Serum Arginase as a Tumor Marker for Hepatocellular Carcinoma

Thesis

Submitted for partial fulfillment of Master Degree
in Internal Medicine

By

Amira Adel Amin Abd El-Aal
M.B.B.ch
Ain Shams University

Under Supervision of

Professor/ Essam Mohamed Bayomy
Professor of Internal Medical and Gastroenterology
Faculty of Medicine, Ain Shams University

Professor/ Moataz Mohammed Sayed
Assistant Professor of Internal Medical and Gastroenterology
Faculty of Medicine, Ain Shams University

Dr/Sarah Abd.Elkader
Lecturer of Internal Medical and Gastroenterology
Faculty of Medicine, Ain Shams University

Faculty of Medicine
Ain Shams University
2016


بسم الله الرحمن الرحيم
وَاتَّقُوْا اللّٰهَ ويُعلِّمُكُمُ اللّٰهُ
وَاللّٰهُ بِكُلِّ شَيْءٍ عَليمٌ
صدق الله العظيم
سورة البقرة – آية ٢٨٢

Acknowledgement

First, I feel always indebted to **Allah**, the Most Kind and the Most Merciful.

I would like also to express my deep appreciation and gratitude to **Prof. Dr./ Essam Mohamed Bayomy**, Professor of Internal Medicine,, Faculty of Medicine – Ain Shams University, for his unlimited help, great efforts and time he has devoted to accomplish this work. I really have the honor to complete this work under his supervision.

I am deeply grateful to **Professor Doctor/ Moataz Mohammed Sayed** Professor of Internal Medicine, Faculty of Medicine – Ain Shams University, for his unlimited help and giving me the privilege to work under his supervision. His care and support are really valuable and precious.

I would like also to express my deep appreciation and gratitude to **Dr./ Sarah Abd.Elkader**, Assistant Professor of Internal Medicine, Faculty of Medicine – Ain Shams University, for her care and support, also for the efforts and time she has devoted to accomplish this work.

Finally, I wish to extend my thanks to my **Family**, especially my **Parents** and **Husband** for their care and support.

Amira Adel

List of Contents

List of Abbreviations

Abbr.	Full-term
AASLD	The American Association for the Study of Liver Diseases
AFP	Alfa feto protien
AFP-L3	Lens culinaris agglutinin-reactive AFP
AFU	Alpha-l-fucosidase
AHA	autoimmune hemolytic anemia
AIH	Autoimmune hepatitis
ALD	Alcoholic liver disease
ALT	alanine aminotransferase
AMA	antimitochondrial autoantibodies
ANA	antinuclear autoantibodies
anti-TPO	antibodies to thyroid peroxidase autoantibodies
APASL	Asian-Pacific Association for the Study of the Liver
AST	serum aspartate aminotransferase
BCLC	Barcelona Clinic Liver Cancer
BUN	Blood urea nitrogen
CBC	Complete blood count
CC	Cholangio-carcinoma
CEUS	Contrast enhanced ultrasound
CF	Cystic fibrosis
CHB	Chronic hepatitis
CHE	Covert hepatic encephalopathy
CLD	Chronic liver disease
CNS	central nervous system
C-P	Child-Pugh
CRCLM	colorectal cancer and liver metastases
CRS	cirrhosis risk score
CT	computed tomography
CTCs	Circulating tumor cells
DCP	Desgamma-carboxy-prothrombin
DIS	Drug Induced Steatosis
EASL-	European Association for the Study of the Liver European
EORTC	Organization for Research and Treatment of Cancer
EGD	esophagogastroduodenoscopy
ELISA	enzyme-linked immunosorbent assay
FFA	Free fatty acids
FGF	fibroblast growth factor
FNA	fine-needle aspiration

FNAB	fine needle aspiration biopsy
GP73	Golgi protein-73
GPC3	Glypican-3
HBV	Hepatitis B
HCC	Hepatocellular carcinoma
HCV	Hepatitis C
Hep Par 1	hepatocyte paraffin 1
HFLs	Hepatic focal lesions
HH	Hereditary hemochromatosis
HIV	human immunodeficiency virus
HLA	human leukocyte antigens
HRS	Hepatorenal syndrome
HSC	hepatic stellate cells
HVPG	hepatic venous pressure gradient
IFN	interferon
IgG	immunoglobulin G
iNO	Inducible nitric oxide
INR	International normalized ratio
IR	Insulin resistance
JH	Juvenile hemochromatosis
JSH	Japan Society of Hepatology
LI-RADS	Liver Imaging Reporting and Data System
LOLA	L-ornithine–L-aspartate
LP	Lichen planus
LPS	lipopolysaccharide
LT	Liver transplantation
MC	mixed cryoglobulinemia
MC	metastatic carcinoma
MELD	model for end-stage liver disease
Mets liver	Metastatic liver
MN	Membranes glomerulonephritis
MPCT	Multiphasic helical ct
MPGN	Membranoproliferative glomerulonephritis
mRECIST	modified Response Evaluation Criteria In Solid Tumors
MRI	magnetic resonance imaging
NAFLD	Nonalcoholic fatty liver disease
NASH	nonalcoholic steatohepatitis
NHL	Non hodgeken lymphoma
NOS	nitric oxide synthase
NPV	Negative predictive value
NSBBs	nonselective beta-adrenergic blockers
OAT	ornithine aminotransferase
ODC	ornithine decarboxylase

