gane&Pilmore, 2002, Fabrizi*et al.,* 2004). HCV infection increases mortality rates in uremic patients, and cirrhosis and other liver-related deaths are more frequent in HCV-infected dialysis patients than in those without the virus (Nakayama *et al.,* 2000). Deaths in HCV infected dialysis patients were 41% higher than in HCV-negative dialysis patients (Martin *et al.,* 2000).

C-reactive protein (CRP) belongs to pentaraxin family (Sezer*et al.,* 2001). It is produced by the liverin response to several inflammatory mediators, the most important of which is interleukin-6 (IL-6) (Espinosa *et al.,* 2001). CRP is a sensitive but nonspecific inflammatory marker (Perez *et al.,* 2006). During inflammation, levels of CRP can be increased up to 1000 folds (Lemos*et al.,* 2006), and as soon as inflammation subsides it comes to normal levels (Alric*et al.,* 2002). Another study reported that, HD patients who had CRP levels of more than 10 mg/L showed 3.5 times higher mortality rate than patients with normal levels of CRP (Kamar*et al.,* 2005).

Interleukin 6 (IL-6) is a cytokine of hematopoetin family (Sezer*et al.,* 2006) which is synthesized by mononuclear phagocytes, vascular endothelial cells, and fibroblasts in response to IL-

1(Fontaine *et al.,* 2001) which is an inflammatory marker, and its level increases in HDs patients (Mizuno *et al.,* 2002; Fabrizi*et al.,* 2003). It is well documented that the immune system of HCV-infected individuals is suppressed, and they have increased tendency of developing diabetes mellitus and tuberculosis and other chronic diseases (Afzal*et al.,* 2011).

Human hepatocyte growth factor (HGF) is a pleiotropic cytokine involved in emberyonic development and repair, regeneration and protection of various organ from injuries. It exhibits mitotic and anti-apoptotic activities, and enhances motility of different cell types including hepatocytes, renal epithelial and proximal tubule cells, and vascular endothelial cells. Following tissue damage, HGF is expressed in mesenchymal cells (e.g. fibroblasts, mononuclear cells, megakaryocytes) (Vargras*et al.,* 2000).

HGF has been identified in the serum of patients with fulminant hepatitis and is known to enhance the proliferation of hepatocytes in rats (Higashio*et al.,* 1990). HGF appears to be a multi-functional factor with diverse physiological activities (Matsumoto &Nakamur, 2003). Therefore, considerable attention has been focused on the relationship between HGF and the onset of hepatitis, the transition from acute to chronic hepatitis (CH), and the occurrence of hepatocellular carcinoma (HCC) (Ishiki*et al.,* 1992; Shimoda*et al.,* 1992).

Whether the liver disease caused by HCV shows a different clinical course in HD patients and in patients with normal renal function is still controversial. Barril (2000) reported that progression time to cirrhosis can be much shorter in HCV-infected HD patients than in patients with normal renal function. However, other studies suggest that HCV-infected HD patients present a lower degree of inflammatory activity and a lower stage of liver fibrosis compared with HCV-infected patients with normal renal function (Cotler*et al.,* 2002; Luzar*et al.,* 2003).

Recent evidence supports the notion that the progression of HCV-related liver disease is probably slower in the dialysis population than in non-uremic patients despite the immune compromise conferred from chronic uraemia; numerous mechanisms have been mentioned to explain it. It appears that the haemodialysis procedure per se reduces the HCV viral load, and the mechanisms by which this phenomenon occurs remain largely speculative (Fabrizi*et al.,*2012). Indeed, the effects of chronic uremia and HD on HCV-related liver disease and on disease progression in HCV-infected patients with ESRD remain unknown.

Aim of the study:

The current study aimed to investigate the impact of chronic renal failure and HD on short term progression of chronic hepatitis C, and to find the possible role of cytokine namely HGF and IL-6 in clinical, biochemical and virologic findings in HCV-infected patients with normal renal function and ESRD receiving HD.

2. Patients and Methods:

This study was conducted on 62 HCV patients (Group I: include 28 with ESRD waiting for HD treatment and group II include 34 HCV infected patients with normal renal function, defined by creatinine<1 mg/dl). Patients were attending National Liver Institute, Menoufiya University and Nephrology & Dialysis unit of Internal Medicine Department, Al-Zahraa University hospital - Al Azhar University. All patients underwent clinical, biochemical, serologic, virologic, and sonographic studies.

