DISCUSSION

Infections with HCV and HIV-1 are among the most frequent chronic infections worldwide. HCV has infected about 3% of the world's population. It is spread primarily by direct contact with human blood mainly through not screened blood transfusions, the use of inadequately sterilized medical equipment, and through needle-sharing among intravenous drug abusers. Although considered rare ways of transmission the vertical route and sexual transmission are also documented. However, in about 20 - 40% of all patients, the route of transmission is still unknown.

Regarding HIV, infection could be acquired through unprotected homo- or heterosexual contact, direct contact with blood and blood products, especially in intravenous drug abusers. Vertical transmission represents a significant mode for transmission of HIV infection.

Coinfection with hepatitis C virus (HCV) and HIV is common in at risk populations because of shared routes of transmission. In some high-risk populations, such as injection drug users, rates of concordance between HIV and HCV infection as high as 60%–80% have been observed.[188]

The advent of HAART, however, has allowed patients infected with HIV to restore and retain immune function, increasing life span and enabling the emergence of morbidity and mortality due to other causes, liver disease has been a major cause of morbidity and mortality in patients with human immunodeficiency virus (HIV) infection.[189]

By the late 1990s, end-stage liver disease (ESLD) or cirrhosis was a leading cause of death in HIV-infected populations. Cirrhosis is a serious liver condition characterized by irreversible scarring of the liver that can lead to liver failure and death. Progression to ESLD in HCV monoinfected patients typically takes 20–30 years after initial infection. With HIV co infection, this process is accelerated.[190] The mechanisms underlying this process are unclear, although HAART-related hepatotoxicity,[191] and immune reconstitution [192] have been implicated.

Until a few years ago Combination therapy with pegylated interferon and ribavirin was approved by the FDA for treatment of Hepatitis C. Unfortunately, more than 50 % of patients with chronic HCV infection are either non-responders or will relapse when therapy is stopped.[193] A new class of direct-acting antiviral agents (DAAs) has revolutionized the treatment of HCV infection. These drugs are genotype-based, target specific enzymes involved in viral replication. The addition of these new protease inhibitors to pegylated interferon and ribavirin is becoming the new standard of care for the treatment of chronic HCV infection.

The liver is the largest organ in the body and performs many functions that are critical for survival. These functions are impaired in patients with chronic liver disease, critically so in patients with ESLD. Regardless of the underlying etiology of chronic liver disease, hepatic fibrosis is a wound-healing process in response to an acute or chronic liver injury to parenchymal cells.[43] Chronic inflammation of the liver can lead to cirrhosis, a stage of organ dysfunction and damage in which scar tissue replaces normal functioning tissue and causes a dramatic, and potentially fatal, decline in liver function. Even in HCV-monoinfected patients, the probability of survival decreases quickly after decompensation.

Traditionally, liver biopsy has been considered the gold standard to diagnose and monitor the progression of fibrosis in patients with chronic viral hepatitis and other liver diseases. However, liver biopsy is an invasive procedure associated with a risk of complications such as sampling errors especially with small sized biopsies, intraobserver and interobserver variation, pain and bleeding.[76, 194] For this reason, liver biopsy has poor tolerance, particularly if it needs to be repeated over time in an individual patient.

Despite the aforementioned limitations, there has been a clear resistance to accept noninvasive diagnosis of liver fibrosis as a viable and preferable alternative to liver biopsy. The reasons for this are various. First, there is a paucity of well-designed studies assessing noninvasive methods, and sufficient external validation for some of the proposed methods is lacking. Second, the number of proposed methods to assess disease severity remains in a state of constant growth and there is practically no time to validate or test them all. Third, liver biopsy itself is not an ideal gold standard. Finally, there is still significant opposition to changing what has long stood as dogma. The aforementioned reasons may explain why the introduction of noninvasive methods in clinical practice is making such slow headway in the field of hepatology.

Ideally liver fibrosis marker should be of high sensitivity and specificity to identify different stages of fibrosis, readily available, safe, inexpensive, reproducible and applicable to the monitoring of disease progression or regression as a part of natural history of liver disease or treatment regimens.

Noninvasive methods include routine biochemical and haematological blood tests, imaging techniques as well as serum fibrotic markers.