OHE	Overt hepatic encephalopathy
OLP	Oral lichen planus
OTC	ornithine transcarbamylase
PBC	Primary biliary cirrhosis
PBMC	peripheral blood mononuclear cell
PCT	Porphyria cutanea tarda
PH	Portal hypertension
PIVKA-II	proteins induced by vitamin K absence
PLT	platelet
PPV	Positive predictive value
PSC	Primary sclerosing cholangitis
PT	prothrombin time
PTT	Partial thromboplastin time
PV	Portal vein
RA	rheumatoid arthritis
RAAS	renin–angiotensin–aldosterone system
RBS	Random blood sugar
ROC	receiver–operator curves
ROS	reactive oxygen species
SAAG	serum albumin ascites gradient
SD	Standard deviation
SNP	single-nucleotide polymorphisms
SNS	sympathetic nervous system
SRTR	Scientific Registry of Transplant Recipients
SS	Sj¨ogren'ssyndrome
SVR	sustained virological response
T2DM	type 2 diabetes mellitus
TGAs	thyroglobulin autoantibodies
TGF-β	Transforming Growth Factor-Beta
TIPS	transjugular intra-hepatic porto-systemic shunt
TMA	tissue microarray
TMAs	Thyroid autoantibodies microsome
TSGF	tumor-specific growth factor
US	ultrasound
WBC	White blood cells
WD	Wilson's disease

List of Tables

List of Figures

ABSTRACT

Objects: To assess the diagnostic value of Serum Arginase as a tumor marker for HCC in comparison with AFP.

Design and methods : Arginase activity, sensitivity and specificity were determined in serum of 60 patients including 20 with HCC, 15 with LC, 15 with metastatic liver and controls which was 10 normal subjects.Serum Arginase was measured by ELISA. Serum Arginase sensitivity and specificity was compared to that of AFP.

Results: The level of Serum Arginase was the highest in HCC group then metastatic group the chronic liver disease group and it was the least in control group.(214,184,112 and 110 respectivily).the sensitivity of Serum Arginase was higher that of AFP(65 and 45 respectivily),but the diagnostic performance of AFP in the diagnosis of HCC is still higher.

Conclusion: Serum Arginase is helpful in screening of cirrhotic patients in adittion to AFP and abdominal US.also it can be used in the diagnosis of HCC.

Key words: Hepatocellular carcinoma,Arginae

Introduction

Hepatocellular carcinoma (HCC) is the third cause of cancer death and leading cause of mortality among cirrhotic patients ***(Forner et al., 2012).***

The annual risk of developing HCC in cirrhotic patients is 5% (1-7%) with a prevalence between 7.4 and 23% found in necropsies of this group of patients. Cirrhosis of the liver is present in 80-90% of this type of cancer ***(Abbasi et al., 2012).***

The main risk factor for the development of HCC is the presence of liver cirrhosis ***(EL-Serag et al., 2012).***

HCC incidence is increasing rapidly due to the current epidemic of hepatitis C (HCV) infection and non alcoholic fatty liver disease world wide prognosis of HCC patients is dependent on tumor stage at diagnosis with curative options available only for patients diagnosed at early stage ***(EL-Serag et al., 2007).***

Alpha fetoprotein (AFP) is a glycoprotein important in the regulation of fatty acid metabolism in both fetal and proliferating adult liver cells and it is a biomarker that is widely used as a serum marker.

For screening cirrhotic patients for Hcc and in follow up HCC patients after different treatment modalities ***(Bertivo et al., 2012).***

However, serum (AFP) levels are not increased in some HCC patients and it may be increased in to chronic benign Liver diseases as liver cirrhosis ***(Richardson et al., 2012).***

The sensitivity and specificity of AFP as a tumor marker for HCC is augmented by search for other serum markers to increased the diagnostic yield ***(Sherman, 2011).***

L-Arginase is an enzyme involved in the metabolism in of L-arginine, Urea and L-ornithine and is involved in urea cycle in normal and malignant cells ***(Feun et al., 2008).***

L-Arginase has two isoenzymes :L- Arginase I and L-Arginase π it was reported that L-Arginase is increased in chronic benign liver disease as liver cirrhosis and also increased in HCC and can be a useful serum marker for diagnosis of HCC ***(Chizanowska et al., 2014).***

Recently it is found that it has also benefit in follow up of HCC after curative treatment and even therapeutic value when use in Transarterial chemoembalization of HCC ***(Store et al., 2012).***

Aim of the Work

The aim of this study is to evaluate Serum Arginase diagnostic value as a tumor marker for HCC in comparison with AFP.