Exclusion criteria for both groups were: coinfection with hepatitis B virus or HIV, current use of steroids, interferon, or ribavirin; other liver diseases; intravenous drug use; diabetes mellitus. myocardial infarction, moderate to severe congestive heart failure, chronic inflammatory diseases, neoplastic diseases, patients under treatment with corticosteroids, anticoagulants or non-steroidal anti-inflammatory.

The control group comprised of 20 apparently healthy volunteers with matched age and sex with the patient group.

The followings were done:

- Full history taking, thorough clinical examination.
- Abdominal ultrasonogrphy.
- Liver and kidney function tests including: ALT, AST, serum albumin, total bilirubin, serum urea, serum and urine cratinine, serum uric acid were done on Hitachi 911 (Roche-Germany). Creatinine clearance was calculated as formula of :

$$\frac{\text{Urine Creatinine (mg dL) x 24 hs Urine Volume (ml)}}{\text{Serum Creatinine (mg/dL) x 1440}}$$

- Hepatitis markers (HBsAg, anti-HBc and HCV antibody) were done by Elecesys 2010 autoanalyzer (Roche- Diagnostic, Branchburg, NJ- Germany).
- Quantitative PCR HCV-RNA levels were analyzed by reverse transcriptase polymerase chain reaction (RT-PCR) using a commercial kit (Roche Diagnostic, Branchburg, NJ) according to the manufacturer's instructions.

- C-reactive protein level was done by Dimension X Pand Plus autoanalyzer (Siemens-Diagnostic, Germany). While IL-6 was determined by an enzyme-linked immunosorbent assay technique, kit that was supplied from BIOSOURCE Int, Inc.
- Estimation of serum Hepatocyte Growth Factor (HGF): The kit supplied by R&D System (Europe, Ltd, United kingdom). This assay employs the quantitative sandwich enzyme immunoassay technique. HGF monoclonal antibody had been coated onto the microtiter plate. Standard and samples were pipetted into the wells and any HGF present was bounded by the immobilized antibody. After any unbound proteins had been washed away, an enzyme linked polyclonal antibody specific for HGF was added to the wells to sandwich the HGF immobilized during the first incubation. Following a wash to remove any unbound antibody- enzyme reagent, a substrate solution was added to the wells and the colour was developed in proportion to the amount of HGF bound in the initial step. The colour development was stopped and the intensity of the colour was measured. A curve was prepared by plotting the optical density versus the concentration of HGF in the standard wells. Hence, the concentration of the HGF in the unknown samples could be determined by comparing the optical density of the samples to that of the standard curve.

All investigations were done once for HCV patients with normal renal function (group I) and control group, the same investigations were done for ESRD patients (group II) three times (before start of HD, 6 and 12 months later after regular HD).

Statistical analysis

The collected data was organized tabulated and statistically analyzed. For the quantitative data, the mean and standard deviation were calculated. The difference between two means was statistically analyzed using the students (t) test. Correlation study was done by person correlation (r). Significance was adopted at $p< 0.05$ for interpretation of results of tests.

3. Results:

Table (1) shows demographic data of the patient groups. Table (2) shows a significant increase in the levels of ALT, AST, Alkaline phosphatase, total bilirubin, S. urea, S. creatinine, uric acid and S. potassium in group I compared to control group. While, S. albumin, S. sodium and creatinine clearance were significantly decreased. As comparing between group I and group II a significant increase was detected in the levels of S. urea, S. creatinine, uric acid, S. potassium in group I, while creatinine clearance was significantly decreased.

The levels of HGF, IL-6 and CRP were significantly increased in group I (ESRD) and group II as compared to control group, while no significant difference was detected in their levels as comparing between both patient groups. As regard viral load, there was no significant difference between both patient groups (Table 3)

In ESRD group (group I), after 6 months of regular HD, the levels of ALT, AST, Alkaline phosphatase, total bilirubin, S. urea, S. creatinine, uric acid and S. potassium were significantly decreased as compared to before HD levels, and more decrease in their levels was detected after one year of regular HD. While, S. albumin and creatinine clearance were significantly increased (Table 4).

