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EVA UATION OF LIVER FIBROSIS MARKERS IN CHRONIC LIVER DISEASES

Thesis Submitted By

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بسم الله الرحمن الرحيم

﴿وَاتَّقُوا اللَّهَ وَيُعَلِّمُكُمُ اللَّهُ وَاللَّهُ بِكُلِّ شَيْءٍ عَلِيمٌ﴾

صدق الله العظيم

(البقرة: الآية ٢٨٢)

قال الله تعالى فى كتابه العزيز:

بسم الله الرحمن الرحيم

(إِنَّمَا يَخْشَى اللَّهَ مِنْ عِبَادِهِ الْعُلَمَاء) (فاطر:٢٨)

(وَلا يُحِيطُونَ بِشَيْءٍ مِنْ عِلْمِهِ إِلَّا بِمَا شَاءَ) (البقرة:٢٥٥)

(وَفَوْقَ كُلِّ ذِي عِلْمٍ عَلِيمٌ) (يوسف:٧٦)

(وَمَا أُوتِيتُمْ مِنَ الْعِلْمِ إِلَّا قَلِيلاً) (الاسراء:٨٥)

(وَقُلْ رَبِّ زِدْنِي عِلْماً) (طـــه:١١٤)

(قَالُوا سُبْحَانَكَ لا عِلْمَ لَنَا إِلَّا مَا عَلَّمْتَنَا إِنَّكَ أَنْتَ الْعَلِيمُ الْحَكِيمُ) (البقرة:٣٢)

(يَرْفَعِ اللَّهُ الَّذِينَ آمَنُوا مِنْكُمْ وَالَّذِينَ أُوتُوا الْعِلْمَ دَرَجَاتٍ) (المجادلة:١١)

ABSTRACT

Liver fibrosis is a dynamic bi-directional process involving phases of progression and regression. Its diagnosis is dependent on histopathological examination of biopsy specimens. Non invasive serum markers of liver fibrosis would be of great clinical benefit as they would allow repeated assessment, with avoidance of the invasiveness of liver biopsy with its complications. This study was carried out on 50 patients (43males and 7 females) with chronic liver disease from the Hepatology ,Gastroenterology and Infectious diseases department of Banha University Hospitals and 10 healthy subjects as a control group. For both groups; estimation of serum matrix metalloproteinase-9 (**MMP-9**), tissue inhibitor of metalloproteinase-1 (**TIMP-1**) and **haptoglobin** was done. Scoring of the age-platelet index (**API**) and AST to platelet ratio index (**APRI**) was also done for the patients group, and finally, **liver biopsy** with histopathological examination for the necroinflammatory grade (A) and fibrosis stage (F) applying the **METAVIR scoring system**.

Results showed that the mean serum levels of MMP-9 were significantly higher in patients than in controls ($p<0.05$) and showed a significant negative correlation with METAVIR grade ($p<0.05$). By using ROC curves to assess MMP-9 for discrimination of significant fibrosis ($F \geq 2$) and cirrhosis (F4), the AUROC were 0.67 ± 0.17 and 0.69 ± 0.18 respectively. The mean values of serum TIMP-1 were significantly higher in patients than in controls ($p<0.05$), with non significant positive correlation with fibrosis progression ($p>0.05$), while it showed a significant increase ($p<0.05$) with METAVIR grades (A). AUROC for $F \geq 2$ and F4 were 0.58 ± 0.2 and 0.53 ± 0.19 respectively, while for $A \geq 2$, it was 0.67 ± 0.17. Haptoglobin levels were non significantly lower in patients than in controls ($p>0.05$) but showed a significant negative correlation with fibrosis progression ($r=-0.4$, $p<0.05$) and AUROC for $F \geq 2$ and F4, were 0.75 ± 0.17 and 0.78 ± 0.15 respectively.

