

The Value of Doppler Sonography in Assessing the Staging of Fibrosis in Chronic Hepatitis C Viral Infection

Thesis

**Submitted for partial fulfillment of
Master degree in Tropical Medicine**

By

Mohamed El-Sayed EL-Sefey
M.B.B.CH., Ain-Shams University

Supervised by

Prof. Dr/ Eman Mohamed Elgindy

Professor of Tropical Medicine

Faculty of Medicine

Ain Shams University

Dr/ Runia Fouad El-Folly

Assistant professor of Tropical Medicine

Faculty of Medicine

Ain Shams University

Dr/Amr Mahmmoud Ahmed

Lecturer of Radiology

Faculty of Medicine

Ain Shams University

Faculty of Medicine

Ain Shams University

2014



Acknowledgment



First and Foremost thanks to Allah, the most merciful and gracious.

*I wish to express my deep appreciation and sincere gratitude to **Prof. Dr. Eman El-Gindy**, Professor of Tropical Medicine, Ain Shams University, for planning , supervising this study and for her valuable instructions and continuous help.*

*My deepest gratitude to **Ass. Prof. Dr. Runia El-Folly**, Assistant Professor of Tropical Medicine, Ain Shams University, who generously supervised my work in a supportive and educational way.*

*I have to proceed with thanking to **Dr. Amr Mahmmoud** Lecturer of Interventional Radiology, Ain Shams University, for his generous time and fruitful help in the radiological part of the work.*

*In addition, I would like to extend my deep thanks to **Prof. Dr. Zakaria Mahran**, head & Professor of Tropical Medicine Department, Ain Shams University for his continuous support for all of us.*

Finally yet importantly, I would like to thank all my Professors and Colleagues for their support and guide at all times.

Mohamed El -Sefey
March; 2014

قَالُوا سُبْحَانَكَ لَا عِلْمَ لَنَا
إِلَّا مَا عَلَّمْتَنَا إِنَّكَ أَنْتَ الْعَلِيمُ
الْحَكِيمُ

صدق الله العظيم

سورة البقرة الآية (32)

List of Contents

Title	Page
· List of Figures	I- II
· List of Tables	III-IV
· List of Abbreviations	V- VIII
· Protocol.....	- -
· Introduction	1
· Aim of the Work	4
· Review of Literature	
Chapter I: Hepatitis C virus	5
Chapter II: Liver fibrosis	32
Chapter III: Doppler ultrasound	66
· Patients and Methods	95
· Results.....	107
· Discussion	125
· Summary	137
· Conclusions.....	141
· Recommendations.....	142
· References.....	143
· Arabic Summary.....	--

List of Figures

Review

Figure No.	Subject	Page
Fig 1	Worldwide distribution of HCV genotypes 1 to 6	8
Fig 2	Duplex system combining real time B mode and a Doppler beam of variable position across the B mode field of view	68
Fig 3	Couinaud's Liver segments	70
Fig 4	Oblique color Doppler image of the porta hepatis. The hepatic artery (HA) accompanies the portal vein (PV) and bile ducts	71
Fig 5	Doppler ultrasound of the portal vein with a continuous hepatopetal flow in a healthy adult	72
Fig 6	Hepatic artery waveform, sharp systolic peak with continuous diastolic flow	73
Fig 7	Crow's foot appearance of the three hepatic veins clearly confirms patency of the hepatic veins	74
Fig 8	(a) Normal hepatic vein Spectral Doppler tracing (b) Simultaneous tracings of an ECG, hepatic vein Spectral Doppler tracing and mitral valve M-mode tracing with correlation to atrial and ventricular systole and diastole	75
Fig 9	Abnormal hepatic venous waveforms	77
Fig 10	An echogenic thrombus seen adherent to the portal vein wall	83

List of Figures

Results

Figure No.	Subject	Page
Fig 1	Age Distribution in the 2 studied groups	109
Fig 2	Sex Distribution in the 2 studied groups	109
Fig 3	Histopathological Staging in study group I	112
Fig 4	Histopathological Grading in study group I	112

List of Tables

Review

Table No.	Subject	Page
Table 1	Child-Pugh-Turcotte scoring system	17
Table 2	METAVIR and Ishak scores	22
Table 3	Classification of NAFLD by subtype	23
Table 4	Metavir classification for staging of hepatitis C liver disease	102