The levels of HGF is significantly increased in Group I patients after 6 months of regular HD, and more significantly increased after one year of regular HD. Although, serum levels of IL-6 and CRP were decreased after dialysis, the difference was not reached the statistical difference (Figure 1 &Table 5). HCV viral load was significantly decreased after 6 months of regular HD, and show more decrease after one year of regular HD (Figure 2&Table 5)

The levels of HGF was significantly correlated to ALT, AST, total bilirubin, serum albumin, S. urea, S. creatinine, uric acid and viral load in group I patients. While IL-6 was only correlated to ALT and CRP was correlated to ALT and AST levels (Table 6)

Table (1) Demographic data of the patients groups

Parameters	Group I (No=28)		Group II (No=34)	
	No	%	No	%
Gender:				
Male	19	67.86%	23	67.65%
Female	9	32.15%	11	32.35%
Aetiology of HCV:				
Surgical procedures	12	42.86%	14	41.17%
Needle stick injuries	2	7.14%	5	14.70%
Drug abuse	3	10.71%	2	5.88%
Unknown causes	11	39.28%	13	38.25%
Aetiology of ESRD:				
Hypertension	4	14.29%	------	------
Diabetes	2	7.14%		
Hypertension & Diabetes	7	25%		
Glomerulonephritis	3	10.71%		
Other nephropathy	4	14.28%		
Mixed causes	6	21.43%		
Unknown causes	2	7.14%		

Table (2) Comparison between studied groups as regard laboratory data

Parameters	**Group I (No=28)** Mean± SD	**Group II (No=34)** Mean± SD	**Controls (No=20)** Mean± SD	***P*-value**
Age (years)	52.4±9.21	49.17±6.67	46.3±4.12	>0.05
ALT (U/L)	87.4±26.1	69.85±23.16	21.2±7.14	<0.01
AST (U/L)	67.4±20.15	57.23±19.54	26.7±5.27	<0.05
Alk. Ph. (U/L)	71.12±4.23	60.17±8.26	41.2±11.23	<0.05
T. bilirubin (mg/dl)	1.56±0.45	1.34±0.38	0.78±0.15	<0.05
Albumin (gm/dl)	3.51±0.37	3.91±0.46	4.02±0.31	<0.05
S. Urea (mg/dl)	179.6±34.7	35.2±6.21	32.1±5. 24	<0.001
S. Creatinine (mg/dl)	8.36±1.32	1.12±0.12	0.69±0.21	<0.001
Uric acid (mg/dl)	9.45±1.27	5.72±0.41	4.84±0.59	<0.01
Serum Na + (mEq/dL)	130.2±4.05	135.7±3.84	133.1±2.97	<0.05
Serum K+ (mEq/dL)	6.11±0.72	4.61±0.37	4.24±0.61	<0.01
Creatinine clearance (ml/min)	21.38±5.16	112.06±3.24	126.08±4.71	<0.01

P<0.05, <0.01&<0.001 are statistically significant, *p*>0.05 is statistically non significant

Table (3) Comparison between studied groups as regard inflammatory markers and viral load

Parameters	**Group I (No=28)** Mean± SD	**Group II (No=34)** Mean± SD	**Controls (No=20)** Mean± SD	***P*-value**
HGF (pg/ml)	1865.2±156.5	1730.8±153.2	168.3±43.7	<0.001
IL-6 (pg/ml)	1365±342	1241±276	642±94	<0.01
CRP (mg/L)	11.63±5.71	10.72±3.57	0.64±0.15	<0.001
Viral load (x1000 copies/ml)	129.15±57.63	134.28±62.17	----------	>0.05

P<0.05, <0.01&<0.001 are statistically significant, *p*>0.05 is statistically non significant

Table (4) Comparison of laboratory data of ESRD patients (Group I), before start HD and among one year of regular HD

Parameters	**Before HD** Mean± SD	**After 6 months** Mean± SD	**After one year** Mean± SD	***P*-value**
ALT (U/L)	87.4±26.1	58.4±9.37	32.23±6.74	<0.01
AST (U/L)	67.4±20.15	45.62±10.95	35.27±4.35	<0.01
Alk. Ph. (U/L)	71.12±4.23	57.60±7.84	34.5±9.56	<0.05
T. bilirubin (mg/dl)	1.56±0.45	1.04±0.43	0.97±0.11	<0.01
Albumin (gm/dl)	3.51±0.37	4.12±0.31	4.98±0.42	<0.05
S. Urea (mg/dl)	179.6±34.7	97.3±10.61	83.1±9.35	<0.01
S. Creatinine (mg/dl)	8.36±1.32	5.72±0.81	4.33±0.71	<0.05
Uric acid (mg/dl)	9.45±1.27	5.11±0.36	5.02±0.65	<0.05
Serum Na + (mEq/dL)	130.2±4.05	137.3±4.13	133.9±2.85	>0.05
Serum K+ (mEq/dL)	6.11±0.72	5.74±0.43	4.01±0.56	<0.01
Creatinine clearance (ml/min)	21.38±5.16	67.43±9.53	79.52±3.62	<0.01

