

Kallistatin as a New and Reliable Biomarker for the Diagnosis of Liver Cirrhosis

Thesis

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List of Abbreviations

Abb.	Full term
AFP	α -fetoprotein
AFP-L3	Lens culinaris agglutinin-reactive AFP
AFU	α -L-fucosidase
ALP	Alkaline phosphatase
ALT	Alanine aminotransferas:
AST	Aspartate Aminotransferases
CT	Computerized Tomography
CTP score	Child-Turcotte-Pugh score
DCP	Des- γ Carboxyprothrombin
DWI	Diffusion-weighted imaging
ET1	Endothelin1
FDA	Food and drug administration
FNAB	Fine needle aspiration biopsy
FNH	Focal nodular hyperplasia
GGT	Gamma-glutamyl transpeptidase
GGT	Gamma Glutamyl Transferase
GP73	Golgi protein 73
GPC3	Glypican-3
HBV	Hepatitis B Virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C Virus
HIFU	High intensity focused ultrasound
HSP	Heat shock protein
HTA	Hepatoma-associated gene
HTERT	Human telomerase reverse transcriptase mRNA
IGF-2	Insulin Growth Factor-2

Abb.	Full term
IgG	Immunoglobulin G
IL- 18	Interleukin-18
INR	International normalized ratio
LC	Liver Cirrhosis
LDL	Low Denisty Lipoprotein
MELD score	Model for End-Stage Liver Disease score
MMP2 and MMP9	Matrix metalloproteinase 2 and 9
MRI	Magnetic resonance imaging
NASH	Non -Alcoholic steatohepatitis
OPTN	Organ Procurement Transplantation Network
PBC	Primary biliary cirrhosis
PDGF	Platelet derived growth factor
PEI	Percutaneous ethanol injection
PELD score	Pediatric End-Stage Liver Disease score
PSC	Primary sclerosing cholangitis and
PT	Prothrombin Time
PWI	Perfusion-weighted imaging
RFA	Radiofrequency ablation
SCCA	Squamous cell carcinoma antigen
TACE	Transcatheter arterial chemoembolization
TAG-72	Tumor-associated glycoprotein 72
TGF-β1	Transforming growth factor-beta
UCSF	University of California at San Francisco
Vil1	Villin1
WD-HCC	Well-differentiated hepatocellular carcinoma

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Kallistatin as a New and Reliable Biomarker for the Diagnosis of Liver Cirrhosis

Abstract

Cirrhosis represents the final common pathological outcome for the majority of chronic liver diseases. Most patients with cirrhosis die from one or more clinical complications including ascites, hepatic encephalopathy and variceal hemorrhage. Among the 1.4 million liver disease-related deaths that occur each year worldwide, over 55%, or 796,000, are directly attributable to cirrhosis. The significantly reduced levels of serum kallistatin in patients with LC hypothesized that serum kallistatin levels could be a potential biomarker for liver cirrhosis as several studies have shown that the liver represents the major site of synthesis and secretion of kallistatin. Aim: To explore the relationship between serum kallistatin and clinical evidence of both cirrhosis and hepatocellular carcinoma, and to determine if serum kallistatin levels could be used as a diagnostic indicator of hepatic health status especially human liver cirrhosis. Most patients with cirrhosis die from one or more clinical complications including ascites, hepatic encephalopathy and variceal hemorrhage. Many of liver disease-related deaths that occur each year worldwide are directly attributable to cirrhosis. The focus of this study was to determine the value of kallistatin in patients with liver cirrhosis and hepatocellular carcinoma and to determine if serum kallistatin levels could be used as a diagnostic indicator of hepatic health status especially human liver cirrhosis. The results in the current study revealed that there was highly significant decrease of kallistatin level in liver cirrhosis patients and HCC patients compared to control group. These findings pointed to the value of kallistatin as a new biomarker for diagnosis of liver cirrhosis.

Keywords: Cirrhosis, kallistatin, hepatocellular carcinoma, encephalopathy.

Introduction

Cirrhosis represents the final common pathological outcome for the majority of chronic liver diseases (*Ratziu et al., 2000*). Most patients with cirrhosis die from one or more clinical complications including ascites, hepatic encephalopathy and variceal hemorrhage (*Bataller et al., 2005*). Among the 1.4 million liver disease-related deaths that occur each year worldwide, over 55%, or 796,000, are directly attributable to cirrhosis (*Poynard et al., 2003*).

It is important to identify reliable biomarkers for the early detection of liver disease and subsequent evaluation of response to therapeutic intervention as recent evidence from animal studies and human clinical observations indicated that even advanced fibrosis can be reversed (*Harrison et al., 2006*). The ability of serum biomarkers of liver function to further discriminate between LC and HCC would add a major advantage, since first identified as a tissue kallikrein-binding protein (KBP), kallistatin mRNA was found in varying amounts in human liver, stomach, pancreas, kidney, aorta, testes, prostate, artery, atrium, ventricle and lung, blood cells and body fluids (*Wolf et al., 1999*).

The significantly reduced levels of serum kallistatin in patients with LC hypothesized that serum kallistatin levels could be a potential biomarker for liver cirrhosis as several studies have shown that the liver represents the major site of synthesis and secretion of kallistatin (*Chen et al., 2001*).

Kallistatin, an endogenous human serine proteinase inhibitor, was originally known as a tissue kallikrein inhibitor (*Chao et al., 1996*). Kallistatin, has vasodilatory, anti-angiogenic, anti-inflammatory, anti-tumor and anti-oxidant effects (*Chao et al., 2006*).

Kallistatin is known to play an important role in prevention of cancer, probably through its anti-angiogenic effects (*Miao et al., 2002*), reduce blood pressure (*Chao et al., 2001*), suppress arthritis (*Wang et al., 2005*) and protect organs and cells against inflammation, fibrosis, and oxidative stress (*Shen et al., 2010*). The anti-oxidative effect of kallistatin, can also inhibit salt-induced renal injury, inflammation, and fibrosis (*Shen et al., 2008*).

Aim of the Study

To explore the relationship between serum kallistatin and clinical evidence of both cirrhosis and hepatocellular carcinoma, and to determine if serum kallistatin levels could be used as a diagnostic indicator of hepatic health status especially human liver cirrhosis.