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Effects of treatment with Interferon alfa on some biochemical indices among hepatitis C patients.

تأثير العلاج بالأنترفيرون الفا في بعض المعايير الكيموحيوية للمرضى المصابين بالتهاب الكبد الفايروسي سي.

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Absrtact

Background: Hepatitis C virus (HCV) is a leading cause of chronic liver disease in the world. Interferon alpha (IFN alpha) has been widely used as therapy for chronic hepatitis C.

Objective :This study was amid to evaluate the efficacy of interferon alpha therapy in patients of chronic hepatitis C for 12 and 24 weeks .

Methods: This study was conducted at Marjan Hospital from May 2014 to December 2014. the patients of hepatitis C (24 males and 26 females) had age range 18-48 years were grouped into study group (n=50) and control group (n=16). Patients had injection monthly by interferon vial 18 mlu. At weeks 0, 12 and 24, blood samples were taken for assay Biochemical indices that include blood sugar, urea, creatinine, direct and indirect and total bilirubin, albumin, aspartate aminotranferases (AST), alanine aminotransferases (ALT), and alkaline phosphatase (ALP).

Results: There are no significant differences in blood sugar and Albumin levels in HCV patients as compare to normal individuals (control). significant decrease were observed in Blood urea ,serum creatinine direct bilirubin , indirect bilirubin, total bilirubin and significant increase in AST, ALT, ALP levels in HCV patients compare to control. Treatment with interferon alfa for 12 and 24 weeks cause significant increase ($P< 0.001$) in Blood sugar and Albumin levels and significant decrease in Blood urea ,serum creatinine direct and indirect and total bilirubin in HCV patients as compare to normal individuals (control). Also there were no significant differences in all studied parameters and the response to treatment between males and females

Conclusions: After 24 weeks of Interferon alfa therapy, patients showed hopeful response to treatment manifested by improve the biochemical induces.

Key words: Hepatitis C virus **,** Interferon alpha (IFN alpha)**,** biochemical indices.

الخلاصة

خلفية البحث : التهاب الكبد الفايروسي سي هو السبب الرئيسي لأمراض الكبد المزمنة في العالم. يستخدم الأنترفيرون ألفا على نطاق واسع كعلاج لالتهاب الكبد الفايروسي سي .

هدف الدراسة :هدفت هذه الدراسة الى تقييم فعالية العلاج بالانترفيرون الفا في المرضى الذين يعانون من التهاب الكبد الفايروسي سي لمدة 12 و 24 أسبوعا.

المواد وطرق العمل : أجريت هذه الدراسة في مستشفى مرجان للمدة من شهر ايار إلى كانون الاول 2014. شملت الدراسة مرضى التهاب الكبد الفايروسي سي (24 ذكور و 26 إناث) تراوحت اعمارهم من 18-48 سنة تم تقسيمها الى مجموعة الدراسة (ن = 50) والمجموعة السيطرة (ن = 16). تم حقن المرضى شهريا بالانترفيرون بجرعة 18 MLU. خلال الأسبوع 0، 12 و 24، وتم أخذ عينة دم لفحص المؤشرات الكيموحيوية التي شملت مستوى السكر في الدم، واليوريا، والكرياتينين، البيليروبين المباشر وغير المباشر والكلي، الالبومين وAST و ALT وALP.

النتائج : اظهرت نتائج الدراسة عدم وجود فروق معنوية في نسبة السكر في الدم ومستوى الالبومين في المرضى المصابين بالتهاب الكبد الفايروسي c مقارنة بالأشخاص الطبيعيين (السيطرة). كما لوحظ انخفاض كبير في اليوريا في الدم، والكرياتينين ومستوى البيليروبين المباشر ، البيليروبين غير المباشر، البيليروبين الكلي وزيادة كبيرة في AST، ALT، ALP في مستويات مرضى HCV مقارنة مع مجموعة السيطرة . تسبب العلاج بالإنترفيرون ألفا لمدة 12 و 24 أسبوعا زيادة معنوية عاليه ($P <0.001$) في نسبة السكر في الدم ومستوى الالبومين وانخفاض معنوي في مستوى اليوريا والكرياتينين و البيليروبين المباشر وغير المباشر والكلي في المرضى مقارنة بالأشخاص الطبيعيين (السيطرة). كما لم تكن هناك فروق معنوية في جميع المعايير التي تم دراستها والاستجابة للعلاج بين الذكور والإناث.

