	ABSTRACT							
	Departments of ¹ Tropical Medicine and Gastroenterology, ² Pathology and ³ Clinical Pathology Faculty of Medicine, Sohag University							
Article	Mahmoud Saif Al-Islam ¹ , Ahmed Ahmed ² and Elham Hamed ³							
Original	LOAD TO THE EXTENT OF LIVER DAMAGE IN PATIENTS WITH CHRONIC HEPATITIS C							
	CORRELATION OF SERUM ALANINE TRANSAMINASE LEVEL AND VIRUS							

Introduction: Hepatitis C virus (HCV) infection is usually monitored by the level of alanine transaminase (ALT) and viral load. However, accumulating data indicate that these parameters are not always correlated with the disease progression.

Aim of the Work: This study aims to evaluate the relationship between serum ALT, serum HCV-RNA titer and the degree of histopathological liver damage in patients with chronic HCV.

Patients and Methods: A total of 150 patients who were recently diagnosed with chronic hepatitis C virus infection were included in our study of which 121 were males and 29 were females. Serum ALT levels, serum HCV-RNA and histopathological grading and staging were recorded.

Results: The patients' age ranged from 20 to 59 years with a mean age of 38.55 ± 10.98 years. The mean ALT level was 45.27 ± 32.31 IU/L, the mean HCV RNA level was $0.98 \times 106 \pm 2.17 \times 106$ IU/mL. Sixty seven patients (44.7%) had an elevated serum ALT level (ALT>40 IU/L) while ALT was normal in 83 patients (55.3%). The degree of liver cell damage (grade) is significantly correlated with the degree of hepatic fibrosis (stage), both grade and stage are significantly more advanced in older patients (*P*= 0.0001). The grade and stage of chronic hepatitis C tend to be significantly higher in patients with elevated serum ALT compared to those with normal ALT levels (*P*= 0.022 and *P*= 0.038, respectively). HCV viral loads had no correlation with serum ALT values, with the extent of histological damage or with degree of fibrosis.

Conclusion: Serum ALT level could reflect the histopathological changes of chronic hepatitis C virus in at least a subset of hepatitis patients while serum HCV-RNA titer had no relationship to the degree of hepatic damage. Histopathological examination of liver tissue is necessary for accurate evaluation of the extent of liver damage.

Keywords: Chronic hepatitis C, hepatitis grade and stage, alanine transaminase.

Corresponding Author: Mahmoud Saif Al-Islam Abd Elfatah, Departments of Tropical Medicine and Gastroenterology, Faculty of Medicine, Sohag University **E-mail:** mahmoud elislam@med.sohag.edu.eg

INTRODUCTION

Hepatitis C virus infection is a global disease with a worldwide prevalence estimated to be around 3% (*Pradat et al. 2000*). Egypt has the highest prevalence of HCV worldwide which was estimated to be more than 15% (*Egyptian Ministry of Health*, 2009).

Parenteral therapy for schistosomiasis, invasive medical procedures, injections, circumcision of boys by "informal" health care providers and complicated birth deliveries were all risk factors for HCV in the past (*Nafeh et al. 2000 and Medhat et al. 2002*).

Unfortunately, 55%-85% of HCV infected patients fail to clear the virus and progress to develop

chronic infection over a period of 20 to 30 years (*Pan et al. 2007*). Approximately 15-25% of HCV infected person progress to a severe liver disease, which may take more than 30 years to develop (*Muhlberger et al. 2009*). Hepatocellular carcinoma develops in 1% to 7% of patients with chronic infection. Currently, no safe and effective vaccine is available to prevent HCV infection (*Pan et al. 2007*).

HCV infection is usually monitored by the level of ALT and histopathological changes in liver biopsy specimens. However, accumulating data indicate that these parameters are not always correlated with disease progression or the response of HCV infection to therapy (*Choi et al. 1999*).

ALT is the best test for monitoring HCV infection and the efficacy of therapy in the intervals between molecular testing. However, in persons with HCV infection ALT levels may be normal or fluctuant and therefore, a single normal value does not rule out active infection, progressive liver disease, or even cirrhosis. Similarly, the normalization of ALT levels with antiviral therapy is not a proof for the success of therapy. Moreover, ALT levels may remain elevated for other reasons even after clearance of the virus (*Lauer and Walker, 2001*). ALT values neither predict the severity of clinical findings nor the degree of histological abnormalities or the patient's prognosis (*David and Rajeev, 2007*).