Results

Table No.	Subject	Page
Table 1	Gender, Age and Clinical presentation among the studied cases.	108
Table 2	Laboratory findings of the 2 studied groups	110
Table 3	The Histopathological findings of study group (group I)	111
Table 4	Comparison between Group I and II as regards to abdominal ultrasonography findings	113
Table 5	Comparison between Group I and II as regards to Doppler ultrasonography findings	114
Table 6	Correlation between Metavair Classification (Stage & Grade) and Doppler Ultrasonographic Parameters	115
Table 7	Multivariate analysis for prediction of Metavair Classification (Staging & Grading) by Doppler Ultrasonographic parameters	116
Table 8	ROC curve for Fibrosis index (by Doppler	118

“ List of Tables

	ultrasound) values plotted against metavir stage at F1 & F4.	
Table 9	ROC curve for Modified liver vascular index (by Doppler ultrasound) values plotted against metavir stage at F1 & F4.	119
Table 10	ROC curve of portal congestive index values plotted against metavir stage at F1 & F4.	120
Table 11	Modified liver vascular index and portal hypertension index (by comparing patients with metavir stages, Mean \pm SD)	121
Table 12	The logistic stepwise Multi regression analysis to predict; the degree of fibrosis among the patient group using laboratory parameters after excluding those with higher P values.	122
Table 13	The logistic stepwise Multi regression analysis to predict the degree of fibrosis among the case group, using abdominal and Doppler Ultrasonographic parameters.	123
Table 14	Proposed model for prediction of Fibrosis in post-HCV chronic liver disease patients	124

List of Abbreviations

AFP	Alpha feto protein
AIH	Auto Immune Hepatitis
Alk P	Alkaline Phosphatase
ALT	Aspartate aminotransferase
APRI	AST Platlet Ratio Index
ARFI	Acoustic radiation force imaging
AST	Alanine aminotransferase
AUC	Area Under Curve
BMI	Body Mass Index
CD	Colour Doppler
CD4	Cluster of differentiation 4
CDI	Colour Doppler Imaging
CDU	Colour Doppler ultrasonography
CHB	Chronic Hepatitis B
CHC	Chronic Hepatitis C
CLD	Chronic Liver Disease
CT	Computed Tomography
CVH	Chronic Viral Hepatitis
D Bil	Direct Bilirubin
DU	Doppler Ultrasound
EASL	European association of the study of the liver
ECG	Electro Cardiogram
ECM	Extracellular matrix
EDV	End diastolic velocity
EIA	Enzyme immune assay
EVR	Early virological response
FI	Fibrosis index

List of Abbreviations

FS	Fibro Scan
FT	Fibro-test
GB	Gall Bladder
GGT	Gamma glutmyl transpeptidase
GTF eta	Growth Transforming Factor beta
HA	Hepatic Artery
HAD	Hepatic Artery Diameter
HAI	Hepatic activity index
HARI	Hepatic Artery Resistive Index
HBcAg	Hepatitis B core Antigen
HBsAg	Hepatitis B surface Antigen
HBV	Hepatitis B Virus
HC	Hepatic cirrhosis
HCC	Hepatocellular Carcinoma
HCV	Hepatitis C virus
HDV	Hepatitis D Virus
HIV	Human immune deficiency virus
HLA	Human leucocyte antigen
HS	Highly significant
HSC	Hepatic stellate cells
HV	Hepatic veins
HVPG	Hepatic venous pressure gradient
HVs	Hepatic Veins
IFN	Interferon
IL	Interleukin
IMP	Inhibitors of Metalloproteinases
INR	International normalized ratio
IU	International unit
IVC	Inferior vena cava

List of Abbreviations

KPa	Kilo pascal
MELD	Model for end stage liver disease
MLVI	Modified liver vascular index
MMP	Matrix metaloprotienase
MRI	Magnetic Resonance imaging
NAFLD	Non Alcoholic Fatty Liver Disease
NASH	Non Alcoholic Steato Hepatitis
NGFR	Nerve growth factor receptor
NK	Natural killer cell
NS	Non-significant
PBC	Primary Biliary Cirrhosis
PCR	Polymerase chain reaction
PDGF	Platelet derived growth factor
PELD	Pediatric End-Stage Liver Disease
PHI	Portal hypertension index
PI	Pulsatility Index
PPFV	Peak portal flow velocity
PSV	Peak systolic velocity
PT	Prothrombin Time
PV	Portal Vein
PVCI	Portal Vein Congestive Index
PVD	Portal Vein Diameter
PVV	Portal vein velocity
RI	Resistive Index
RIBA	recombinant immunoblot assay
ROC	receiver operator characteristic
ROS	Reactive oxygen species
RVR	Rapid virological response
S	Significant