الاستنتاجات : يستنتج من الدراسة الحالية بعد مرور 24 اسبوعا من العلاج بالأنترفيرون ألفا اظهر المرضى المصابين بالتهاب الكبد الفايروسي استجابة جيدة للعلاج توضحت في تحسن المعايير الكيموحيوية .
كلمات مفتاحية : التهاب الكبد الفايروسي سي ، الانترفيرون الفا . المعايير الكيموحيوية .

Introduction:

Hepatitis C virus (HCV) infection is one of the main causes of chronic liver disease worldwide, The World Health Organization (WHO) estimates that about 3% of the world's population has been infected with HCV, that mean there are more than 170 million chronic carriers who are at risk of developing liver cirrhosis and/or liver cancer (1). HCV is spread when your blood comes into contact with the blood of a person who is infected with the virus. This can happen when people share needles, pipes, straws or other implements for drug use or when unsterile or contaminated needles or ink are used for piercing (2). There are three types of Interferons that are used to treat hepatitis C :Type I interferon, II and PEG-IFN-lambda. The type I interferon is known as alpha or beta and is made up of proteins produced by the body in response to a viral infection (3).Treatment of chronic hepatitis C is currently based on monotherapy by interferon type I or combination of (IFN) alfa and ribavirin, and a number of new anti-HCV therapies are in development (4). The present study aimed to investigate the influence of interferon alfa therapy in some biochemical parameters in patients infected with hepatitis C .

MATERIALS AND METHODS

Fifty adult patients with chronic hepatitis C infection who had no previous treatment for HCV were eligible for the study. Participants were patients who visited Marjan medical city in Babylon provence of Iraq, at the period between may – until December 2014 . Patients were enrolled after HCV- RNA viral load detectable by polymerase chain reaction (PCR) ,16 healthy individual with negative viral result mentioned as a control group. The patients of chronic hepatitis C (24 males and 26 females) had age range 18-48 years were grouped into study group (n=50) and control group (n=16). Patients injection monthly by interferon vial 18 mlu. At weeks 0, 12 and 24, blood samples were taken for assay Biochemical indices For all patients and control .screening for hepatitis viruses were done according to manual procedure of Biokit Company . Biochemical laboratory assays tests : blood sugar, blood uera and serum albumin total serum bilirubin (TSB) Direct and Indirect ,liver transaminase (AST and ALT) and Alkaline Phosphatase were carried out for all serum samples by using a Cobas C111 automatic analyser according to the enzymatic method (5). The patients groups are classified according to treatment applicable protocol as pretreatment group ,before treatment , after 12 weeks from drug application and after 24 weak.

Statistical Analysis

The data obtained were compiled and analyzed using student t- test and L.S.D, by the SPSS version 17.0. Results of the data were expressed as mean ± SEM (Standard error of mean). Test of significance was compared using ($p< 0.05$) and ($p< 0.001$).

Results

Effects of treatment of interferon type I on some biochemical indices among hepatitis C patients.

The result showed as illustrated in (table 1) there is no Significant differences in glucose level ($P < 0.05$) were observed in HCV patients as compare to control . After treatment with interferon alfa for 12 and 14 weeks the level of glucose is significantly increase ($P< 0.05$) in patients compare to before treatment.

Urea is Significant reduce ($P < 0.05$) in HCV patients as compare to control individuals. Interferon alfa therapy for 12 weeks cause significantly increase in urea patients compare to before treatment. Creatinine levels are Significant reduction ($P < 0.05$) in HCV patients as compare to normal individuals, Interferon alfa therapy for 12 and 24 weeks of caused significantly increase of

creatinine levels compare to before treatment and control group .Direct and indirect bilirubin and total bilirubin levels of Hepatitis C patients increased significantly (P > 0.001) as compared to control individuals. After interferon therapyfor 12 week the 117epatiti bilirubin significantly decrease (P > 0.001) and close to the normal level of control after treatment with interferon for 24 weeks.

