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ESTIMATION OF SERUM INTERLEUKIN-18 IN HEPATITIS C PATIENTS IN ZAGAZIG UNIVERSITY HOSPITALS

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ABSTRACT

Background: HCV is a contagious blood-borne virus that attacks the liver and can be deadly despite often having no visible health warnings. IL-18 is an important proinflammatory cytokine secreted from Kupffer cells. It is involved in the pathogenesis of HCV infection through modulating immune functions by regulating IFN-γ production and promoting the development of Th1 immune responses.

Objective: The aim of this study is to measure serum level of Il-18 in chronic hepatitis C patients and compare between Il-18 levels and the degree of liver fibrosis.

Subjects & Methods: This is a case control study. It was conducted in Clinical Pathology and Tropical Medicine Departments, Faculty of Medicine, Zagazig University Hospitals during the period from June 2017 to August 2017. Eighty four subjects were included in this study; they were classified into three groups as follows: Group 1: composed of 28 (17 males,11 females) apparently healthy subjects their ages ranged from 27 to 61 years old . Group 2 :composed of 28 patients (15 males,13 females) with HCV infection diagnosed as HCV RNA positive serum by RT-PCR with normal liver enzymes(ALT,AST), their ages ranged from 25 to 63 years old. Group 3 :composed of 28 patients (16 males,12 females) with HCV infection diagnosed as HCV RNA positive serum by RT-PCR with elevated liver enzymes (ALT,AST) their ages ranged from 29 to 64 years old. Formal consent was obtained from all individual and the study protocol was approved by the Zagazig medical research ethical committee. Seven ml of venous blood was withdrawn by sterile venipuncture and used for routine investigations including, complete liver function tests, HCV antibodies by ELISA and HCV-RNA by RT-PCR and IL-18 serum level by ELISA technique.

Results: Group III showed highly statistically significant increased ALT and AST when compared to both group I and group II. There were high statistical significant differences between the three studied groups as regard Albumin level, Prothrombin time, Concentration (%) and INR. There was statistical significant increase in viral load by PCR in Group III compared to Group II. There were high statistical significant differences between Group III compared to both Group I and Group II in IL-18 level. there were statistical significance increase in IL-18 level with increase degree of liver fibrosis in both Group II & Group III. There was positive significant correlation between IL-18 level and AST in Group III. There was positive high significant correlation between IL-18 level and viral load in Group III.

Conclusion: Serum IL-18 is significantly increase in chronic HCV patients and is correlated with liver fibrosis staging determined by fibroscan. So, IL-18 can be used as a non-invasive pro inflammatory marker for detection of the chronicity and severity of liver fibrosis in CHC.

Key words: HCV infection, Interleukin-18, IFN-γ

INTRODUCTION

Hepatitis C is a serious disease that is widely distributed in most parts of the world especially in Egypt[1]. It was formerly identified as a putative viral hepatitis occurring after transfusion of blood products or intravenous drug use. There was evidence that hepatitis C could lead to persistent infection in a high proportion of infected individuals, and could progress to chronic liver disease, cirrhosis and hepatocellular carcinoma (HCC)[2].

Approximately 30% of patients with chronic HCV infection have persistently normal ALT levels. the majority of these patients have some degree of histological liver damage that may be significant in up to 20% of cases and might progress towards a more severe degree of liver fibrosis[3]. The assessment of disease progression not only provides useful information for diagnosis and therapeutic supervision judgment but also for monitoring disease[4].

persistent exposure of kupffer cells to HCV will continuously activate kupffer cells leading to the ongoing release of cytokines like IL-18 attracting and activating more leukocytes. Likewise, continuous activation of infiltrating leukocytes leads to ongoing production of IL-18 that indirectly activate kupffer cells[5].

Proinflammatory cytokines play a dual role in virus infection. In acute infection, these cytokines act as an antiviral and help to clear infection. On the other hand, these cytokines may stimulate inflammatory processes in chronic infection. Therefore, HCV-mediated activation of IL-18 from macrophages may activate quiescent hepatic stellate cells toward fibrosis and may be a potential target for therapeutic modalities[6].