The most common fibrosis markers used in current assays involve measuring products of extracellular matrix synthesis or degradation and the enzymes that regulate their production or modification including hyaluronic acid, serum collagenases and their inhibitors (tissue inhibitor of metalloproteinase [TIMP]), and profibrogenic cytokines (such as transforming growth factor β1).[89]

HA is a high molecular weight glycosaminoglycan, which is an essential component of extracellular matrix in virtually every tissue in the body. In the liver, HA is mostly synthesized by the hepatic stellate cells and degraded by the sinusoidal endothelial cells.[180] Liver disease will therefore reduce the rate of clearance of HA in addition, activation of stellate cells during fibrogenesis may increase the hepatic synthesis of HA resulting in elevated plasma HA levels. In chronic hepatitis C virus (HCV), HA levels increase with the development of liver fibrosis. Moreover, in patients with cirrhosis, HA levels correlate with clinical severity. [195, 196]

The aim of the current study was to evaluate the effectiveness of serum HA in assessment the extent of liver fibrosis and its ability to predict risk of serious liver events in patients with chronic HCV infection and in patients with HCV/HIV co- infection in comparison to ultrasound findings and liver function tests.

And to study difference in serum HA in two comparison groups, one before initiation of PEG IFN+ RBV therapy and the other after completion of 48 weeks course of PEG IFN+ RBV therapy in patients with chronic HCV infection to identify the relationship between the level of this marker and the effectiveness of Interferon therapy.

This cross sectional comparative study was conducted on eighty four subjects divided into three main groups. The first group consisted of twenty four patients represented patients fit for IFN therapy that was divided into two sub groups, one before initiation of the treatment (group Ia) and the other had completed a 48- weeks course of it (group Ib). The second group enrolled twenty four patients with HCV monoinfection, twelve patients had compensated liver insufficiency (group IIa) while the other twelve patients had decompensated liver disease (group IIb). The last group included thirty six patients divided into three subgroups, twelve patients had HCV/HIV co infection with liver disease (group IIIa), twelve patients with HCV/HIV co infection with no liver disease (group IIIb) and twelve patients with HIV infection (group IIIc).

Regarding demographic data of the study population, males constituted the majority of patients in group Ia as they were 8 (66.7%) versus 4 patients (33.3%) were females, the age of group Ia ranged from 25 to 42 years with a mean of 34.75 years. In group Ib, the number of male patients was 8 (66.7%) while females were 4 (33.3%), the age ranged from 27 to 46 with a mean of 35.25 years. Patients of group IIa consisted of 10 females (83.3%) versus 2 males (16.7%), ages ranged from 29 to 56 years with a mean of 43.5. Group IIb patients were 10 males (83.3%) and 2 females (16.7%) with ages ranged from 44 to 73 with a mean of 56.33 years. In group III the vast majority of patients were males with numbers of 12 (100%), 11 (91.7%) and 10 (83.3%) in groups IIIa, IIIb and IIIc respectively with age means of 36.92, 31 and 30.08 years successively. It was found that there was statistically significant difference in age between group II and group III (P=0.000, 0.009 respectively), with the highest mean of age reported in group IIb (56.33 years) follwed by group IIa (43.5) while the mean of age in group IIIa (HCV/HIV co infection with liver insult) was 36.92 years indicating the acceleration of progression of liver disease in patients of HCV/HIV co infection rather than HCV monoinfection.

Gender analysis of the study population showed that the majority of patients were males in all groups with the exception of group IIa and this came in agreement with Poynard et al., (2002)[197]; Abo Alazm and El Sheikh (1996)[198] whose studies showed significant association between the male gender and fibrosis progression. Moreover, Pinzani (2004)[199] reported that male gender (for groups of age >50 years) has been shown to be a predictor of the development of significant fibrosis or, at least, of a faster progression to cirrhosis which is consistent with the current study finding of presence of the most severe form of the disease in group IIb in which males constituted 83.3% and mean of age was 56.33 years. Also, it was found that male sex predominated in group III representing 100% of patients of group IIIa, 91.7% of group IIIb and 83.3% of group IIIc. Jam et al[200] in their cross sectional study that was done in Iran studied a total of 642 patients with HIV/AIDS attending the HIV Clinic at Imam Khomeini Hospital in Tehran, Iran found that the majority of patients enrolled in this study were males (87%) while females were (13%) which is more or less similar to what was reported in the present study. On the other hand, Enawgaw et al[201] in their comparative cross sectional study that was done in Ethiopia on a total of 290 HIV/AIDS infected patients reported that mean age of HIV patients presented in their study was 35 years and the majority of patients included in their study 184(63.4%) HIV infected patients were females, while only 106 (36.6%) patients were males. The difference in the prevailing gender in different studies may be attributed to the different rate of exposure among both sexes in different communities which could be explained by presence of risk of acquiring infection in 100%, 91.7% and 100% in groups IIIa, IIIb and IIIc respectively and by the type of risk most reported in

group III which was intravenous drug addiction that was present in 100% in group IIIa ,75% in group IIIb and 83% in group IIIc patients.