List of Abbreviations

SARI	Splenic artery resistivity index
SD	Standard deviation
STAT 3	signal transducer and activator of transcription 3
SVR	Sustained virological response
T Bil	Total Bilirubin
TE	Transient elastography
TGFB1	Transforming growth factor B1
TH	T helper cell
TIPS	Transjugular intrahepatic portosystemic shunt
TNF	Tumour Necrosis Factor
TRAIL	TNF-related apoptosis inducing ligand
UDCA	Ursodeoxy Cholic Acid
US	Ultrasound
Vmax	Time average maximum velocity
Vtam	Time average mean velocity
WBCs	White Blood Cells
WHO	World health organization

Introduction

Hepatitis C virus (HCV) infection is one of the main causes of chronic liver disease worldwide. The long-term impact of HCV infection is highly variable, from minimal changes to extensive fibrosis and cirrhosis with or without hepatocellular carcinoma (HCC). The number of chronically infected persons worldwide is estimated to be about 160 million, but most of them are unaware of their infection. Clinical care for patients with HCV-related liver disease has advanced considerably during the last two decades, due to an enhanced understanding of the pathophysiology of the disease, and because of developments in diagnostic procedures and improvements in therapy and prevention (*EASL, 2014*).

Liver fibrosis results from chronic damage to the liver in conjunction with the accumulation of extracellular medullary (ECM) proteins, which is a characteristic of most types of chronic liver disease (*Friedman, 2003*). The main causes of liver fibrosis include chronic HCV infection, alcohol abuse, and nonalcoholic steatohepatitis (NASH) (*Albanis and Friedman, 2001*).

The accumulation of ECM proteins distorts the hepatic architecture by forming a fibrous scar, and the subsequent development of nodules of regenerating hepatocytes defines cirrhosis. Cirrhosis produces hepatocellular dysfunction and increased intrahepatic resistance to blood flow, which result in

hepatic insufficiency and portal hypertension (*Piscaglia et al., 2001a*).

Liver biopsy remains the reference method for diagnosis of cirrhosis. The risk of severe complications is very low (1/4,000 to 1/10,000). Based on the abundant literature; In chronic hepatitis C alternative, non-invasive methods can now be used instead of liver biopsy to assess liver disease severity prior to therapy at a safe level of predictility (*Castera et al., 2005*).

Despite the limited value of *abdominal ultrasound*, it is still the most established method for diagnosis and follow-up of chronic liver disease primarily because of its availability. Although a coarse echo pattern of the liver and periportal fibrosis may be detected, sonographic findings are normal in many cases (*Withers and Wilson, 1998*).

Hepatic fibrosis is a known cause of several regional hepatic hemodynamic changes, including the resistive index, hepatic blood flow, and the velocity of blood inportalvein and hepatic arteries (*Piscaglia et al., 2001b*).

In cirrhosis, portal blood inflow, hepatic resistance, and portal venous pressure increase. Despite the initial increase, portal blood inflow decreases with increasing sinusoidal resistance and development of porto-systemic collateral vessels. These hemodynamic changes influence the degree of portal hypertension and liver dysfunction (*Bosch and Garcia-Pagan, 2000*).

The use of *Colour Doppler Ultrasonography (CDU)* in diagnosis and staging of chronic viral liver disease has been based on the hypothesis that alteration of liver haemodynamics due to chronic inflammatory changes may indirectly reflect histological alterations (*Bernatik et al., 2002 and Lim et al., 2005*).

Doppler Ultrasonography is a noninvasive diagnostic modality based on hemodynamic parameters. Hemodynamic changes might have developed even in cases with normal findings on B-mode sonography (*Shapiro et al., 1998*).

Therefore, assessment of these alterations has importance for early diagnosis and for close follow-up of previously diagnosed cases. Alterations of liver hemodynamics in CVH and cirrhosis have been observed in various studies. Some authors evaluated these changes for CVH, some evaluated them for cirrhosis, and some did for both. Limitations of different values from many simple Doppler parameters of liver vasculature made observers use some new indices for more reliable evaluations, such as *the modified liver vascular index, congestion index, arteriportal ratio (Hirata et al., 2001), and portal hypertension index (Piscaglia et al., 2001a)*.