The aim of this study is to measure serum level of Il-18 in chronic hepatitis C patients and compare between Il-18 levels and the degree of liver fibrosis in hepatitis C viral infection.

SUBJECTS AND METHODS

This is a case control study. It was conducted in Clinical Pathology and Tropical Medicine Departments, Faculty of Medicine, Zagazig University Hospitals during the period from June 2017 to August 2017. Formal consent was obtained from all individual and the study protocol was approved by the Zagazig medical research ethical committee.

Eighty four subjects were included in this study; they were classified into three groups as follows:

Group 1: composed of 28 (17 males,11 females) apparently healthy subjects their ages ranged from 27 to 61 years old .

Group 2 :composed of 28 patients (15 males,13 females) with HCV infection diagnosed as HCV RNA positive serum by RT-PCR with normal liver enzymes(ALT,AST), their ages ranged from 25 to 63 years old.

Group 3 :composed of 28 patients (16 males,12 females) with HCV infection diagnosed as HCV RNA positive serum by RT-PCR with elevated liver enzymes (ALT,AST) their ages ranged from 29 to 64 years old.

Inclusion criteria:

- Patients with HCV infection who were conducted at department of Tropical Medicine in Zagazig University Hospitals.
- The diagnosis was supported by positive HCV-RNA detection by real time PCR.

Exclusion criteria:

- Patients with liver diseases other than HCV.
- Patients with other medical diseases .
- Administration of antiviral drugs.

Each group was subjected to the following:

A. Control group:

1. Routine laboratory investigations:
   a. Complete blood count.
   b. Liver, kidney function tests and random blood sugar.
2. Measurement of serum IL-18 levels.

B. Patient group:

1. Complete history taking
2. Clinical examination
3. Routine laboratory investigations: Complete blood picture, Liver, kidney function tests and random blood sugar.
4. Viral markers including: HCV antibody. -HBsAg.
5. PCR
6. Specific laboratory investigations: Serum IL-18 level (has been determined by Enzyme-Linked Immunosorbent Assay using SunRed ELISA kit (Shanghai Sunred Biological Technology Co.).

   Imaging study: Abdominal ultrasonography, Fibroscan(Philips – IU22 MATRIX).

STATISTICAL ANALYSIS

The collected data were computerized and statistically analyzed using SPSS program version 18.0. Qualitative data were represented as frequencies and

relative percentages. Results are expressed as means ± SD. Comparison between groups was done by Chi-Square test. Mann Whiteny test was used when data is not normally distributed. ANOVA F-test was used to compare between more than two groups. Pearson's correlation coefficient was used to test correlation between variables. P<0.05 was considered to be statistically significant.

RESULTS

Table 1 Comparison of demographic data of the three studied groups

Variable	Group I (n=28)		Group II (n=28)		Group III (n=28)		F	p
Age (years) Mean ± SD Range	45.39 ± 9.31 27 – 61		42.75 ± 11.62 25 - 63		43.64 ± 10.23 29 - 64		0.47	0.36 NS
	No	**%**	**No**	**%**	**No**	**%**	**χ^2**	**p**
Sex Female Male	11 17	39.3 60.7	13 15	46.4 53.6	12 16	42.9 57.1	0.29	0.86 NS

SD: Standard deviation, F: ANOVA test, χ^2: Chai square test. P: probability value. NS: non-significant (P>0.05)

There were no statistical significant differences between the three studied groups in age or sex distribution (p value >0.05).

Table 2 Comparison between different studied groups regarding ALT and AST

Variable	Group I (n=28)	Group II (n=28)	Group III (n=28)	Test	P	LSD
ALT(U/L) Mean ± SD Range	20.64 ± 6.73 11 – 32	28.04 ± 7.32 14 – 40	119.5 ± 74.04 47 - 348	**K** **61.01**	**<0.001****	0.52 NS [1] **<0.001**** [2] **<0.001**** [3]
AST (U/L) Mean ± SD Range	30.5 ± 5.63 19 – 40	31.29 ± 5.90 20 – 40	101.18 ± 45.61 46 – 204	**K** **55.47**	**<0.001****	0.91 NS [1] **<0.001**** [2] **<0.001**** [3]

F: ANOVA test K:Kruskal Wallis test LSD: Least significance difference
NS: Non significant (p>0.05) **:Highly significant (p<0.01) *:Significant (p<0.05)
P1: Group I versus Group II, P2: Group I versus Group III P3: Group II versus Group III

This table shows that there were high statistical significance differences between the three studied groups as regard serum ALT and AST. The difference was between Group III compared to both group I and II but no difference was found between Group I and Group II.