Regarding clinical findings, the most common complaints reprted by the patients of group I were dyspepsia that was found in 5 (41.7%) patients of group Ia and 3 (75%) patients of group Ib and abdominal pain that was found in 3 (75%) patients in group Ia and 7 (58.3) patients of group Ib. In group IIa the most common reported complaints were dyspepsia and abdominal pain by 9 (75%) of patients. In group IIb dyspepsia,abdominal distension and abdominal pain were reported by 100% of patients followed by heamatemesis by 75% of patients. In group IIIa the most frequent symptom was fever found in 12 (100%) of patients followed by diarrhea found in 10 (83.3%) patients while in group IIIb fever also found in 100% of patients followed by diarrhea in75% and in group IIIc fever and diarrhea found in 100% and 91.7% of patients respecvtively.

Regarding clinical signs, hepatomegaly was the most frequent sign found in 7(58.3%) patients of both sub groups Ia and Ib, found in 12 patients (100) of group IIa, 8 (66.7%) patients of group IIb and 10 patients (83.3%) of group IIIa. Ascites was found in all patients of group IIb (100%) and in one patient (8.3%) of group IIIa while hepatic encephalopathy was found in 5 patients (41.7%) in group IIb and in one patient (8.3%) of group IIIa.

In the current study, it was observed that serum hyaluronic acid had statistically significant difference among all studied groups with the highest level observed in group IIb with a mean of 148.33 ng/ml followed by group IIIa with a mean of 58.59 ng/ml then group IIa with a mean of 48.94 ng/ml and group Ia with a mean of 44.12ng/ml.

Regarding the IFN therapy group (group I), serum hyaluronic acid level had statistically significant difference before initiation of the treatment (group Ia) and after completion of the treatment (group Ib) (P= 0.001). Serum HA level was higher in group Ia than group Ib indicating the decrease of its level after treatment with IFN.

A similar study conducted in the Tropical Medicine Department, Mansoura University Hospitals, Mansoura, Egypt on 52 HCV patients (37 male and 15 female; aged 21 - 48 years) between May 2009 and March 2011 showed that the levels of HA was increased with the severity of fibrosis and decreased after PEG IFN therapy treatment even in non-responders and relapsers patients. HA was considered the best markers for discriminating F3 versus F1/F2 with AUC 0.981.[202]

Another study conducted on 109 patients with HCV-associated liver disease measuring serum type IV collagen, amino-terminal peptide of type III procollagen (PIIIP), hyaluronic acid (HA), YKL-40 levels and biochemical Parameters by RIA or ELISA. Eighty-eight patients underwent liver biopsy, and 67 of 109 patients received interferon (IFN) therapy to investigate the relationship between the concentrations of serum fibrosis markers and histological fibrosis scores (METAVIR), and evaluate the changes of the levels of fibrosis markers before and after the IFN therapy. Results showed increase in serum levels of all markers, particularly HA (F = 13.128, P<0.0001) correlated with the progression of liver fibrosis, based on the receiver operating curve (ROC), the ability of serum HA exceeded the abilities of other serum markers to determine fibrosis score 4 from fibrosis score 0-3 (AUC = 0.854). But according to this study only YKL-40 values significantly decreased not only in the responder group, but also in the non responder

group (P = 0.03).[203] This is agreed with the study conducted by Arain et al. on hepatitis C patients which reported that HA is not a reliable marker for selecting treatment decisions.[204]

In the current study, there was positive correlation between serum hyaluronic acid (HA) and the degree of liver fibrosis according to the criteria proposed by the Ishak system in group Ia (P =0.000, R =0.856) and group Ib (P= 0.007, R= 0.755).

Jérôme Guéchot et al., studied the role of HA level to detect improvement of HCV liver fibrosis after α-interferon therapy. This study concluded that serum HA level correlated with the extent of liver fibrosis both before and after α-interferon therapy, but not with the histopathological indices of liver inflammation or necrosis. Parallel changes in serum HA and liver fibrosis occurred, serum HA levels were decreased significantly in patients in whom fibrosis improved, increased significantly in patients in whom fibrosis worsened and did not change significantly in patients in whom fibrosis was unmodified.[205]

Regarding HCV monoinfection group (group II), there was significant difference between patients with compensated liver disease and patients with decompensated liver disease regarding serum HA level. It was higher in patients with decompensated liver disease (group IIb) than patients with compensated liver disease (group IIa) with means of 148.33 ng/ml and 48.94 ng/ml respectively (P= 0.000).