Histological evaluation of a liver biopsy specimen remains the gold standard for determining the progression of HCV-related liver disease and histopathological staging remains the only reliable predictor of prognosis (*Yano et al. 1996*). A biopsy may also help to rule out other concurrent causes of liver disease. Therefore, biopsy is generally recommended for the initial assessment of persons with chronic HCV infection (*National Institutes of Health, 1997*).

PATIENTS AND METHODS

Patients: Our study was a prospective study conducted at the departments of Tropical Medicine and Gastroenterology, Pathology and Clinical Pathology, Sohag University Hospitals from July to December 2012. Ethical permission was obtained from Sohag Faculty of Medicine Research Ethical Committee. One hundred and fifty five hepatitis C virus infected patients were initially included in the study. Five patients were excluded from the study, for being HCV RNA negative. Patients who had serological evidence of hepatitis B or human immuno-defficiency virus infection, patients with history of current alcohol and/or drug abuse and those who are known to have other diseases as diabetes mellitus or heart disease were excluded.

Methods: A venous blood sample of 10 ml was obtained from each subject, in the appropriate vacutainers provided, EDTA samples were subjected to complete blood picture on cell Dyne -2700 fully automated cell counter. The Na-citrated samples were used for determination of PT and aPTT on SYSMEX fully automated system. Random serum glucose, renal function tests and liver function tests including ALT samples were determined by Beckman SYNCHRON CX9, fully automated chemical auto analyzer. According to *Valva et al.* (2011) serum ALT levels of higher than 40 IU/L were considered elevated. Anti-HCV detection was performed by Axsym Abbott System, MEIA (microparticle enzyme immunoassay) technology.

Estimation of HCV RNA in Serum: Reverse Transcription-polymerase Chain Reaction (RT-PCR): Using Four Steps:

- RNA extraction. Total RNA was extracted from 100 μl of serum using a QIAamp viral RNA kit (QIAGEN, Germany) following manufacturer's instructions.
- b. Conversion to c-DNA (RT-Step): A cocktail of RT reaction was prepared with a final volume of 25 μl and reaction at RT took place in the thermal cycler. One cycle of thermal cycling includes annealing, extending and then inactivating reverse transcriptase where the tubes were incubated at 40°C for 45 min. followed by another 15 min. at 70°C.
- c. DNA amplification: PCR reaction was prepared with a final volume of 50 µl. PCR took place in the thermal cycle according to the following protocol: initial denaturation at 95°C for 5 min.; 40 cycles of denaturation at 94°C for 1 min. annealing at 55°C for 1 min. and extension at 72°C for 2 min. and final extension at 72°C for 10 min.
- d. Detection: The RT-PCR amplicon was detected by 2% agarose gel electrophoresis using a Miniprep electrophoresis chamber and the gel was then examined under the UV light by ethidium bromide staining. The expected HCV PCR band was at the level of 265 bp.

Procedure of Liver Biopsy: Liver biopsy for histopathological evaluation was obtained from all patients. The biopsies were indicated to decide the interferon treatment for the participating patients. Informed written consent was pre-taken from every patient. The biopsy was performed under local anaesthesia using 17 G quick-cut needles under ultrasound guidance. The prothrombin time and platelet count were determined within 2 days before the procedure. The procedure was performed if the baseline prothrombin time was not prolonged more than three seconds than the control value and the platelet count was at least 100.000/mm3. The patients were followed at 15 minute intervals for one hour and then at 30 minute intervals for another two hours. Patients were discharged 24 hours after the biopsy (Mamun et al. 2009).

Histopathological Evaluation of Chronic Hepatitis C: The obtained tissue cores were 1 to 2 cm long. They were fixed in 10 % formaldehyde, processed as usual, embedded in paraffin and sections of 4 µm thickness were prepared and stained with hematoxylin and eosin. Histopathological evaluation was performed without knowledge of the patients' clinical or blood samples data. All liver biopsies were examined by a single pathologist and hepatitis lesions were evaluated according to Scheuer's scoring system *(Scheuer, 1991)* for grade of necro-inflammation and stage of fibrosis. The grade of hepatitis ranged from 0 to 4 based on degree of portal inflammation, periportal inflammation/piecemeal necrosis and lobular inflammation and the stage of the disease ranged also from 0 to 4 based on extension of fibrosis (Table 1).