As showed in figure (1) there is no Significant differences(P > 0.05) in albumin level in HCV patients as compare to control. After 12 weeks treatment with interferon alfa there is significant increase (P >0.05) in albumin levels compare to control group, But after 24 weeks of interferon alfa treatment there is significantly increase (P >0.05) comparative to all group .

In this study ALT, AST and ALP levels were significantly raised (P > 0.001) in hepatitis c patients as compared to control and significantly decrease(P > 0.001)after treatment with interferon alfa for 12 and 24 weeks. As illustrated in figure 2,3,4 respectively.

Table (3): Effects of treatment of interferon type alfa on some biochemical indicters among hepatitis C patients.

Parameters	Group	N	Mean± SD
Blood Sugar µmol/L	After 24 w	16	6.35±2.90 a
	After 12 w	16	6.11±2.57 a
	Before treat	18	5.14± 0.77
	Control	16	5.60±1.09
	LSD 0.73		
Urea µmol/L	After 24 w	16	7.91±10.32 b
	After12w	16	5.07± 2.38 a
	Before treat	18	4.88±1.70 a
	Control	16	7.09±2.47
	LSD 2.2		
serumcreatinine µmol/L	After 24 w	16	66.31±32.90 b
	After12w	16	62.00±20.49 a
	Before treat	18	64.15±28.16 a
	Control	15	72.13±11.93
	LSD 4.1		
Total Serum Bilirubin µmol/L	After 24 w	16	11.18±7.23 b
	After12w	16	15.62±11.68 b
	Before treat	18	80.22±65.05 a
	Control	16	8.25±2.35
	LSD 25.4		
Direct Bilirubin µmol/L	After 24 w	16	3.62±1.85 b
	After12w	16	4.81±4.32 b
	Before treat	18	19.72±18.69 a
	Control	16	2.81±.83
	LSD 6.03		
Indirect Bilirubin µmol/L	After 24 w	16	7.56±5.44 b
	After12w	16	10.81±7.62 b
	Before treat	18	59.89±48.47 a
	Control	16	5.43±1.71
	LSD 19.2		

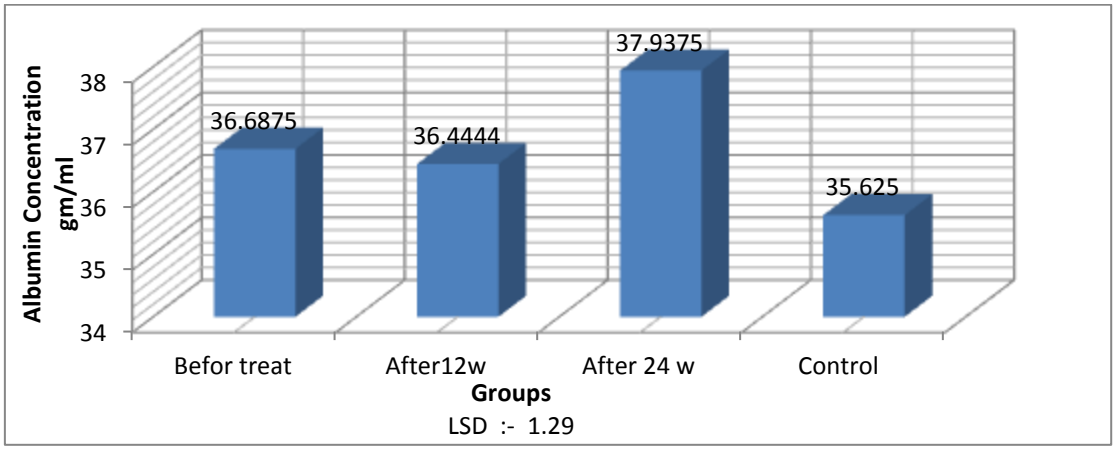

Figure 1: Effects of treatment of interferon alfa on Albumin concentration in HVC patients.

