Evaluation Of GALECTIN-3 As An Inflammatory Marker In HCV Positive Patients With And Without Chronic Kidney Disease

Thesis

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BY

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CONTENTS

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List of Abbreviations

Aa	Aminoacids
AGE	Advancedglycationendproduct;
AKI	Acute kidney injury
ALE	Advanced lipoxidationendproduct.
AUC	Area under curve
AVG	Arteriovenous grafts
bvdv	Bovine viral diarrhea virus
C.pneumoniae	Chlamydia pneumoniae
C1	Complement 1
C3	Complement 3
C4	Complement 4
CHC	Chronic hepatitis c
CKD	Chronic kidney disease
CML	Nε-carboxymethyllysine
CRD	Carbohydrate recognition domain
CRH	Corticotropin releasing hormone
CRP	C -reactive protein
CSFV	Classic swine fever virus
CTL	Cytotoxic T lymphocytes
CVD	Cardiovascular diseases
DcR3	Decoy receptor 3
Denv-1	Dengue virus 1
Denv-2	Dengue virus 2
EMT	Epithelial to mesenchymal transition
EPO	Erythropoietin
ERK	Extracellular signal-regulated kinase
ESRD	End stage renal disease
FCR	Fractional catabolic rate
GFR	Glomerular filteration rate
GM-CT-01	Galactomannan
GR-MD-02	Galactoarabino-rhamnogalaturonan
HCC	Hepatocellular carcinoma

- HCV Hepatitis c virus
- HD Hemodialysis
- HDL High density lipoprotein
- HFD High fat diet
- HIV Human immunodeficiency virus
- HLA Human leuckocyte antigen
- ho-1 Heme-oxygenase-1
- HSC Hepatic satellatecellss
- Hs-CRP High Senstive CRP
- IBD Inflammatory Bowel Disease
- Icam-1 Intercellular Adhesion molecule 1
- IFN-γ Interferon-γ
- IgA Immunoglobulin A
- igf-1 Insuline like growth factor 1
- IgG Immunoglobulin G
- IL Interleukin
- IL-1 Interleukin-1
- IL-10 Interleukin-10
- IL-1β Interleukin-1 β
- IL-6Rα Interleukin-6 receptor alpha
- IL-8 Interleukin-8
- IRS-1 Insulin receptor substrate-1
- JEV Japanese encephalitis virus

KDW Kidney disease wasting

- KCs Kupffer cells
- KDIGO Kidney disease improving global outcomes
- LDL Low densietylipoprotien
- LPS Lipopolysaccaride
- LSECs Liver sinusoidal endothelial cells;
- M1 Activated macrophage

Mcp-1 monocyte chemotactic protein-1

- MIP Macrophage inflammatory protein
- NASH Non –alcoholic steatohepatitis
- NK Natural Killer Cells
- Pecam-1 Platelet endothelial cell adhesion molecule-1

- PGE2 Prostaglandin E2
- PTX3 Pentraxin 3
- RAGE Receptor for AGEs
- ROS Reactive oxygen species.
- SAA Serum amyloid A
- SAP Serum amyloid protein

SLE Systemic lupus erythematosis

- Tgf-ß Transforming growth factor beta
- TH-1 T-helper 1
- TNF- α Tumor necrosis factor alpha
- TSAT Serum ferritin and transferrin saturation

UUO Unilateral uritic obstruction

- VAT Visceral Adipose Tissue
- Vcam-1 Vascular Cell Adhesion Molecule-1
- VWF Von Willebrand Factor
- WHO World Health Organization
- WNVWest Nile Virus
- YFV Yellow fever virus

List of Tables

List of Figures

INTRODUCTION

It is estimated that 3-4 million people are infected with HCV each year. 130-170 million people are chronically infected with HCV and at risk of developing liver cirrhosis and/or liver cancer. More than 350,000 people die from HCV-related liver diseases each year ***(WHO, 2012) .***

HCV infection is found worldwide. Countries with high rates of chronic infection are Egypt (14.7 %) ***(Egypt Demographic and Health Survey, 2008)***, Pakistan (4.8%) and China (3.2%) ***(WHO, 2012).***