 Table 1: Scheuer's scoring system of chronic hepatitis.

Grade				Stage			
	Portal/periportal activity	Lobular activity		Degree of fibrosis			
0	None	None	0 None				
1	Portal inflammation	Inflammation but no necrosis	1	Enlarged, fibrotic portal tracts			
2	Mild piecemeal necrosis Focal necrosis		2	Periportal or portal-portal septa but intact architecture			
3	Moderate piecemeal necrosis	Severe focal cell damage	3	Fibrosis with architectural distortion but no obvious cirrhosis			
4	Severe piecemeal necrosis	Bridging necrosis	4	Probable or definite cirrhosis			

Statistical Analysis:

The data was analyzed by IBM-SPSS version 19.0 for Windows; IBM Inc. Variables were presented as counts, percentages and means \pm SD. Association between histopathological findings and serum ALT and HCV-RNA titer was evaluated by Spearman's correlation test, between histopathological findings and groups of serum ALT and HCV-RNA titer by χ^2 test and between continuous variables by Pearson's correlation test. P values of less than 0.05 were considered significant.

RESULTS

A total of 150 patients were included in our study; 121 were males and 29 were females. The patient's demographic features and characteristics of ALT level, HCV virus load and grade and stage of chronic HCV are summarized in Table (2). The serum level of ALT ranged from 4 to 229 IU/L, with mean and median values of 45.3 ± 32.31 IU/L and 37.3 IU/L, respectively. A great proportion of the investigated patients (55.3%) had normal ALT level (<40 IU/L), while serum level of ALT was within two times normal in 51 (34%) patients and within three times normal or more in 16 (10.7%) patients. The level of HCV RNA in the serum varied greatly between 695 and 18.5x106 IU/mL. The mean value was 0.98×106 ± 2.17×106 IU/mL and the median was 0.29x106 IU/mL. The degree of necro-inflammatory lesions varied between grades 0 to 4. The most frequent was hepatitis with mild necro-inflammatory lesions; Grade 2 which represented 61.3% (92 patients) of the investigated cases. The degree of fibrosis varied between none (stage 0) that occurred in 12 patients (8%) to liver cirrhosis (stage 4) that occurred in three patients (2%). The most frequent was stage 2 fibrosis which was detected in 66 patients (44%).

- 1. Correlation between Grade and Stage of Chronic Hepatitis C: The histopathological changes of chronic hepatitis C were evaluated in all investigated patients. There was a statistical significant association between necro-inflammatory lesions and degree of fibrosis, r = 0.77; P < 0.01 (Figure 1). Patients who had mild necro-inflammatory lesions tend to have low stage of fibrosis while fibrosis stage 3 or 4 was usually encountered in patients with high grade disease.
- 2. Correlation of Patients' Age with Grade and Stage of Chronic Hepatitis C: There was a statistically significant correlation between patients' age and both hepatitis grade (r = 0.36, P < 0.01) and fibrosis stage (r = 0.37, P < 0.01). The necro-inflammatory lesions and fibrosis tend to be more extensive in older compared to younger patients (Figure 2).

Variable	Category	Number	Total
Sex	Male Female	121 (80.7%) 29 (19.3%)	150
Age	Minimum Maximum Mean±SD Median	20 59 38.55±10.98 40	150
ALT (IU/L)	Minimum Maximum Mean±SD Median <40 (normal) 40-80 81-120 121-160 >160	4 229 45.27±32.31 37.3 83 (55.3%) 51 (34%) 11 (7.3%) 4 (2.7%) 1 (0.7%)	150
Virus load (IU/mL)	$\begin{array}{l} \mbox{Minimum} \\ \mbox{Maximum} \\ \mbox{Mean} \pm \mbox{SD} \\ \mbox{Median} \\ < 0.2 \times 10^6 \\ 0.2 \times 10^6 \\ - 0.6 \times 10^6 \\ 0.6 \times 10^6 \\ - 1.4 \times 10^6 \\ > 1.4 \times 10^6 \end{array}$	$\begin{array}{c} 695\\ 18.5 \times 10^{6}\\ 0.98 \times 10^{6} \pm 2.17 \times 10^{6} \ 0.29 \times 10^{6}\\ 70 \ (46.7\%)\\ 30 \ (20\%)\\ 15 \ (10\%)\\ 4 \ (2.7\%)\\ 31 \ (20.7\%)\end{array}$	150
Grade	0 1 2 3 4	1 (0.7%) 20 (13.3%) 92 (61.3%) 25 (16.7%) 12 (8%)	150
Stage	0 1 2 3 4	12 (8%) 48 (32%) 66 (44%) 21 (14%) 3 (2%)	150