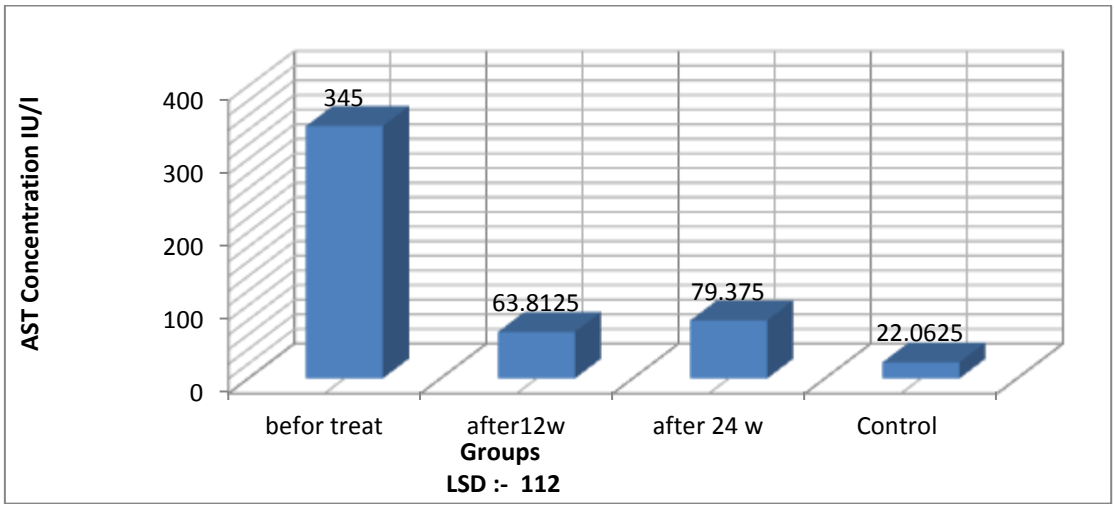

Figure 2: Effects of treatment with interferon type alfa on AST concentration in HVC patients.

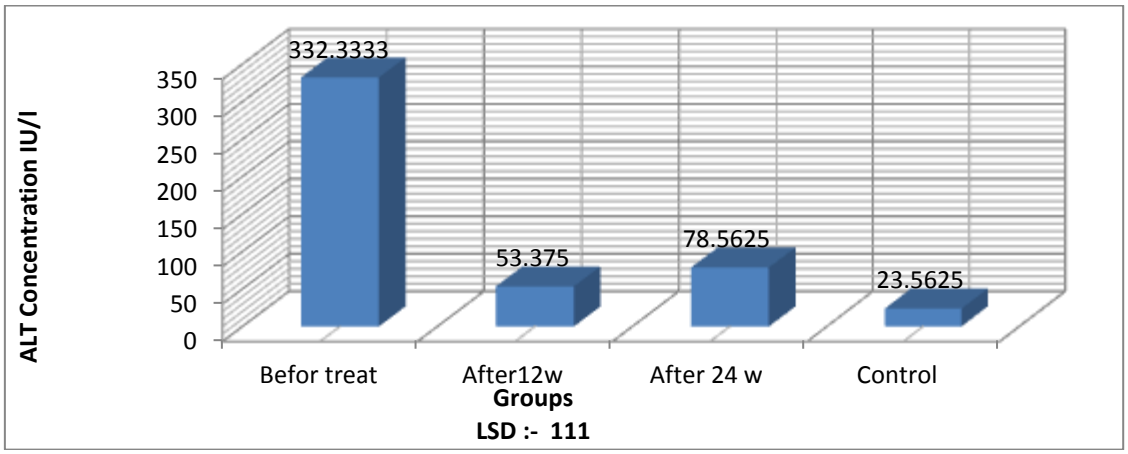

Figure 3: Effects of treatment with interferon alfa on ALT concentration in HVC patients.

