Summary

Fibrosis is a non specific response to injuries which implies the synthesis of an extra-cellular matrix (ECM). In fibrotic liver there are quantitative and qualitative ECM changes and the progression of fibrosis leads to cirrhosis.

Histologic examination of the liver is an integral part of the evaluation of patients with chronic hepatitis C (CHC). Knowledge of the stage of liver fibrosis is essential for prognosis and decisions on antiviral therapy.

Liver biopsy remains the gold standard method in the diagnosis and staging of liver fibrosis. Although liver biopsy in general a safe procedure, it is costly and does carry a small risk for complication, in addition there could be sampling error, inter- and intra-observer discrepancies in assessing hepatic fibrosis. Hence, there is a need to develop accurate and reliable non invasive means to assess the severity of hepatic fibrosis.

Matrix metalloproteinases (MMPs) and their inhibitors (TIMPs) have been discussed as potential serum markers of liver fibrosis.

The MMPs and their inhibitors are involved in the control of matrix degradation. In chronic liver disease, the investigations have centered on MMP-2 (gellatinase or 72 KDA type IV collagenase), membrane- type metalloproteinase-1 or -2 which activate latent MMP-2 and TIMP-1 & TIMP-2.

MMP-1 shows a substrate specificity for interstitial collagen type I and III, while MMP-2 has a substrate collagen type IV, V, VII, X elastin and fibronectin.

TIMPs can irreversibly bind the proenzyme or active forms MMPs and inactivate them. Excess production of TIMPs relative to MMPs may be important factor for progression of liver fibrosis.

HSCs are the principal source of MMP-2 in the human liver and activation of MMP-2 require interaction with hepatocytes. TIMP-1 is produced by HSCs and hepatocytes.

Hyaluronic acid (HA) is a glycosaminoglycan component of ECM. Increased levels of HA are due to decreased hepatic removal, increased production or both.

The aim of the present study was to assess the value of estimation of HA, MMP-1, MMP-2, TIMP-1 as non invasive markers of liver fibrosis and to correlate them with the stage of liver fibrosis assessed histo-pathologically by liver biopsy. Age-platelet index (API) and AST to platelet ratio index (APRI) were also assessed.

This study was carried out on 46 patients with chronic hepatitis C (HCV-Ab positive and positive HCV RNA by PCR) visiting Hepatology, Gastroenterology and Infectious diseases Department at Banha University Hospitals.

All patients included in this study were subjected to full history taking and thorough clinical examination, full laboratory investigations (including: complete blood count, platelet count, liver profile tests, exclusion of other causes of hepatitis e.g. HBsAg, HBcAb, autoimmune hepatitis, shistosomiasis, abdominal ultrasonography, percutaneous liver biopsy with histopathological grading and staging by METAVIR scoring system.

Serum estimation of MMP-1, MMP-2,TIMP-1 and HA were done for all patients. Scoring of the API and APRI were also done.

The mean age of the studied cases was 36.7± 9.4 years. Males represented 73.9%.

In the present study:

- There was positive correlation between age and fibrosis stage.
- There was no correlation between the duration of disease and METAVIR stage.
- There was a decrease in albumin as the activity increased.
- There was a statistically significant decrease in white blood cells with progressive fibrosis.
- There was a statistical significant increase in the spleen size with progressive fibrosis.
- There was a significant correlation between liver appearance in ultrasound and advanced stage of fibrosis.
- There was no correlation between prothrombin time (PT) and fibrosis progression
- HA level increased significantly with progression of fibrosis, also had positive strong correlation with significant fibrosis with good sensitivity (80%), good specificity (71%) and area under ROC (AUC 0.79).

- The cut-off value of HA used to discriminate significant fibrosis was 26.4 ng/ml and it was a dependant predictor factor for diagnosis of fibrosis.

- There was strong positive correlation between HA and METAVIR activity.

- The serum levels of TIMP-1 were positively correlated with METAVIR stage and TIMP-1 detection was a useful test for discriminating cases of significant fibrosis with good sensitivity 86.7% but bad specificity 64.5%, AUC (0.75) and no correlation with METAVIR activity.

- Serum level of MMP-1 had no statistical significant change with increasing necro-inflammatory activity or with progressive fibrosis and no correlation between MMP-1 concentration and METAVIR grades and stages.

- There was no statistical significant change in serum MMP-2 level with active necro-inflammation but there was highly statistical significant increase with progressive fibrosis.

- MMP-2 level in serum can be used as independent predictor to discriminate progressive fibrosis (METAVIR stage > or equal 2 with cut-off level detected by ROC curve was 384.5 ng/ml.

- By studying ROC curve of MMP-2 revealed that it was an excellent test to discriminate progressive fibrosis with AUC (0.82), good sensitivity 93.3% but bad specificity 67.7%.

- The age-platelet index (API) showed significant strong positive correlation (P value < 0.01) with METAVIR stage activity grade.

- By studying of ROC of API for discrimination of significant fibrosis (F> or equal 2) showed AUC (0.74) with bad specificity 61.3% and good sensitivity 73.3% when API > 2.5 which indicating that it was a useful test for discrimination of significant fibrosis.

- The AST to platelet ratio index (APRI) showed significant positive correlation with METAVIR activity grade and stage (p value > 0.01), and by using APRI for prediction of significant fibrosis and cirrhosis (METAVIR stage > or equal 2), the AUC was (0.89) with good sensitivity 93.3% and good specificity 74.2%.

Finally, by Stepwise linear regression between METAVIR score and significant variables with correlation, the serum level of MMP-2 can be used as an independent predictor of significant fibrosis, while other studied markers are dependent predictors of significant fibrosis.