Table 2: Demographic, laboratory and histopathological characteristics of the investigated cases







Figure 2: Association of patients' age with grade (A) and stage (B) of chronic hepatitis C. Both grade and stage of chronic hepatitis C were significantly higher in older patients. The horizontal bars represent the median values, the boxes represent the 50th percentiles, whiskers represent the range of data and the numbers refer to the number of cases in each group.

3. Correlation of Patients' Serum ALT Levels with Grade and Stage of Chronic Hepatitis C: Among patients with normal ALT levels (n=83); normal liver tissue, minimal, mild, moderate and severe chronic hepatitis was found in 1.2%, 12%, 69.9%, 14.5% and 2.4% respectively compared to 0%, 14.9%, 50.7%, 19.4% and 14.9% in patients with elevated ALT levels (n=67). There was a statistically significant difference of necro-inflammatory activity between patients with elevated liver enzymes versus those without; χ^{2} = 5.22, *P* = 0.022. The majority of patients with normal ALT had minimal to mild chronic hepatitis as compared with patients with elevated ALT, who showed more necro-inflammatory changes (Table 3).

Categories		Grading							Total
		0	1	2	Total	3	4	Total	TOLAI
Normal ALT	(n) %	(1) 1.2	(10) 12	(58) 69.9	(69) 83	(12) 14.5	(2) 2.4	(14) 17	(83) 55.3%
Elevated ALT	(n) %	(0) 0	(10) 14.9	(34) 50.7	(44) 65.7	(13) 19.4	(10) 14.9	(23) 34.3	(67) 44.7%
Total		1	20	92	113	25	12	37	150

Table 3: Grades of chronic hepatitis C in different serum ALT profiles.

Comparison between the two groups: χ^2 = 5.22, P = 0.022.

We also investigated the correlation between necro-inflammatory grade and the actual values of serum ALT level without categorization into normal and elevated groups. There is a steady rise of serum ALT level as the disease progresses from Grade 0 to Grade 4 (Figure 3), however this association does not reach the 95% confidence level (r = 0.10, P = 0.19).



Figure 3: Correlation of serum ALT level with grade of chronic hepatitis C. The circles refer to the cases and the sloping line refers to the association.

Patients with normal ALT levels had no fibrosis, portal fibrosis, peri-portal fibrosis, septal fibrosis and cirrhosis in 9.6%, 32.5%, 50.6%, 6% and 1.2%, respectively compared to 6%, 31.3%, 35.8%, 23.9% and 3% in patients with elevated ALT (Table 4).

There was a statistically significant difference of stage of fibrosis between patients with elevated serum ALT enzymes versus those without (χ 2= 4.23, *P* = 0.038).

Categories		Staging							Tatal
		0	1	2	Total	3	4	Total	rotai
Normal ALT	(n) %	(8) 9.6	(27) 32.5	(42) 50.6	(77) 92.8	(5) 6.0	(1) 1.2	(6) 7.2	(83) 55.3%
Elevated ALT	(n) %	(4) 6.0	(21) 31.3	(24) 35.8	(49) 73	(16) 23.9	(2) 3	(18) 27	(67) 44.7%
Total		12	48	66	126	21	3	24	150

Table 4: Stage of chronic hepatitis C in different serum ALT profiles.

Comparison between two groups: χ^2 = 4.287, P = 0.038

Most patients with stage 0 or 1 fibrosis had lower values of serum ALT compared to fibrosis stage 3 or 4 who had higher values (Figure 4). However

the 95% confidence of this relationship was not significant (r = 0.11, P =0.14).



Figure 4: Correlation of serum ALT level with stage of hepatic fibrosis in chronic hepatitis C. There is a tendency of serum ALT to rise as chronic hepatitis C progresses to higher stage. The circles refer to the cases and the sloping line refers to the association.