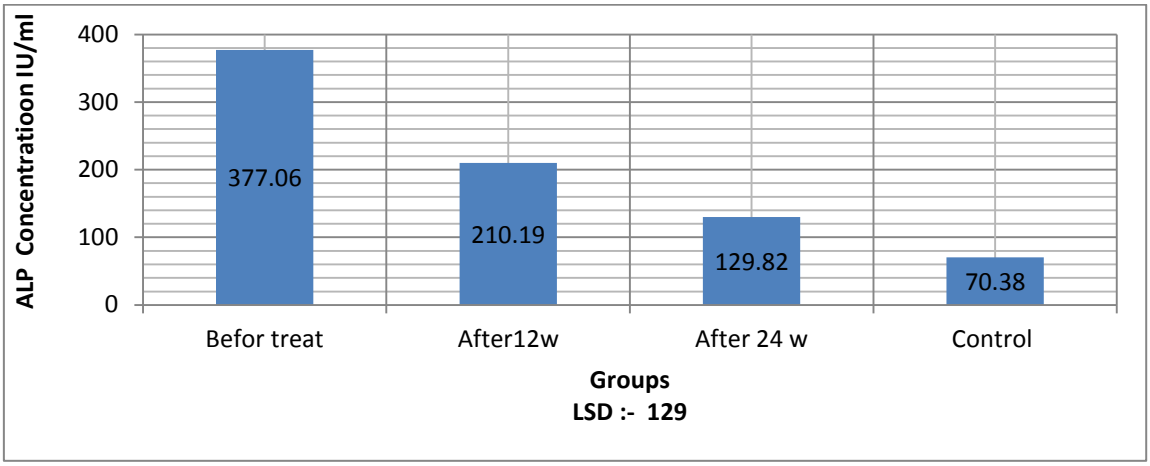

Figure 4: Effects of treatment with interferon alfa on ALP concentration in HVC patients.

Effects of sex of on some biochemical indicters among hepatitis C patients.

The results of the current study (Table 2) indicated that there was no significant differences (P > 0.05) in the levels of all parameter (Blood sugar ,Blood urea ,serum creatinine and Albumin levels Total serum bilirubin direct and indirect bilirubin, ALP, AST, ALP) that was studied between males 24 and females 26 infected with HVC.

Table (2) Biomarker Concentrations in Patients With HCV according to sex group .

SEX		***N***	***Mean± SD***	***P. Value***
Blood Sugar µmol/L	Male	24	5.92 ±2.08	0.603
	Female	26	5.66±2.00	
Urea µmol/L	Male	24	7.38±7.26	0.099
	Female	26	5.09±2.54	
Serum Creatinine µmol/L	Male	24	67.40±27.19	0.655
	Female	26	64.64±22.27	
Total Serum Bilirubin µmol/L	Male	24	31.75±51.44	0.816
	Female	26	29.09±40.69	
Direct Bilirubin µmol/L	Male	24	9.49±15.73	0.382
	Female	26	6.83±7.54	
Indirect Bilirubin µmol/L	Male	24	22.25±36.03	0.266
	Female	26	21.97±33.32	
AST **IU/ml**	Male	24	168.75±322.30	0.256
	Female	26	101.59±130.66	
ALP **IU/ml**	Male	24	174.35±444.40	0.276
	Female	26	85.03±92.40	
ALT **IU/ml**	Male	24	199.41±161.42	0.876
	Female	26	205.06±129.41	
Albumin gm/ml	Male	24	36.91±4.82	0.677
	Female	26	36.44±4.21	

Discussion

the hepatitis C virus (HCV) attacks the liver and leads to inflammation (6). Liver plays an important role in the body considering its function in detoxification of metabolic processes (7). The liver helps maintain normal blood glucose concentration in the fasting and postprandial states.. In this study there is no Significant differences in glucose level ($P < 0.05$) were observed in HCV patients as compare to control individuals, this agreed with sabry *et al*.,(2007) (8).After treatment with interferon alfa for 12 weeks the level of glucose is significantly increase in patients compare to before treatment, this agreed with the finding of Alev *et al*.,(2007)(9) that showed the interferon treatment affected glucose metabolism in patients with chronic hepatitis C and Yu-Li et al.(2013)(10) that suggest fasting glucose levels should be monitored closely in patients receiving interferon therapy.