Table 3 Comparison between different studied groups regarding mean values of Total and Direct bilirubin, Albumin level, Prothrombin time, Concentration (%) and INR

Variable	Group I (n=28)	Group II (n=28)	Group III (n=28)	Test	P	LSD
T.Bilirubin (mg/dl)				F		
Mean ± SD	0.69 ± 0.22	0.80 ± 0.28	0.83 ± 0.20	2.74	0.07	-----
Range	0.40 - 1	0.5 – 1.2	0.3 – 1.5		NS	
D.Bilirubin (mg/dl)				K		
Mean ± SD	0.14 ± 0.07	0.16 ± 0.07	0.18 ± 0.10			
Range	0.1 - 0.3	0.1 – 0.3	0.1 – 0.4	2.13	0.16 NS	----
Albumin (mg/dl)				**F**		**0.04*** [1]
Mean ± SD	4.75 ± 0.35	4.52 ± 0.28	4.26 ± 0.55	**10.03**	**<0.001****	**<0.001**** [2]
Range	3.4 – 5.1	4.1 – 5.1	2.7 – 4.5			**0.03*** [3]
Prothrombin(sec.)				**F**		**0.04*** [1]
Mean ± SD	12.21 ± 0.28	12.43 ± 0.29	12.75 ± 0.66	**10.36**	**<0.001****	**<0.001**** [2]
Range	12.3 – 13.3	12.3 – 13.3	12.3 – 14.8			**0.009*** [3]
Concentration (%)				**F**		**0.03*** [1]
Mean ± SD	89.29 ± 4.11	92.91 ± 4.25	96.93 ± 9.22	**10.23**	**<0.001****	**<0.001**** [2]
Range	80 – 95	85 – 95	87.5 - 100			**0.003**** [3]
INR				**F**		**0.02*** [1]
Mean ± SD	0.98 ± 0.07	1.02 ± 0.05	1.06 ± 0.08	**9.74**	**<0.001****	**<0.001**** [2]
Range	1 – 1.05	1 – 1.15	1 – 1.24			**0.02*** [3]

F: ANOVA test K:Kruskal Wallis test LSD: Least significance difference
NS: Non significant (p>0.05) **:Highly significant (p<0.01) *:Significant (p<0.05)
P1: Group I versus Group II, P2: Group I versus Group III P3: Group II versus Group III

This table shows that there were high statistical significant differences between the three studied groups as regard Albumin level, Prothrombin time, Concentration (%) and INR but there were no statistical significant differences between the three studied groups as regard Total and Direct bilirubin. In Albumin level, Prothrombin time, Concenteartion and INR the difference was between all groups.

Table 4 Comparison of PCR results among the two patient groups

Variable	Group II (n=28)	Group III (n=28)	MW	P
PCR:				
Mean ± SD	1113300 ± 815062	1408600 ± 610970		
Range	11500 - 2360000	174000 – 2930000	**2.38**	**0.04***

MW: Mann Whiteny test *:Significant (p<0.05)

This table shows that there were statistical significant increase in viral load by PCR in Group III compared to Group II.

Table 5 Comparison between different studied groups regarding mean values of IL-18 (ng/l)

Variable	Group I (n=28)	Group II (n=28)	Group III (n=28)	K	P	LSD
IL-18 (ng/l)						
Mean ± SD	19.98 ± 12.45	23.46 ± 12.13	37.21 ± 16.2			0.06 NS [1]
Range	9 – 25	6 - 45	14 – 64	**13.56**	**0.003****	**<0.001**** [2]
						<0.001** [3]

K:Kruskal Wallis test LSD: Least significance difference
**: Highly Significant (p<0.01) NS: Non significant (P>0.05)
P1: Group I versus Group II, P2: Group I versus Group III P3: Group II versus Group III

This table shows that there were high statistical significant differences between the three studied groups in IL-18. Using LSD to find difference between groups showed that the difference was between Group III compared to both Group I and Group II.

