

Evaluation of Serum Fibrosis Markers CTGF and IL-17 Versus Liver Biopsy for Detection of Hepatic Fibrosis in Egyptian Patients with Chronic Hepatitis C

Thesis

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To My Dear Parents

My Beloved Husband

My Beautiful Clara and Karen

And My Supporting Brothers

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List of Abbreviations

| | | |
|--------------|-------|--|
| a a | | Amino acids |
| ALT | | Alanine aminotransferase |
| APRI | | AST to platelet ratio index |
| AST | | Aspartate aminotransferase |
| AT | | ActiTest |
| AUC | | Area Under Curve |
| BMI | | Body mass index |
| CBC | | Complete blood picture |
| CCN | | Cysteine rich angiogenic protein growth factor overexpressed |
| CD | | Cluster of differentiation |
| cDNA | | Complementary DNA |
| CT | | C-terminal domain |
| CT | | Cycle threshold |
| CTGF | | Connective tissue growth factor |
| EDHS | | Egyptian Demographic Health Survey |
| EIA | | Enzyme immunoassays |
| ELISA | | Enzyme-linked immunosorbent assays |
| ECM | | Extracellular matrix |
| EMT | | Epithelial-to-mesenchymal transition |

ANOVA Analysis of variation

FDA Food and drug administration

FT FibroTest

GGT γ -glutamyl-transferase

H & E Hematoxylin and eosin

HBV Hepatitis B virus

HCC Hepatocellular Carcinoma

HCV Hepatitis C virus

HIV Human immunodeficiency virus

HSC Hepatic stellate cells

IDUs Injection drug users

IL-17 Interleukin 17

IHA Indirect hemagglutination

iTh Innate T helper

IU International units

INF Interferons

INR International normalization ratio

IGFBP Insulin-like growth factor binding protein

kDa kilo Dalton

mDC Myeloid dendritic cells

MFB Myofibroblasts

MAP kinase ... Mitogen-activated protein kinase

MRP2Multidrug resistance-associated protein 2
MSMultiple sclerosis
NPVNegative predictive value
O.DOptical density
OROdds ratio
P-valueProbability that statistics results get by chance
PATparenteral-antischistosomal-therapy
PCRPolymerase chain reaction
PPVPositive predictive value
PTProthrombin time
rPerson correlation coefficient
RArheumatoid arthritis
RnRox normalization
ROCReceiver Operating Characteristics
ROSreactive oxygen species
SDStandard deviation
SPSSStatistical Package for Social Science
t-testStudent t-test
TMATranscription mediated amplification
TGFTransforming growth factor
ThT helper
TMATranscription mediated amplified

UMann-Whitney U Test

μgMicrogram

μLMicrolitre

μmolMicromole

μMMicromolar

vWC von Willebrand type C repeats

WISPs Wnt-induced secreted proteins

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INTRODUCTION

Hepatitis C virus infection, with an estimated prevalence of more than 170 million people infected worldwide, is a major health problem (*Lauer & Walker, 2001*).

Schistosomiasis is also of significant concern as it is endemic in Egypt (*Gryseels et al, 2006*). The presence of both HCV and Schistosoma is of significant concern as patients with co infections have been shown to have higher HCV RNA titers, increased histological activity, greater incidence of cirrhosis/hepatocellular carcinoma, and higher mortality rates than patients suffering from single infections (*Kamal et al, 2001*)

For evaluation of the severity of the liver disease and diagnostic decision-making, liver biopsy remains the golden standard to date (*Gebo et al., 2002*).

However, liver biopsy is associated with problems that sometimes limit its applicability as diagnostic procedure. Interpretation and diagnosis could be compromised by sampling errors and observer variability that may lead to under-staging particularly in diseases that exhibit a patchy rather than homogenous distribution within the liver (*Rousselet et al., 2005*).

In addition, liver biopsy is an invasive and painful procedure, with rare but potentially life-threatening complications. Among the complications of percutaneous liver biopsy are pain (10%-30%), bleeding, biliary peritonitis, and pneumothorax. In large series, mortality has been reported to range from 0.1%-0.01%. Percutaneous liver biopsy is contraindicated in the presence of coagulopathy, thrombocytopenia, and ascites (*Bravo et al., 2001*). Thus, many patients with CHC are reluctant to undergo liver biopsy and may be discouraged from starting therapy for this reason (*Castera et al., 2009*).

CTGF is a multi-functional protein that drives many cellular processes, but has received special focus with respect to its fibrotic actions in several organs systems. It is shown that CTGF mediates expression of fibrotic markers during HCV infection. CTGF produced in response to HCV may act locally on nonparenchymal cells, such as HSCs or myofibroblasts as well as hepatocytes to enhance expression of markers that are associated with fibrosis. Recent studies have indicated an association between CTGF and stage of fibrosis in patients with chronic HCV infection and high levels of CTGF in plasma and liver biopsy samples of HCV infected patients (*Kovalenko et al., 2009*). Findings demonstrating increased CTGF expression in HCV infected hepatocytes also underscore the importance of hepatocytes in producing CTGF during HCV infection (*Nagaraja et al., 2012*). Previous studies have indicated the

contribution of parenchymal liver cells to CTGF production in normal and diseased liver (*Tong et al., 2009*).

Several reports have shown that the number of Th-17 cells was increased in the portal areas of livers from patients with chronic HCV infection (*Harada et al., 2009*). HCV antigen-specific Th17 cells were also induced in the peripheral blood from patients with chronic HCV infection, which were suppressed by virus-induced transforming growth factor- β (*Rowan et al., 2008*). However, the role of IL-17 in HCV infection has not been investigated. It is plausible to speculate that IL-17 may play an important role in stimulating liver inflammation during HCV infection, similar to HBV infection (*Lafdil et al., 2010*).