Egypt has a very high prevalence of HCV and a high morbidity and mortality from chronic liver disease, cirrhosis, and hepatocellular carcinoma ***(Lehman and Wilson, 2009).***

Liver fibrosis is defined as an abnormal accumulation of extracellular matrix in the liver. Its endpoint is liver cirrhosis which is responsible for a significant morbidity and mortality. Cirrhosis is an advanced stage of fibrosis, characterised by formation of regenerative nodules of liver parenchyma separated by fibrotic septa, which result from cell death, aberrant extracellular matrix deposition and vascular reorganisation. Advanced liver fibrosis results in cirrhosis, liver failure, and portal hypertension and often requires liver transplantation ***(Saile B et.al,2007 and Ramadori G et.al,2004)*** .

Removing the insult and stopping the persistent inflammatory stimuli is probably the best way to prevent progression of fibrosis; this has been shown in many patients with chronic hepatitis C and in smaller numbers of patients with autoimmune hepatitis. Clinical data confirmed that, providing appropriate, targeted treatment to patients with histologically advanced liver disease, especially those with autoimmune hepatitis, may improve their long-term outcome ***(Malekzadeh R et.al, 2004) .***

Nevertheless, prevention of the progression of fibrosis to cirrhosis remains the major clinical goal. The poor prognosis of cirrhosis is aggravated by the frequent occurrence of hepatocellular carcinoma ***(Saile B***

et.al,2007) .Inflammation is a key factor in the initiation and maintenance of fibrotic processes within the liver ***(Karlmark et al., 2008).***

Hepatitis C virus (HCV) is also associated with a wide spectrum of clinical and biological extrahepatic manifestations ,In chronically infected patients, the virus can trigger an impairment in lymphoproliferation with cryoglobulin production ***(Zignego AL et.al,2007).***

Mixed cryoglobulinemia with its complications (skin, neurological, renal, and rheumatologic) is the most significant extrahepatic manifestation of HCV infection ***(Stefanova-Petrova et.al, 2007) .***

In addition to the risk of renal disease progression, the overall prognosis for patients with HCV-related nephritis is poor because of the high incidence of co-infections and associated cardiovascular disease. A retrospective cohort study involving more than 470,000 adult veterans showed that patients with HCV infection were more likely to develop end stage renal disease (4.3 per 1000 person-year) than HCV-seronegative patients (3.1 per 1000 person-year). A cross-sectional study showed that

HCV-infected patients had a 40% higher likelihood for developing renal insufficiency—defined as serum creatinine levels greater than or equal to 1.5 mg/dL—compared with seronegative subjects ***(Chadban SJ et.al,2005) .***

Chronic kidney disease (CKD) represents a significant global health problem with few therapeutic options currently known to slow its progression. The prevalence of moderate to advanced stages of CKD has increased by an alarming 42% over the past decade ***(Okamura DM et.al,2011).***

Progressive renal disease is the consequence of expansion of interstitial extracellular matrix which leads to nephron loss. Two critical pathways have a significant impact in renal injury; tubular apoptosis and defective tissue remodeling characterized by the imbalance between matrix synthesis and matrix degradation ***(Li Y et.al,2009).***

Renal tubular cell apoptosis and subsequent tubular atrophy are an important cause of progressive loss of kidney functional decline. Apoptosis is the end result of a complex regulatory system balancing survival factors and cell activation/injury signals ***(Zhang G et.al,2003)*** .

Apoptosis occurs principally through two separate yet interlinked signaling mechanisms: the extrinsic pathway, activated by pro-apoptotic receptor signals at the cell surface, and the intrinsic pathway, activated by mitochondrial signals from within the cell. ***(Zhang G et.al,2003 and Kang EH et.al,2009)***.

During the final phases of classical repair of the tubular cell injury,extracellular matrix synthesis and degradation reach equilibrium, and normal tissue architecture is restored. By contrast, in progressive kidney disease, this final phase is altered and the normal architecture is irreversibly damaged ***(Zhang G et.al,2003 and Kang EH et.al,2009).***

Lectins are carbohydrate-binding proteins that have an affinity for specific oligosaccharides ***(Ostalska-Nowicka D et.al,2009)*** .

Galectins are low molecular weight,calcium-independent, β-galactoside-binding lectins. Galectin-3