- 4. Correlation of patients' viral load with grade and stage of chronic hepatitis C: In our study, there was no relationship between virus load and either grade of chronic hepatitis (r = -0.003, P = 0.97) or degree of fibrosis (r = -0.06, P = 0.45).
- 5. Correlation between Serum ALT Level and Viral Load: There was no significant association between serum ALT and viral load (Figure 5 A), between serum ALT and different categories of viral load (Figure 5 B) or between virus load and different categories of normal and elevated serum ALT level.



Figure 5: Correlation between serum ALT level and HCV RNA titer (A), ALT level and HCV load categories (B). The circles refer to the cases and the sloping line refers to the association. The horizontal bars represent the median values, the boxes represent the 50th percentiles, whiskers represent the range of data, the stars refer to extreme values and the numbers refer to the number of cases in each group.

DISCUSSION

This study included 150 patients with chronic hepatitis C virus infection as proved by PCR with an age ranged from 20 to 59 years. The exact time of acquiring HCV infection is unknown in all patients. Considering the wide age range, it is likely that different durations of HCV infection are covered in this study. Only one case had neither necroinflammatory lesions nor fibrosis of the liver (Grade 0 and stage 0) while 149 patients showed varieties of either or both lesions. The patient with Grade 0/ stage 0 was a 23 years old female patient with ALT level of 12 IU/L and virus load of 16100 IU/mL. The absence of histological findings in this patient suggests a recent HCV infection or a healthy carrier state. Overall, there was a statistically significant association between the necro-inflammatory lesions and the degree of fibrosis (r = 0.77; P <0.01). This implies a relatively accurate coordinate histopathological evaluation.

Both grade and stage of chronic hepatitis C were significantly higher in older age patients, (P < 0.01). This could be explained by the progression of the disease with prolongation of duration of infection. Lu et al. (2003) observed an increase in degree of fibrosis with the increase of age.

It has been reported that approximately 30% of patients with chronic HCV infection show persistently normal ALT levels and hence formerly referred to as healthy or asymptomatic HCV carriers. Although those patients were historically excluded from antiviral treatment, it has now become clear that the majority of them have some degree of histological liver damage and 20% of them might progress toward a more severe degree of liver fibrosis (*Puoti et al. 2010*).

Serum ALT levels cannot serve as a parameter to assess the degree of liver damage in patients with chronic hepatitis C virus infection. It is not easy to explain the reason for the presence of normal or near normal ALT levels in patients presenting with severe liver damage (*Liu et al. 2009*). Bantel et al.(2001) explained this discordance by death of hepatocytes without cell membrane injury leading to normal or even reduced release of transaminases.

These results showed that 83 (55.3%) patients had a normal serum ALT level while 67 (44.7%) patients had elevated serum ALT level. We found that necroinflammatory lesions are significantly different in patients with normal versus elevated serum ALT $(\chi 2 = 5.22, P = 0.022)$. In patients with normal serum ALT, the majority (69=83%) had either normal liver histology or Grade 1 or 2 while a minority (14=17%) had either Grade 3 or 4. In patients with elevated serum ALT, slightly higher percentage of patients 23 (34.3%) had Grade 3 or 4. 113 (75.3%) of the total cases had Grade 0, 1 or 2 necro-inflammatory lesions of which 69 (61.1%) had normal ALT and 44 (38.9%) had elevated ALT while 37 (24.7%) had Grade 3 or 4 of which 14 (37.8%) had normal ALT and 23 (62.2%) had elevated ALT. It is interesting to document that our study included 12 patients with sever necro-inflammatory lesions (Grade 4), of which 10 had elevated serum ALT and two hadn't.

This result agrees with *Mohamed et al. (2009)* who reported that mild hepatitis was the most common histological finding representing 73.3% of CHC patients with normal liver enzymes and 39.1% of patients with elevated liver enzymes. Also, *Puoti et al.(2002)* concluded that mild hepatitis was the most common finding in chronic HCV infected patients. In contrast to our results, *Puoti et al. (1997)* reported that moderate to severe hepatitis is present more frequently among subjects with normal ALT than those with elevated ALT. Another study reported that ALT values do not differ with the increased severity of inflammation (*Neuman et al. 2012*).