P<0.05, <0.01 &<0.001 are statistically significant, *p*>0.05 is statistically non significant

Table (5) Comparison of ESRD patients (Group I), before start HD and among one year of regular HD as regard inflammatory markers and viral load

Parameters	**ESRD before HD** Mean± SD	**After 6 months** Mean± SD	**After one year** Mean± SD	***P*-value**
HGF (pg/ml)	1865.2±156.5	2392.8±144.3	2784.3±123.7	<0.01
IL-6 (pg/ml)	1365.4±342.2	1241.3±276.5	1236.1±198.2	>0.05
CRP (mg/L)	11.63±5.71	10.72±3.57	9.843±2.65	>0.05
Viral load (x1000 copies/ml)	129.15±57.63	83.43±36.51	68.11±27.32	<0.001

P<0.05, <0.01 &<0.001 are statistically significant, *p*>0.05 is statistically non significant

Table (6) Correlation HGF, IL-6, CRP and some studied parameters in ESRD group (before start of HD)

Parameters	HGF		IL-6		CRP	
	r	*P*	r	*P*	r	*P*
ALT	0.311	<0.05	0.012	<0.05	0.023	<0.05
AST	0.298	<0.05	0.179	>0.05	0.304	<0.05
Alkaline phos.	0.124	>0.05	0.201	>0.05	0.057	>0.05
Total bilirubin	0.396	<0.05	0.165	>0.05	0.132	>0.05
Albumin	0.437	<0.01	0.063	>0.05	0.215	>0.05
S. Urea	0.466	<0.01	0.129	>0.05	0.041	>0.05
S. Creatinine	0.493	<0.01	0.203	>0.05	0.206	>0.05
Uric acid	0.475	<0.01	0.025	>0.05	0.107	>0.05
Viral load	0.210	>0.05	0.114	>0.05	0.172	>0.05

P<0.05 &<0.01 are statistically significant, *P*>0.05 is statistically non significant

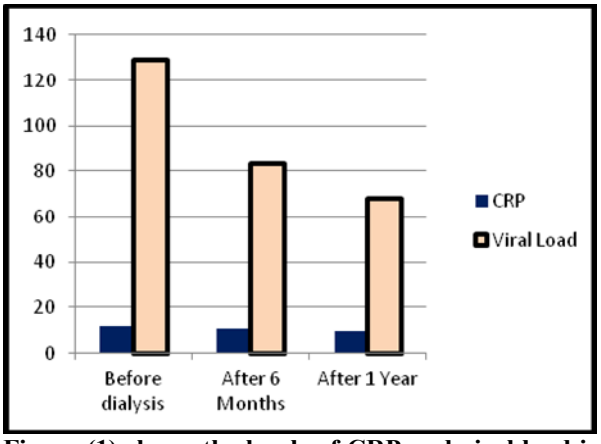

Figure (1) shows the levels of CRP and viral load in ESRD before and after HD.

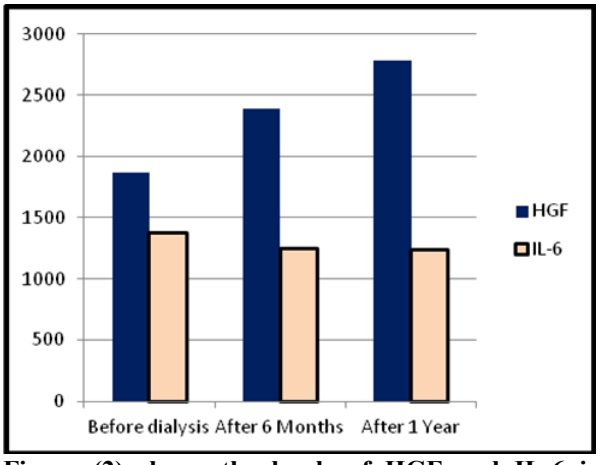

Figure (2) shows the levels of HGF and IL-6 in ESRD before and after HD.