Patel et al. reported that HA is an important marker for predicting cirrhosis in HCV patients. They reported an HA cutoff value of 110 μg/L with 79% sensitivity and 89% specificity to diagnose cirrhosis vs. fibrosis.[206]

McHutchison et al. observed that a cutoff value of < 60 μg/L is the best way to exclude cirrhosis and/or advanced fibrosis. They indicated that one-third of patients with liver cirrhosis have been predicted by the ≥ 60 μg/L of HA level. In their final conclusion they reported that HA cannot replace the liver biopsy, and histological findings are more reliable.[97]

Valva et al. showed that the combination of serum levels of HA, PIIINP and TGFβ is more reliable to evaluate the degree of liver fibrosis in comparison with each marker alone.[207]

Regarding HCV/HIV co infection, in the current study serum HA showed significant increase in HCV/HIV coinfcted patients who had liver disease but there was no statistically significant difference between HCV/ HIV patients who had no liver disease and those with only HIV infections. Based on these results, serum HA could be used as a diagnostic marker which can predict risk of serious liver events in people living with HIV and HCV co-infection.

Compared with a prospective study conducted on 1252 people enrolled in the EuroSIDA cohort aimed to identify if elevations in serum hyaluronic acid are associated with an increased risk of serious liver-related events in people with HIV and viral hepatitis co-infections, Peters et al. found that the median baseline value for all participants in the study was within range at 33.9ng/ml. It was higher in people with chronic HCV (37.7ng/ml), than in people with chronic HBV (31.4ng/dl) and people who had had cleared

their HCV infection (27.5ng/ml). Participants in the study were followed-up for a median of 8.2 years. During this time there were 84 serious liver-related events (7%; 52 liver-related deaths and 32 hepatic encephalopathy). The median baseline hyaluronic acid level was 221.6ng/ml among people experiencing a liver-related event compared to 31.8ng/ml for people whose disease did not progress. Participants were divided into three groups according to whether their baseline hyaluronic acid levels were within the normal range, mildly elevated (75-250ng/ml) or markedly elevated (above 250ng/ml). People with normal levels had a 1% five-year risk of a liver-related event compared to a 12% risk for individuals with moderate elevations and a 45% risk for those with markedly elevated hyaluronic acid. This study concluded that baseline HA was a strong predictor of later hepatic encephalopathy or liver-related death in HIV-1 patients co-infected with HBV and/or HCV Patients and plasma HA may be useful, either alone or in combination with other non-invasive markers, to monitor progression of liver disease and risk of complications in patients with chronic viral hepatitis. [208]

In another study conducted on one hundred and thirty seven HIV/HCV co-infected persons were randomly selected from the Johns Hopkins HIV Clinic cohort by Kelleher et al., ninety five patients had complete testing for fibrosis markers in sera collected at the time of liver biopsy. Biopsies were scored according to Ishak modified histological activity index (F0 no fibrosis to F6 cirrhosis). Fibrosis was evaluated against alanine aminotransferase (ALT), aspartate aminotransferase (AST), AST to platelet ratio (APRI), albumin, total bilirubin, hyaluronic acid (HA) and YKL-40. Results showed that fibrosis scores > or =F3 were found 27 times more often in persons with HA levels >86 ng/ml and 5.5 times more often in persons with HA levels 41-86 ng/ml.[209]

According to Nunes et al., HIV co-infection did not reduce the value of noninvasive biomarkers to detect and measure fibrosis in HCV infected patients.[210]

It is well known that liver function tests play an important role in estimating the severity of liver disease. In this study, prothrombin activity is significantly lower in patients with HCV decompensated liver disease patients with a mean of 38.99% (group IIb) followed by HCV/HIV patients who had liver disease with a mean of 67.33%. By comparing prothrombin activity with levels of serum HA, there was a significant negative correlation between level of HA and prothrombin activity (R= - 0.673). This finding is consistant with that concluded by Vincent et al., who studied the role of PT activity as an indirect marker of severe liver fibrosis. They concluded that The prothrombin index was well correlated with pathological liver fibrosis score and was not influenced by other pathological lesions.[211] On the other hand, these results disagree with Coverdale et al., who reported that PT activity failed to correlate with fibrosis progression and advised not to rely upon it.[212]