Table 6 Description of IL-18 results and degree of liver fibrosis in patients groups

Fibrosis	N	IL-18		K	P
		Mean ± SD	Range		
F1	19	16.53 ± 5.19	6 – 20		
F2	12	22.3 ± 6.10	16 – 25	**19.9**	
F3	14	32.15± 11.5	20 – 38		**<0.001****
F4	11	50.29 ± 21.91	29 - 64		

K:Kruskal Wallis test **: Highly Significant (p<0.01)

This table shows that there was positive high relation between degree of liver fibrosis and level of IL-18 in HCV patients.

Table 7 Correlation between IL-18 and age, PCR results, Liver Fibrosis & laboratory parameters of the three studied groups

Variable		IL-18		
		Group I (n=28)	Group II (n=28)	Group III (n=28)
Age	r	0.11	0.03	0.36
	p	0.59	0.87	0.06
PCR results	r	-----	0.12	**0.55**
	p		0.55	**<0.001****
Liver Fibrosis	r	**----**	**0.80**	**0.78**
	p		**<0.001****	**<0.001****
ALT	r	0.24	0.13	0.14
	p	0.22	0.12	0.49
AST	r	0.17	0.06	**0.32**
	p	0.40	0.76	**0.03***
T.Bilirubin	r	-0.11	-0.05	0.01
	p	0.59	0.81	0.95
D.Bilirubin	r	-0.10	-0.02	0.08
	p	0.61	0.94	0.70
Albumin	r	-0.29	-0.03	-0.09
	p	0.06	0.89	0.64
Prothrombin Time	r	0.06	0.15	0.22
	p	0.76	0.45	0.26
Concentration	r	-0.07	-0.15	-0.22
	p	0.78	0.45	0.26
INR	r	0.21	0.15	0.22
	p	0.25	0.45	0.26

r =Pearson correlation coefficient **: Highly Significant (p<0.01) *:Significant (p<0.05)

This table shows that there were high statistical significant positive correlation between IL-18 level and liver fibrosis in both Group II & Group III. Also there were positive significant correlation between IL-18 level and AST in Group III. Also, there were positive high significant correlation between IL-18 level and viral load in Group III.

DISCUSSION

HCV infection is a major health problem in Egypt as the nation bears the highest prevalence rate worldwide[7]. Chronic infection with HCV is the leading cause of end stage liver disease, HCC and liver-related death in the country[8].

liver function tests are insensitive for predicting disease progression. Serum ALT may be elevated in patients without significant histological abnormality. Similarly, normal values do not exclude progressive liver disease or cirrhosis[9]. Different invasive and non-invasive methods are applied to diagnose the disease from initial to end stage[10].

Percutaneous liver biopsy has been considered the golden standard for the histological assessment of liver fibrosis[11]. However, liver biopsy has several limitations. The procedure is invasive and painful, with the risk of rare but potential life-threatening complications[12]

FibroScan is a non-invasive test that assesses stiffness in the liver[13]. Its results had good correlation with the histology of liver fibrosis in patients with hepatitis C[14]. However, measurements can be difficult to obtain in obese patients or in those who have narrow intercostal spaces, and is impossible to achieve in patients with ascites[15].

Once hepatocytes are productively infected with HCV, cellular defenses become activated. Hepatocytes trigger kupffer cells to produce cytokines such as IL-18 to recruit IFN-γ producing NK cells to the liver[16]. IL-18 is a proinflammatory cytokine with immunomodulatory functions by enhancing T cell responses, regulating IFN-γ production and promoting the development of Th1 immune responses[17]. Hepatic inflammatory activity in chronic hepatitis C was shown to be closely associated with an increased amount of IL-18[18].