Urea is a nutritional pointer connected to protein intake and It is formed in the liver and carried by the blood to the kidneys for excretion. There is Significant reduce ($P < 0.05$) in urea level were observed in HCV patients as compare to control individuals, that agreed with Mastoi *et al*., (2010) (11) and Nasir and Kalsoom, (2013) (12). Urea synthesis is reduced in liver disease, and the reduction in the maximal capacity for urea production in patients with hepatitis is due to a decreased activity of all five urea-cycle enzymes (13). Interferon alfa therapy for 12 weeks cause significantly increase in urea in HVC paitents compare to before treatment. Which agreed with the finding of Feng *et al*.,(2011) (14) that showed Antiviral therapy based on interferon alfa can significantly increase urea in patients with chronic hepatitis C.

creatinine originates from the non-enzymatic conversion of creatinine in muscle and is filtered by the kidney (15). Creatinine levels were also studied in this study. It was observed that there are Significant reduction ($P< 0.05$) of serum creatinine levels in HCV patients as compare to normal individuals, which were agreed with result of. Beddhu et al. 2002(16) ;Bruchfeld *et al*., (2003) (17) and Abbas *et al*., (2008) (18). Interferon alfa therapy for 12 weeks cause slightly raise in creatinine level but it wasn't significant, after 24 weeks of treatment the levels of creatinine singnifcantly increased and it close from control creatinine levels. This finding is agreed with work of Tavakoli *et al*., (2012) (19) that demonstrated the plasma urea and creatinine level became normal after therapy with interferon.

Bilirubin concentration is marker of liver function, as elevation of total bilirubin concentration causes haemolysis or red blood cells in the liver (20) .In the present study it was observed the direct and indirect bilirubin and total bilirubin levels of Hepatitis C patients increased significantly ($P > 0.05$) as compared to control individuals. The change in the concentrations of bilirubin may indicate the state of the liver and the type of damage (21) After interferon therapy for 12 week the 120epatiti bilirubin significantly decrease and close to the normal level of control after treatment with interferon for 24 weeks. The reduction of 120epatiti bilirubin may attribute of activity of interferon substance, where is found the exogenous and endogenous interferons decrease the levels of serum indirect bilirubin (22). This reflect the activity of interferon to improve liver function.

Albumin is synthesized by the liver is the major form of protein present in the blood, and its low concentration is a marker of liver damage (23). In this study albumin level in patients is higer than its level in control but this increase wasn't significant, that agreed with Berry et al (2005)(24) and Nagao and Sata ,2010 (25). That demonstrated Albumin levels are normal until late-stage disease. After 12 and 24 weeks of treatment with interferon alfa the albumin level is increase significantly comparison to before treatment and control. This finding is agreed with Haruna and Inoue (2014) (26) that showed the Antiviral therapy based on interferon alfa can significantly increase albumin levels .

Measurement of enzyme activity is a valuable tool in clinical diagnosis because it provides information on the effect and nature of pathological damage to tissues. Furthermore, damages to biological tissues can be assessed by changes in their enzyme activity, which indicate the catalytic influence of various factors such as inhibitors and activators, during pathological conditions.

In this study ALT ,AST and ALP levels were significantly raised in HVC patients as compared to control .this agreed with Sabry *et al*.,(2007)(8) Bushra *et al*.,(2011) (27) The most common causes of elevated AST levels are chronic hepatitis B and C .Abnormal level of serum amino trans aminases may lead to the prognosis of HCV infection (28). ALT is most intense in liver and released into the bloodstream as the result of liver damage that fairly indicates liver status (29). Elevation of ALP is observed in patients who have some form of extra hepatic and intra hepatic bile duct obstruction. The AST enzymes used for many biochemical reactions in the living cell. Elevation of this enzymes in the blood is therefore an indication of tissue damage and altered membrane permeability. After treatment with interferon for 12 and 24 weeks the level of these enzyme Significantly decreased and are return to the normal level in the control group. These results agreed with previous studies (30 ; 31; 32) that found statistical significant reduction in the mean values of ALT AST and ALP after 24 weeks of anti-viral treatment by interferon alfa .

IN this study the statistical analysis revealed that There is no significant differences among all studied parameters after comparison between male and female infected with HCV and control group. That agreed with Bushra *et al*.,(2011) (28) patients infected with HCV males or females have the same abnormal markers that reflect activity of viral factors in liver grading for disease progression.

Conclusion

Interferon therapy for ,12 and 24 weeks produces significant biochemical response in chronic hepatitis C patients. However, there was no relation between gender and the response to treatmentment.