The studv showed statistically significant difference of fibrosis stage between patients with normal versus elevated serum ALT levels (P =0.038). Fibrosis stage 2 is the most common in our study being recorded in 50.6% of patients with normal serum ALT profile and in 35.8% of patients with elevated serum ALT. In patients with normal serum ALT 77 (92.8%) had either normal liver histology or stage 1 or 2 fibrosis while 6 (7.2%) patients had stage 3 or 4. There is a tendency of serum ALT to rise as CHC progresses to a higher stage. This is in contrast to Mohamed et al. (2009) as their staging results showed that F1 stage was the most common in CHC patients where it was present in 46.7% of patients with normal enzymes and 39.1% of patients with elevated enzymes, with no significant difference in fibrosis staging between the two groups (P = 0.51).

The severity of liver disease is independent of serum levels of hepatitis C virus. The precise mechanism by which hepatitis C virus damages the liver remains poorly understood. Until recently, a direct cytopathic effect of the virus was considered as the primary cause of liver injury. It has been suggested that the degree of liver damage is the result of a complicated interaction between the virus and immune response of the host (*Rehermann,* 2000). Immune mediated liver damage is believed to be initiated by HCV-specific T lymphocytes and is enhanced by HCV-induced HLA-A, B and C and intracellular adhesion molecules (*Ballardini et al.* 1995 and Nelson et al. 1997).

In this study, we found that HCV load has no significant correlation with both the grades of liver necro-inflammatory activity (r = -0.003, P = 0.97) and the stage of liver fibrosis (r = -0.06, P = 0.45). Our results were in agreement with Liu et al. (2009) who found non significant connection between serum HCV-RNA titer and the grades of liver necroinflammatory activity (r = 0.50, P = 0.667) or the stage of liver fibrosis (r = 0.20, P = 0.80). Also, Saleem et al. (2004) found no significant correlation between serum HCV RNA levels and grade or stage of the disease. Puoti et al. (1997) concluded that the severity of liver damage and the clinical features had no correlations with HCV load or ALT level. Similarly, De Moliner et al. (1997) reported absence of correlation between viral load and degree of liver injury. On the other hand, Kato et al. (1993) observed significantly higher HCV RNA titer in patients with chronic active hepatitis and cirrhosis compared to those with milder histological abnormalities such as chronic persistent hepatitis. Similarly, *Fanning et al.* (1999) in a study on Irish women found a significant correlation between serum HCV loads and the degree of hepatic inflammation. Also, *Zechini et al.* (2004) observed a statistically significant correlation between HCV RNA levels and histological activity index (r = 0.25, P = 0.008).

In our study, serum ALT level showed no correlation with viral load or virus load categories. This result is in accordance with the findings of *Butt et al.* (2007) who showed insignificant difference in viral load between patients with elevated ALT levels and those without. Also, *Liu et al.* (2009) reported that serum HCV-RNA titer had no significant relationship with ALT level (r = 0.40, P = 0.695). It should be noted, however, that some authors have reported higher viral load in patients with high ALT levels (*Hassan et al.* 2002). On the contrary, Ito et al. (2004), reported higher viral load in chronic HCV patients with persistently normal ALT levels.

REFERENCES

Ballardini, G., Groff, P., Pontisso, P., et al. 1995. Hepatitis C virus (HCV) genotype, tissue HCV antigens, hepatocellular expression of HLA-A,B,C, and intercellular adhesion-1 molecules. Journal Clinical Investigation 95:2067-2075.

Bantel, H., Lügering, A., Poremba, C., et al. 2001. Caspase activation correlates with the degree of inflammatory liver injury in chronic hepatitis C virus infection. Hepatology 34(4 pt 1):758-767.

Butt, A. A., Tsevat, J., Ahmad, J., et al. 2007. Biochemical and virologic parameters in patients coinfected with hepatitis C and HIV versus patients with hepatitis C mono-infection. American Journal Medical Sciences 333(5):271-275.

Choi, Y., Putti, T., Win, K., et al. 1999. Correlation of viral RNA, alanine aminotransferase and histopathology in hepatitis C virus-associated hepatitis. Molecular Diagnosis 4(3):251-254.

David, C. W., and Rajeev, V. 2007. Hepatits viral. Medscap Journal:21.

De Moliner, L., Pontisso, P., De Salvo, G. L., et al. 1998. Serum and liver HCV RNA levels in patients with chronic hepatitis C: Correlation with clinical and histological features. Gut 42(6):856-860.