Similarly, serum albumin level significantly decreased in HCV decompensated liver disease (group IIb), its mean was 2.205 mg/dl which came in agreement with Friedman et al., who reported that hypoalbuminemia correlates with the severity of liver diseases.[213]And there was strong negative correlation between level of HA and serum albumin level (R= -0.718) which is consistent with the findings of a study showed a significant correlation between serum hyaluronate and serum albumin, prothrombin time, factor V concentration and serum γ-globulins which suggested that HA levels reflect both active fibrosis and hepatic failure and may be a quantitative marker of severity of hepatic injury.[214]

Regarding other liver function tests, Serum alanine aminotransferase (ALT) is one of the oldest markers used to assess liver disease. Pradat et al. have shown that serum ALT is beneficial to measure due to its high sensitivity and specificity (2.25-fold greater than the normal levels predicts liver histology).[215] In this study there was significant difference regarding serum ALT level among the different studied groups with the highest level reported in HCV/HIV with a mean of 58.67 u/l followed by HCV patients who had compensated liver disease with a mean of 41.67 u/I and there was positive but not significant correlation between HA level and ALT(R= 0.048).

The current study showed that AST was significantly higher in HIV/ HCV patients who had liver disease than those who had no liver disease and HIV only patients (P= 0.000), also it is significantly higher before IFN therapy than after IFN therapy(P= 0.002) and it had positive correlation with HA level(R=0.243).

Also total and direct serum bilirubin had significant increase in HCV decompensated patients and HCV/HIV with liver disease patients in comparison to other groups and both had high positive significant correlation with serum HA (R = 0.484 and 0.515 respectively).

Ultrasound (US) is a non-invasive, cheap and reliable method and can be used to detect severity of liver fibrosis. In this study the ultrasound findings vary considerably between the different studied groups, in group Ia there was 7 patients (58.3%) had mild fibrosis vs 2 patients (16.7%)had moderate fibrosis and 3 patients (75%) were normal, the same was group Ib. regarding group IIa 6 (50%) patients had moderate fibrosis vs 3 patients had mild fibrosis and 3 patients had severe fibrosis. 100% of group IIb patients had severe fibrosis. In group IIIa 5 patients (41.7%) had mild fibrosis, 5 patients (41.7%) had moderate fibrosis and 2 (16.7%) patients had severe fibrosis while all patients in groups IIIb and IIIc had normal liver in their ultrasound findings. In this study when comparing ultrasound findings with liver biopsy findings in group I, it was found that normal US finding had fibrosis score ranged between 0-1 while the mild US finding had fibrosis score ranged between 1-2 and the moderate US finding had fibrosis score 3, this indicates that US can be used to assess degree of liver fibrosis. Also according to this study there was positive correlation between HA and ultrasound findings.

In a similar study was done to investigate the use of US with HA for more accurate detection of liver fibrosis. At a cutoff value of 163.59 μg/L, the diagnostic specificity of serum hyaluronate was 80.8% similar to the specificity of ultrasonography. However, hyaluronate had a higher sensitivity of 80% and an accuracy of 80.6%, suggesting that serum hyaluronate concentration is the useful variable for screening compensated liver cirrhosis. When diagnosis was based on a combination of hyaluronate concentration and ultrasound data, the diagnostic sensitivity for cirrhosis was 92.9%, the specificity was 65.3%, and the accuracy was 72%.[216]

Some limitations of this study included the small sample size of the studied groups and the evaluation of changes in serum HA in two different groups of the IFN therapy.

SUMMARY

Hepatitis C virus is the leading cause of chronic liver disease worldwide, It is estimated that about 170 million people are chronically infected with HCV, with the highest prevalence in Egypt where about 15-20% of the population are infected. Chronic hepatitis C is a major cause of cirrhosis, hepatocellular carcinoma and HCV-related end stage liver disease. The infection is often asymptomatic, but chronic infection can lead to scarring of the liver and ultimately to cirrhosis, which is generally apparent after many years.

Until a few years ago Combination therapy with pegylated interferon and ribavirin was approved by the FDA for treatment of Hepatitis C. Recently a new class of direct-acting antiviral agents (DAAs) has revolutionized the treatment of HCV infection.

Human immunodeficiency virus (HIV) is a lentivirus a member of retrovirus family that causes acquired immunodeficiency syndrome (AIDS), a condition in human in which progressive failure of the immune system allows life threatening opportunistic infections. Coinfection with hepatitis C virus (HCV) and HIV is common in at risk populations because of shared routes of transmission.