The present study was carried on 84 subjects classified into 3 groups: Group I included 28 healthy subjects, 17 were males(60.7%) and 11 were females(39.3%), their ages ranged from 27 to 61 years with mean ages 45.39 ± 9.31, Group II included 28 patients with chronic hepatitis C with normal liver enzymes, 15 were males(53.6%) and 13 were females(46.4%), their ages ranged from 25 to 63 years with mean ages 42.75 ± 11.62 and Group III included 28 patients with chronic hepatitis C with elevated liver enzymes, 16 were males(57.1%) and 12 were females(42.9%), their ages ranged from 29 to 64 years with mean ages 43.64 ± 10.23 with no statistical significant differences between the three studied groups in age or sex distribution (p value >0.05).

The present study showed high statistical significant differences between the three studied groups as regard serum ALT (K=61.01) and AST (K=55.47). The difference was between Group III compared to both group I and II (p value<0.01) but no difference was found between Group I and Group II (p value >0.05). Increases of serum AST activity generally parallel those of ALT and are therefore considered to be a sensitive marker for hepatocellular injury[19]. However, Wedemeyer et al., found that the cause of normal liver enzymes in patients with chronic hepatitis C may be related to host factors particularly immunologic, where possible equilibrium between HCV replication and host immune response results in weak or no cell mediated response directed to HCV infected cells[20].

In the present study there were high statistical significant differences between the three studied groups as regard Albumin level (F=10.03), Prothrombin time (F=10.36), Concentration(%) (F=10.23) and INR (F=9.74) ,but there were no statistical significant differences between the three studied groups as regard Total and Direct bilirubin (p value >0.05).The difference in Albumin level, Prothrombin time, Concenteartion and INR was between all groups (p value<0.05). Sherlock & Dooley, stated that the liver function tests usually indicate the type and severity of liver injury[21]. Both decreased Albumin and the Albumin/Globulin (A/G) levels were indicators of serious liver damage[22].

In the present study there was statistical significant increase in viral load by PCR in Group III compared to Group II (MW=2.38 , p value<0.05). Determination of HCV RNA levels has become an essential part of patient care, from early diagnosis of infection to treatment monitoring[23].

The present study showed high statistical significant level of IL-18 in group III when compared with both group I and II (p value <0.001) while there was no statistically significant difference between group I and group II regarding IL-18 level (p value =0.06). This explained that group II with normal enzymes not associated with viral activity that accompanied with proinflammatory expression of IL-18. Zhang et al., showed that IL-18 level in the serum of the chronic hepatitis C group was higher than that of the healthy control group[24]. The same findings were observed by Niu et al., who demonstrated a positive association between CHC and plasma IL-18 levels[25].

In the present study there was positive high relation between degree of liver fibrosis and serum level of IL-18 in HCV patients (K=19.9, P value <0.001). It is possible that up-regulation of IL-18 production has a role in the development of chronicity and accelerates the evolution of chronic hepatitis towards cirrhosis[26]. In accordance with these results, Said et al., observed positive correlation between IL-18 serum level both METAVIR necroinflammatory grade and fibrosis stage[27].

The present study showed no correlation between IL-18 and age, ALT, T.Bilirubin, D.Bilirubin, Albumin, Prothrombin Time, Concentration, INR. However, there was non-significant positive correlation between serum IL-18 and AST in group II (r =0.06, P value =0.76) while there was significant positive correlation between serum IL-18 and AST in group III (r=0.32, P value =0.03). This is in agreement with some authors who suggested that serum aminotransferases, especially the AST level, were associated with liver damage explaining more release of AST from liver cell injury in group III[28].

In the present study there was positive high significant correlation between IL-18 level and viral load in Group III (r=0.55, p value<0.01). Patients treated with PEG-IFN and ribavirin showed high relation between serum IL-18 level and HCV-RNA titers[29].

CONCLUSION

This study revealed that Serum IL-18 is significantly increase in chronic HCV patients and is correlated with liver fibrosis staging determined by fibroscan. So, IL-18 can be used as non-invasive pro inflammatory marker for detection of the chronicity and severity of liver fibrosis in chronic hepatitis c patients. Further studies are needed on large number of subjects to investigate IL-18 response to infection with various genotypes of HCV (specifically genotype 4). Follow up of patients is recommended to detect the association between serum IL-18 levels and response to different treatment modalities.

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