4. Discussion:

Hepatitis C virus (HCV) remains the most common cause of liver damage in patients with chronic kidney disease including patients on long-term dialysis (Gane&Pilmore, 2002). The natural history of HCV infection in patients with chronic kidney disease is not fully elucidated despite the adverse effect of HCV infection on survival in patients receiving long-term dialysis. Impairment of quality of life due to HCV has also been suggested to explain the diminished survival in this setting (Fabrizi*et al.,* 2012).

In this study, a significant increase in the levels of serum urea, creatinine, S. potassium, and uric acid and decrease in the levels of S. albumin, S. sodium and creatinine clearance in HCV infected patients with ESRD before HD in comparison to normouremic HCV infected patients and healthy controls. After HD their levels were significantly improved compared to before HD levels, indicating that good clearance of urea creatinine and uric acid and other toxic molecules by HD.

Our results showed that HCV-infected patients on HD had less impaired liver functions (ALT, AST, total bilirubin) and lower viral load, and less inflammatory cytokines (IL-6 and CRP) after 6 months and one year of regular HD. That results strongly suggest that chronic hepatitis C is less aggressive in HD patients than in nonuremic patients. Lopes *et al.* (2009) and Afzal*et al.*(2011) reported the same finding. The high levels of CRP and IL-6 in HCV-positive patients which might be due to hepatocellular injury could affect CRP production.

Sezer*et al.* (2001) have reported that the longer the time on HD, the lower the degree of liver inflammation. Sterling *et al.* (1999) have also reported that inflammatory activity and fibrosis were less intense in HD patients, although these differences were restricted to patients with elevated ALT as observed in our patients. In addition, HD patients have been described to have less advanced fibrosis and a lower degree of liver inflammation when compared with chronic renal failure patients not requiring dialysis (Martin *et al.*, 2000; Lemos*et al.*, 2007) or to patients who underwent renal transplantation (Alric*et al.*, 2002; Kamar*et al.*, 2005; Perez *et al.*, 2006).

The mechanism by which uremia and HD may exert a protective effect on HCV liver inflammation remains unknown. The dysfunction of B and T cells (Yoon *et al.*, 2006), elevated levels of hepatocyte

growth factor (Rampino*et al.*, 1999), and changes in the antioxidant system in the serum of HD patients (Sezer*et al.*, 2006) are factors that may be associated with less liver inflammation. Regardless of the reasons, the less liver inflammation in HD patients may contribute to a delay in the progression of liver disease because the rate of inflammatory activity is associated with fibrosis progression (Fontaine *et al.*, 2001).

Afzal*et al.* (2011) observed 56% of HD patients had a high level of CRP, while Panichi and co-workers (2000) found that 47% of HD patients had high CRP levels, and in Park *et al.* (2002) fewer number of HD patients (36%) of HD showed high levels of CRP. In our study, 46% of the patients had CRP levels greater than 10 mg/L, which is in agreement with the previous study done by Razeghi and colleagues (2008) who found a CRP level greater than 10 mg/L in 41% of HD patients. In the literature, there are multiple reports on CRP levels; Adriana and colleagues (2008) also observed 25% of haemodialysis patients had CRP levels greater than 16.7 mg/L.

In the present study, levels of IL-6 in HD patients and in HCV-positive patients compared to control group, which accords with many other studies (Borazan*et al.*, 2004; Nascimento*et al.*, 2005; Rao*et al.*, 2005; .Zumrutdal*et al.* 2007; and Afzal*et al.*, 2011).

Iseki *et al.* (1999) reported that HD patients with CRP levels of more than 10 mg/L had significantly high mortality rate during 7 years of the study period as compared to those with CRP levels of less than 10 mg/L. Apparent increase in CRP levels in HD patients indicated inflammation, and therefore, it was designated as a sensitive and independent marker for malnutrition. These findings also matched with the findings of a study done by Nascimento and co-workers (2005).