With the advent of HAART, end-stage liver disease or cirrhosis was a leading cause of death in HIV-infected populations. Cirrhosis is a serious liver condition characterized by irreversible scarring of the liver that can lead to liver failure and death. Progression to ESLD in HCV monoinfected patients typically takes 20–30 years after initial infection. With HIV co infection, this process is accelerated.

Hepatic fibrosis is a wound-healing process in response to an acute or chronic liver injuries to parenchymal cells. Chronic inflammation of the liver can lead to cirrhosis, a stage of organ dysfunction and damage in which scar tissue replaces normal functioning tissue and causes a dramatic, and potentially fatal, decline in liver function.

Historically, liver biopsy has been considered the gold standard to diagnose and monitor the progression of fibrosis but it is an invasive procedure associated with a risk of complications thus, identification of surrogate markers of liver fibrosis would be useful to reduce the number of liver biopsies in patients with chronic liver diseases. In the liver, HA is mostly synthesized by the hepatic stellate cells and is degraded by the sinusoidal endothelial cells. Serum HA levels increase directly with the progression of chronic hepatic disease.

The aim of this work was to study serum HA as anon invasive marker which can assess the extent of liver fibrosis and can predict risk of serious liver events in patients with chronic HCV infection and in patients with HCV/HIV co- infection and to evaluate changes of its level before and after Interferon therapy in patients with chronic HCV.

This study was conducted on eighty four patients divided into three main groups, the first was the IFN therapy group which was subdivided into before treatment and after treatment groups. The second group was chronic hepatitis C group which subdivided into compensated liver disease and decompensated liver disease groups. The third group is the HIV/HCV group which was divided into HCV/HIV with liver disease and HCV/HIV with no liver disease and pure HIV group as a control group, each group consisted of twelve patients.

Patients with the following criteria were excluded from the study; patients who had liver fibrosis due to any other cause, severe systemic disease, diseases that may affect results of hyaluronic acid as rheumatoid arthritis, active osteoarthritis, progressive systemic sclerosis, systemic lupus erythematosus, scleroderma, malignant tumors and pregnant females.

All patients were subjected to the following after their informed consent:

1. Detailed history and thorough clinical examination
2. Laboratory investigations including:
   - Routine investigations: CBC, Fasting blood glucose level, serum urea and creatinine
   - Liver function tests and liver enzymes including serum alanine transaminase (ALT), serum aspartate transaminase (AST), serum albumin, serum bilirubin (total, direct), prothrombin activity, alkaline phosphatase (ALP) and gamma glutamyl transferase (GGT) .
   - Viral markers: hepatitis C Virus anti-bodies (HCV Abs), hepatitis B surface antigen and quantitative polymerase chain reaction for patients with HCV
   - ELISA and Western Blot for diagnosis of HIV.
   - For patients who received interferon therapy ,the following investigations were done: TSH, Anti- shistosomal antibodies, ANA alfa feto protein and liver biopsy.
3. Ultrasonographic examination of the abdomen.
4. Measuring level of Hyaluronic acid using ELISA assay.

Results were obtained, tabulated and statistically analysed.

The main results were:-

- Serum hyaluronic acid had statistically significant difference among all studied groups with the highest level observed in HCV patients with decompensated liver disease with a mean of 148.33 ng/ml followed by HCV/HIV patients who had liver disease with a mean of 58.59 ng/ml then HCV patients with compensated liver disease with a mean of 48.94 ng/ml and HCV patients before IFN group with a mean of 44.12 ng/ml.
- There was positive correlation between serum hyaluronic acid (HA) and the degree of liver fibrosis according to the criteria proposed by the Ishak system in IFN group.
- Regarding other liver function tests, there was positive but not significant correlation between HA level and ALT in all studied groups (R= 0.048). Also AST ,total serum bilirubin and direct serum bilirubin had positive correlation with HA level (R=0.243, 0.484 and 0.515 respectively). On the contradictory were prothrombin activity and albumin which had a strong negative correlation with HA level (R= - 0.673 and -0.718 respectively).
- Regarding US findings, the results were in consistence with liver biopsy in group one and had positive correlation with HA level in all groups.

From the previous results, it was concluded that serum HA is a useful non-invasive marker of liver fibrosis that could be useful in taking treatment decisions and monitoring of treatment response. Also, it has positive correlation with the severity of liver disease in patients with HCV infection and it can predict serious liver events in patients with HCV/HIV co infection.