References

1. **Page, K. ; Morris, M.D. ; Hahn, J.A. ; Maher, L. and Prins, M. (2013)**. Injection Drug Use and Hepatitis C Virus Infection in Young Adult Injectors: Using Evidence to Inform Comprehensive Prevention. Clinical Infectious Diseases, 45, S32- S38**.**
2. **Davis, G.L ; Alter, M.J ; El-Serag, H. ; Poynard, T. and Jennings, L.W.(2010). Agingof hepatitis C** virus (HCV)-infected persons in the UnitedStates: a multiple cohort model of HCV prevalence and disease progression. Gastroenterology, 138(2):513-521.
3. **Franciscus ,A.(2012).** Interferon, Ribavirin & HCV Protease Inhibitors **.HCSP .,2: 1-5.**
4. **Pawlotsky, J.(2006).** Therapy of Hepatitis C: From Empiricism toEradication.Hepatology, 43(2) Suppl., **1:S207-S220.**
5. **Kamili, S.; Drobeniuc, J.; Araujo, A. C., and Hayden, T. M.(2012).**Laboratory Diagnostics for Hepatitis C Virus Infection. Clin. Infect. Dis., 55 (1):44-48.
6. **Thomas DL, Seeff LB.(2005).** Natural history of hepatitis C. Clin Liver Dis.,(3):383–98.
7. **Helal, E., S.; Zahkok, G.Z.A.; Soliman, M. Al-Kassas and Abdel Wahed, H. (2008).** Biochemical studies on the effect of sodium nitrite and/or glutathione treatmentment on male rats. Egypt. J. Hosp. Med., 30: 25-38.
8. **Sabry, A., El-Dahshan, K., Mahmoud, K., El-Husseini, A., Sheashaa, H. and Abo-Zenah, H. (2007).** Effect of Hepatitis C virus infection on haematocrit and haemoglobin levels in Egyaptian haemodialysis patients. European Journal of General Medicine 4(1): 9-15.
9. **Alev, A. ; Uzum, A.K.; Tatli A.M. ; Fatih Oner Kaya F.O. ; Dik,I and Bedir,B.(.2007).**The effect of interferon treatmentment on glucose metabolism in patients with chronic hepatitis. Endocrine 1(4) P:70 -78.
10. **Yu-Li, L. ; Pi-Jung, H. ; Shyi-Jang, S. and Kun-Der, L.(2013).** Diabetes and Interferon Therapy – A Case Reportand Literature Review.Formos J Endocrin Metab.,4 (1): 18-21.
11. **Mastoi, A.B. ; Devrajani, B.R. ; Shah, S.R. ; Rohopoto, Q. ; Memon,S.A. ; Baloch,M. ; Qureshi M.G. and Sami, W. (2010).** Metabolic investigations in patients with hepatitis B and C World J Gastroenterol., 16(5): 603–607.
12. **Nasir, I. and Kalsoom, A.A.(2013).**Evaluation of alteration of serum total bilirubin, Gama glutamylatr ansferase(GGT), Blood urea nitrogen(BUN), serum creatinine as potential markers of kidney function in hepatitis C infected individuals. International Journal of Humanities, Arts, Medicine and Sciences., 1 (3): 49-54.