Egyptian Ministry of Health. 2009. Egyptian Ministry of Health annual report.

Fanning, L., Kenny, E., Sheehan, M., et al. 1999. Viral load and clinicopathological features of chronic hepatitis C (1b) in a homogeneous patient population. Hepatology 29(3):904-907.

Hassan, M. I., Kassim, S. K., Ali, H. S., et al. 2002. Evaluation of nitric oxide (NO) levels in hepatitis C virus (HCV) infection: Relationship to schistosomiasis and liver cirrhosis among Egyptian patients. Disease Markers 18(3):137-142.

Ito, H., Yoshioka, K., Ukai, K., et al. 2004. The fluctuations of viral load and serum alanine aminotransferase levels in chronic hepatitis C. Hepatology Research 30(1):11-17.

Kato, N., Yokosuka, O., Hosoda, K., et al. 1993. Quantification of hepatitis C virus by competitive reverse transcription-polymerase chain reaction: Increase of the virus in advanced liver disease. Hepatology 18(1):16-20.

Lauer, G. M., and Walker, B. D. 2001. Hepatitis C virus infection. New England Journal Medicine 345(1):41-52.

Liu, P., Li, Y., and Sun, C. M. 2009. Correlations of serum hepatitis C virus RNA and alanine transaminase with liver histopathological changes in patients with chronic hepatitis C. Laboratory Medicine 40(3):167-169.

Lu, L. G., Zeng, M. D., Mao, Y. M., et al. 2003. Relationship between clinical and pathologic findings in patients with chronic liver diseases. World Journal of Gastroenterology 9(12):2796-2800.

Mamun-Al-Mahtab, M., Rahman, S., Khan, M., et al. **2009.** Liver histopathological features of HBeAg-negative chronic hepatitis B in young Bangladeshis. Hepatitis Monthly 9(1):29-33.

Medhat, A., Shehata, M., Magder, L. S., et al. 2002. Hepatitis C in a community in Upper Egypt: Risk factors for infection. American Journal of Tropical Medicine and Hygiene 66(5):633-638.

Mohamed, H. R., Abdel-Azziz, M. Y., Zalata, K. R., and Abdel-Razik, A. M. 2009. Relation of Insulin Resistance and Liver Fibrosis Progression in Patients with Chronic Hepatitis C Virus Infection. International Journal Health Science 3(2):177-186.

Muhlberger, N., Schwarzer, R., Lettmeier, B., et al. 2009. HCV-related burden of disease in Europe: A systematic assessment of incidence, prevalence, morbidity and mortality. BMC Public Health 9:34.

Nafeh, M. A., Medhat, A., Shehata, M., et al. 2000. Hepatitis C in a community in upper Egypt: I. Crosssectional survey. American Journal of Tropical Medicine and Hygiene 63(5-6):236-241.

National Institutes of Health Consensus Development Conference Panel statement. **1997.** Management of hepatitis C. Hepatology 26(1):2S-10S.

Nelson, D. R., Marousis, C. G., Davis, G. L., et al. **1997.** The role of hepatitis C virus-specific cytotoxic T lymphocytes in chronic hepatitis C. Journal Immunology 158(3):1473-1481.

Neuman, M. G., Schmilovitz-Weiss, H., Hilzenrat, N., et al. 2012. Markers of inflammation and fibrosis in alcoholic hepatitis and viral hepatitis C. International Journal Hepatology 2012:231210.

Pan, Q. W., Henry, S. D., Scholte, B. J., et al. 2007. New therapeutic opportunities for Hepatitis C based on small RNA. World Journal of Gastroenterology 13(33):4431-4436.

Pradat, P., and Trépo, C. 2000. HCV: Epidemiology, modes of transmission and prevention of spread. Baillière's Best Practice Research Clinical Gastroenterology 14(2):201-210.

Puoti, C., Bellis, L., Guarisco, R., et al. 2010. HCV carriers with normal alanine aminotransferase levels: Healthy persons or severely ill patients? Dealing with an everyday clinical problem. European Journal of Internal Medicine 21(2):57-61.

Puoti, C., Castellacci, R., Montagnese, F., et al. 2002. Histological and virological features and follow-up of hepatitis C virus carriers with normal aminotransferase levels: The Italian prospective study of the asymptomatic C carriers (ISACC). Journal Hepatology 37(1):117-123.