In the current study, we found that the serum concentration of HGF is considerably increased in patients with ESRD before HD, this finding is consistent with other studies that have reported elevated serum HGF level in patients with chronic renal failure and particularly in those in the end-stage phase (Sugimura*et al.,* 1997; Rampino*et al.,* 1998; Malatino*et al.,* 2000), HGF has a short half-life and is cleared mainly by the liver (Sugimura *et al.,*in ESRD are still unclear, it appears that this phenomenon does not represent the mere effect of reduced removal of this substance by the diseased kidneys.

Surprisingly, the levels of HGF is significantly increased in ESRD after 6 months of regular renal dialysis, and more significantly increased after one year of regular HD. this was in agree with Lohr*et al.* (2000) who reported that serum HGF level is also increased with ESRD. Mizuno *et al.* (2000) demonstrated that HGF induction in chronic renal disease (CRD) was beneficial in tending to preserve normal kidney structure and function. Yang and Liu (2003) reported that HGF not only prevents the onset and progression of CRD but also exhibits therapeutic efficacy even when tissue injury is already established. Cruzado*et al.* (2004) demonstrated that exogenous HGF can markedly ameliorates diabetic nephropathy in both mouse and rat models.

Han L & Shi-xiang, (2010) measured a prolonged and marked production of hepatocyte growth factor (HGF) during HD sessions, and have suggested a beneficial effect of HGF to hepatocyte proliferation and accelerated liver repair. Badalamenti*et al.* (2003) observed that interferon (IFN)-alpha levels markedly increased after dialysis when using both cellulose and synthetic membranes. This increase in endogenous IFN could contribute to a reduction in viremia in HCV infected patients on maintenance dialysis.

The levels of HGF is significantly correlated to ALT, AST, Total bilirubin, serum albumin, S. urea, S. creatinine and uric acid in patients of ESRD. These results are partially in agreement with results of Taman *et al.,* study (1997), who found a significant positive correlation with creatinine, urea, and a negative correlation with creatinine clearance and disagree with Malatino*et al.,* study (2000) who found no correlation between HGF and serum albumin or serum potassium levels.

As regard to viral load before and after HD in this study, a significant increase was found before HD and it was significantly decreased after HD. These results were in agreement with the finding of Fabrizi*et al.* (1998) and Han & Shi-xiang (2010) who reported a decline in viral load occurs in patients under HD than in non-nephropathic infected patients.

Several findings support a different course of HCV in dialysis patients versus the non-uremic population. The HCV viral load tend to be lower in HD patients with HCV despite the immune compromise caused by chronic uremia; the histologic abnormalities seem to be milder, and a severe clinical course of chronic hepatitis C is unusual in most HD patients. It appears that the HD procedure per se can preserve patients from an aggressive course of HCV by reducing the viral load (HCV RNA). It has been suggested that the HD procedures lowers HCV RNA levels by various mechanisms (Furusyo*et al.,* 2000), the HCV RNA particle is entraped onto the membrane surface of the dialyzers and destroyed (Fabrizi*et al.,*2009), and the production of cytokines and other substances during HD sessions (Fabrizi*et al.,*2012).

In the current study, IL-6 was only correlated to ALT, and CRP was only correlated to ALT and AST. In the Afzal*et al.* (2011) study, no correlation was found between high levels of IL-6 or CRP and liver or kidney function tests.

Rampino*et al.* (1999) who reported that, ALT

& AST were significantly higher in patients without renal disease than in those on regular dialysis treatment. Shiota*et al.* (1995) stated that serum HGF level exhibited a significant correlation with AST but there wasn't any correlation with ALT. Also, Yue*et al.* (2003) observed that HGF accelerated normalization for recovery of total bilirubin and ALT level. Also, Ogura and colleagues (2001) reported that HGF accelerates serum albumin recovery quickly due to its stimulation of albumin synthesis. On the contrary Borawski and Mysliwiec (2002) found no statistically significant association between HGF level and albumin.

Clemens *et al.*(2004) stated that, in HCV positive patients, subjected to HD, liver damage caused by the HCV was reduced compared to HCV positive patients without renal disease and lower HGF serum levels, suggesting that HGF may be responsible for this anti-hepatitis effect.

Conclusion:

Taken together of these results, we conclude that, increased HGF serum level in chronic HCV patients with and without renal failure and increasing its level after regular HD with improvement of liver functions represent a part of reparative reaction and protective effect against liver damage. In the future, the implication of HGF agonist as a therapeutic intervention in patients with HCV infection and renal failure may play a role in HCV progression.

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