To conclude, MMP-9 was a fair marker of fibrosis as well as necroinflammatory activity, and TIMP-1 was a sensitive and to a lesser extent specific marker of advanced liver disease, discriminating necroinflammatory activity rather than fibrosis stage. On the other hand, haptoglobin, API, and PT were the most sensitive predictors of significant fibrosis, while haptoglobin and API were the most sensitive predictors of cirrhosis. **Finally, these serum assays, although promising, are still in need of being refined with further prospective studies.**

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Contents

LIST OF ABBREVIATIONS

ALT	Alanine transaminase.
API	Age platelet index
APRI	AST to platelet ratio index
AST	Aspartate transaminase.
AT	Acti Test.
AUROC	Area under ROC curve.
bFGF	Basic fibroblast growth factor.
Ca^{++}	Calcium ion.
CAH	Chronic active hepatitis.
CLD	Chronic liver disease.
CPH	Chronic persistent hepatitis.
CT	Computerized tomography.
CTGF	Connective tissue growth factor.
ECM	Extracellular matrix.
EFF	Efficacy.
EGF	Epidermal growth factor.
ELISA	Enzyme linked immunosorbant assay.
ERCP	Endoscopic retrograde. cholangio-pancreatography.
ET-1	Endothelin-1.
ET-AR	Endothelin A receptor.
FAK	Focal adhesion kinase.
FN	False negative.
FP	False positive.
FT	Fibro Test.
GAGs	Glycosaminoglycans.
GGT	Gamma-glutamyl transpeptidase.

GS	Glutamine synthetase.
H & E	Haematoxylin and eosin.
HA	Hyaluronic acid.
HAI	Histological activity index.
HBcAg	HB core antigen.
HBsAg	HB surface antigen.
HBV	Hepatitis B virus.
HCC	Hepatocellular carcinoma.
HCV	Hepatitis C virus.
HGF	Hepatocyte growth factor.
HSC	Hepatic stellate cells.
hTIMP-1	Human tissue inhibitor of metalloproteinase-1.
ICAM-1	Intracellular adhesion molecule-1.
IHA	Immune haemagglutination.
IL	Interleukin.
INF-γ	Interferon-γ.
KC	Kupffer cells.
KD	Kilo Dalton.
LN	lobular necrosis.
LRP	Lipoprotein receptor-related protein.
M.T-MMP	Membrane-type-matrix metalloproteinase.
MCP-1	Monocyte chemotactic protein-1.
METAVIR (A)	Necroinflammatory grade.
METAVIR (F)	Fibrosis stage.

MF	Myofibroblast.
MIP-1B	Macrophage inflammatory protein-1B.
MMP	Matrix metallo-proteinases.
MRC	Magnetic resonance-cholangiography.
Na^+	Sodium ion.
NAFLDs	Non alcoholic fatty liver diseases.
NASH	Non alcoholic steatohepatitis.
OAT	Ornithine aminotransferase.
ORFs	Open reading frames.
P	Probability of error.
P^-	Negative predictive value.
P^+	Positive predictive value.
PBC	Primary biliary cirrhosis.
PCR	Polymerase chain reaction.
PDG F	Platelet-derived growth factor.
PIII NP	Procollagen type III amino-terminal peptide.
PMN	Piecemeal necrosis.
PSC	Primary sclerosing cholangitis.
r	Correlation coefficient.
RIBA	Recombinant immunonblot assay.
RID	Radial immune diffusion assay.
RNA	Ribonucleic acid.
ROC	Receiver operator characteristic curve.
ROS	Reactive oxygen species.
RT-PCR	Reverse transcription polymerase chain reaction.

SD	Standard deviation.
SN	Sensitivity.
SP	Specificity.
SPARC	Secreted protein acidic rich in cysteine.
t	Student test.
TN	True negative.
TH0	T helper 0.
TH2	T helper 2.
TP	True positive.
TGF	Transforming growth factor.
TIMP	Tissue inhibitors of matrix metalloproteinases.
TNF	Tumour necrosis factor.
VLA	Very late antigen.
$\overline{X}$	Arithmetic Mean.
X^2	Chi-square test.
YKL-40	The glycoprotein chondrex.
Z	Wilcoxon rank sum test.
α	Alpha.
β	Beta.
γ	Gamma.

LIST OF TABLES