Puoti, C., Magrini, A., Stati, T., et al. **1997.** Clinical, histological and virological features of hepatitis C virus carriers with persistently normal or abnormal alanine transaminase levels. Hepatology 26(6):1393-1398.

Rehermann, B. 2000. Interaction between the hepatitis C virus and the immune system. Seminars in Liver Disease 20(2):127-141.

Saleem, N., Mubarik, A., Qureshi, A. H., et al. 2004. Is there a correlation between degree of viremia and liver histology in chronic hepatitis C? Journal of the Pakistan Medical Association 54(9):476-479.

Scheuer, P. J. 1991. Classification of chronic viral hepatitis: A need for reassessment. Journal Hepatology 13(3):372-374.

Valva, P., Casciato, P., Diaz Carrasco, J. M., et al. **2011.** The role of serum biomarkers in predicting fibrosis progression in pediatric and adult hepatitis C virus chronic infection. PLoS One 6(8):e23218.

Yano, M., Kumada, H., Kage, M., et al. 1996. The long-term pathological evolution of chronic hepatitis C. Hepatology 23(6):1334-1340.

Zechini, B., Pasquazzi, C., and Aceti, A. 2004. Correlation of serum aminotransferases with HCV RNA levels and histological findings in patients with chronic hepatitis C: The role of serum aspartate transaminase in the evaluation of disease progression. European Journal Gastroenterology and Hepatology 16(9):891-896.

ملخص البحث

العلاقة بين مستوى الألنين ترانس أميناز في السيرم ومستوى الفيروسات الى درجة تلف الكبد في مرضى العلاقة بين مستوى الألنين ترانس أميناز في المرض سي

محمود سيف الإسلام عبد الفتاح', أحمد رشدى حامد', إلهام عمر حامد" أقسام طب المناطق الحارة و الجهاز الهضمى', الباثولوجي'، الباثولوجيا الاكلينيكية"- كلية الطب، جامعة سوهاج, مصر

المقدمة: عادةً ما يتم متابعة الإلتهاب الكبدى سي (HCV) بواسطة مستوى الألنين ترانس أميناز (ALT) فى السيرم ومستوى الفيروس الكبدى سي (HCV- RNA) فى الدم. غير أن دراسات كثيرة تشير إلى أن هذه المعايير ليست مرتبطة دائما مع تطور المرض.

الهدف من الدراسة: تهدف هذه الدراسة إلى تقييم العلاقة بين مستوى الألنين ترانس أميناز في السيرم ، مستوى الفيروسات الكبدية سي في االدم ودرجة تلف الكبد النسيجية في مرضى الإلتهاب الكبدى الفيروسي سي المزمن.

المرضى والطرق: ولقد تم أدراج عدد 150 مريض في دراستنا من مرضى الإلتهاب الكبدى المزمن سي ممن تم تشخيصهم حديثا منهم 121 من الذكور و 29 من الإناث. وتم تسجيل مستوى الألنين ترانس أميناز فى السيرم و مستوى الفيروسات الكبدية سي فى الدم ودرجة إلتهاب و تليف الأنسجة الكبدية .

ولقد أثبتت النتائج أن درجة إلتهاب الكبد grade)) مرتبطة بدرجة كبيرة مع مقدار تليف الكبد (stage) وايضا يوجد ارتباط ذو دلاله احصائيه كبيرة بينهما وبين السن المتقدم. و تميل درجة التهاب الكبد ودرجة التليف إلى أن تكون أعلى بكثير في المرضى الذين يعانون من ارتفاع في مستوى الألنين ترانس أميناز مقارنة بالذين عندهم مستوى طبيعى منه.

ولم يتم العثور على ارتباط ذي دلاله احصائيه بين مستوى الفيروس الكبدي سي و مستوى الألنين ترانس أميناز و درجة تلف الكبد و تليفه.

الخلاصة: ولقد تم استنتاج أن مستوى الألنين ترانس أميناز في السيرم يمكن الي درجة ما ان يعكس التغيرات النسيجية المرضية لفيروس الإلتهاب الكبدى المزمن سي على الأقل في مجموعة فر عية من المرضى بينما مستوى الفيروس الكبدى سي في الدم لا ينبئ بدرجة تلف خلايا الكبد. و لا يزال فحص الأنسجة الكبدية ضروري للتقييم الدقيق لمدى تلف الكبد.