13. **Weiner D ;William E. Mitch ; Jeff M. Sands(2014)** .Urea and Ammonia Metabolism and the Control of Renal Nitrogen Excretion Clin J Am Soc Nephrol 2014Clinical Journal of the American Society of Nephrology., 103 :1-15.
14. **Feng, B. ;Eknoyan, G. ;Guo,Z. Jadoul, M. ; Rao, H. ; Wei Zhang,W. and Lai Wei,L.(2011).** Effect of interferon-alpha-based antiviral therapy on hepatitis C virusassociatedglomerulonephritis: a meta-analysis Nephrol Dial Transplant., 0: 1–7
15. **Hosten. A.O. (2014)**.Clinical Methods: The History, Physical, and Laboratory Examinations. 3rd edition.Chapter 193 .BUN and Creatinine.
16. **Beddhu S, Bastacky S, Johnson JP. (2002)**. The Clinical and Morphologic Spectrum of Renal Cryoglobulinemia. Medicine; 81: 398–409.
17. **Bruchfeld A, Lindahl K, Stahle L.(2003).** Interferon and ribavirin treatment in patients with hepatitis C-associated renal disease and renal insufficiency. Nephrol Dial Transplant.,18: 1573–1580
18. **Abbas, G. ; Hussain, S and Shafi, T.(2008). Effect of antiviral therapy on hepatitis C virus related glomerulopathy. Saudi J Kidney Dis Transplant; 19: 775–780.**
19. **Tavakoli, M. ; Manshadi, M.Y. ; Naderi, N. ; Dehghan, A. and Azizi, S. (2012)**.Unusual Side Effects of Interferon Beta-1a in Patient with Multiple Sclerosis. Mater Sociomed.,24(3): 203–205.
20. **Singh, A. ; Bhat, T.K. and Sharma, O.P. (2011).** Clinical Biochemistry of Hepatotoxicity. J Clinic Toxicol S4:001.
21. **Ashafa, A.O.T ; Yakubu, M.T. ; Grierson, D.S. and Afolayan, A.J. (2009).** Effects of aqueous leaf extract from the leaves of Chrysocoma ciliate L. on some biochemical parameters of Wistar rats. Afr. J. Biotechnol., 8:1425-1430
22. **Onji, M. ; Miyaoka,H ; Michitaka,K. Norio Horiike,N. and Yasuyuki Ohta,Y. (1993).**Serum unconjugated bilirubin levels are decreased by interferon. International Hepatology Communications 5; 1(2):91-96.
23. **Nicholson, I.P.; Wolmarans, M.R. and Park, G.R. (2000).** The role of albumin in critical illness British Journal Anaesth., 85: 599–610.
24. **Berry,V. ; Rajeev Arora,R. and Paul P.(2005).**Hepatitis C-Clinical Outcome and Diagnosis JK SCIENCE., 7(3):129-132.
25. **Nagao, M. and Sata, T. (2010).** Serum albumin and mortality risk in a hyperendemic area of **HCV infection in Japan Yumiko., Virology Journal 2010, 7:375**
26. **Haruna, Y. and Inoue, A. (2014) .**Minimal dose interferon suppository treatmentment suppresses viral replication with platelet counts and serum albumin levels increased in chronically hepatitis C virus-infected patients: a phase 1b, placebo-controlled, randomized study. J Interferon Cytokine Res., 34(2):111-6.
27. **Bushra I, Waqar A, Fouzia J, Sana G, Sarwar M, Humera, K, Sultan A, Shah J, Saba, K, Imran S, Aleena S,Sajida H.(2011).** Association of laboratory parameters with viral factors in patients with hepatitis C. Virology journal., 8:36:55-63.
28. **Murakami, S. ; Okubo, K. ; Tsuji, Y.; Sakata, H. ;Takahashi, T. Kikuchi, M. and Hirayama, R .(2004).**Changes in liver enzymes after surgery in anti-hepatitis C virus-positive patients. World J Surg., 28(7):671-4.
29. **Lee, Y.S. ; Yoon, S.K. ; Chung, E.S. ;Bae, S.H. ; Choi, J.Y. ; Han, J.Y. ; Chung, K.W. ; Sun, H.S. ; Kim, B.S. and Kim, B.K. (2001)** The relationship of histologic activity to se- rum ALT, HCV genotype and HCV RNA titers in chro- nic hepatitis C. Journal of Korean Medical Science., 16: 585-591.
30. **Kalantari, H. ; Kazemi F. and Minakari, M.(2007).** Efficacy of triple therapy with interferon alpha-2b, ribavirin and amantadine in the treatment of naïve patients with chronic 122epatitis. Journal of Research in Medical Sciences ., 12(4): 186-192.
31. **Al-Jiffri, O.(2013**).Liver Enzymes and Virologic Response to Combined PegylatedInterferon-Ribavirin Therapy in Saudi Chronic Hepatitis C Infected Patients.Middle-East Journal of Scientific Research 13 (1): 101-106.
32. **Thuy, P. ; Bunchorntavakul, C.; Dat, H. and Reddy, H.(2012).** A randomized trial of 48 versus 24 weeks ofcombination pegylated interferon and ribavirintherapy in genotype 6 chronic hepatitis C. Journal of Hepatology., 56: 1012-1018.