Serum Dickkopf-1 in Early Detection of Hepatocellular Carcinoma in Egyptian Cirrhotic Patients

Thesis

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Abstract

Background: Dickkopf-1 is a secreted protein involved in embryonic development. Previous studies have shown that DKK1 is overexpressed in HCC tissue but is not detectable in corresponding non-cancerous liver tissue. **Objective:** Study assess the value of serum DKK1 in early detection of HCC in Egyptian Cirrhotic Patients. **Study design:** A comparative cross sectional study was conducted on 170 patients divided into 2 groups HCC group consisted of 90 patients and control group consisted of 80 patients (40 patients with liver cirrhosis and 40 healthy persons) conducted at Internal Medicine department and Hepatology outpatient clinic in Ain Shams University Hospitals.

Results: serum DKK1was significantly higher in HCC group than in control group so, serum DKK1 may serve as a good diagnostic biomarker for the diagnosis of HCC.

Conclusion: The current study showed that the serum DKK1 may serve as a good diagnostic biomarker for the diagnosis of HCC at cut off point ≥ 5 ng/ml. Serum DKK1 is superior to AFP in the diagnosis of HCC. Adding both AFP and DKK did not yield better diagnostic characteristics.

Recommendations: Screening and follow up of cirrhotic patients using serum DKK1 is recommended due to its higher sensitivity and specificity in HCC detection.

Further study is required to establish an optimal DKK-1 cutoff value and its use as a prognostic marker for HCC.

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Key words: Dickkopf-1, hepatocellular carcinoma, tumor marker.

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Dedication

I would like to extend my deepest thanks to people who inspired me and supported me through out my entire life,

My Mother & Father

My husband ,

My Sisters,

And My Son

To Everyone of You, My Life is Dedicated.

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List of Abbreviations

Abbrev.	Meaning
A1AT	: Alpha-1 Anti-trypsin
AASLD	: American Association for the Study of Liver Diseases
AFB1	: Aflatoxin B1
AFP	: Alpha-fetoprotein
AFP-L3	: Lens culinaris agglutinin-reactive AFP
AFU	: Alpha-l-fucosidase
AIH	: Autoimmune hepatitis
AST	: Aspartate aminotransferase
BCLC	: Barcelona-Clinic Liver Cancer
BMI	: Body mass index
CEUS	: Contrast enhanced ultrasound
CLD	: Chronic liver disease
CLIP	: Cancer of the Liver Italian Program
CT	: Computed Tomography
CTL4	: Cytotoxic T-lymphocyte-associated protein 4
CTP	: Child-Turcott-Pugh
CXCL5	: Epithelial neutrophil-activating peptide
DCP	: Des-gamma carboxyprothrombin
DEBs	: Drug eluding beads

DKK1 : Dickkopf related protein 1

ECLIA : electro chemo-luminescence

EPO : Erythropoietin

ERs : Estrogen receptors

FFA : Free fatty acids

FLT3 : FMS-like tyrosine kinase-3 receptor

FNA : Fine needle aspiration

Fz : Frizzled receptor

GP73 : Golgi protein 73

GPC3 : Glypican-3

Gsk3 : Glycogen Synthase Kinase 3

GSTM1 : Gluthatione S-Transferase M1

HBV : Hepatitis B virus

HBx : (HBV) x protein

HCC : Hepatocellular carcinoma

HCV : Hepatitis C virus

HGF : Hepatocyte growth factor

IGF : Insulin like growth factor

KIT : Stem-cell factor receptor

LCA : Lens culinaris agglutinin

LDLT : Living-donor liver transplantation

LRP : Low-density lipoprotein receptor-related protein

MELD : Model for End-Stage Liver Disease

MOH : Ministry of Health

MRI : Magnetic Resonance Imaging

MWA : Microwave ablation

NA : Nucleos(t)ide analogs

NAFLD : Non-alcoholic Fatty Liver Disease

NASH : Nonalcoholic steatohepatitis

OCs : Contraceptives

OCT4 : Octamer-binding transcription factor 4

OLT : Orthotopic liver transplantation

OS : Overall survival

PBC : Primary biliary cirrhosis

PD : Programmed death

PDGFR-β : Platelet-derived growth factor receptor beta

PEI : Percutaneous ethanol injection

PIVKA-II : Protein induced by vitamin K absence

PST : Performance Status

RET : Glial cell line-derived neurotrophic factor receptor

RFA : Radiofrequency ablation

SBRT : Stereotactic body radiation therapy

SCCA : Squamous cell carcinoma antigen

SELDI-TOF MS: Surface-enhanced laser desorption/ionization time of flight mass spectrometry

SSTR : Specific somatostatin receptors

STAT3 : Signal transducer and activator of transcription 3

TACE : Transcatheter Arterial Chemoembolization

TGF β 1 : Transforming growth factor beta 1

TNF : Tumor necrosis factor

TNM : Tumor, Node, Metastasis staging

TPO : Thrombopoietin .

UCSF : University of San Francisco

UNOS : Network for Organ Sharing

US : Ultrasound

USA : United States of America

VEGF : Vasoendothelial growth factor

WHO : World Health Organization

WNT : Wingless-related integration site

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Introduction

Hepatocellular carcinoma (HCC) is a major health problem, being the sixth most common malignant disease and the third leading cause of cancer-related death worldwide. Its incidence continues to increase all over the world ***(Venook et al., 2010).***

Hospital-based studies from Egypt have reported an overall increase in the relative frequency of all liver related cancers in Egypt (>95% as HCC), from approximately 4% in 1993 to 7.3% in 2003 ***(El-Zayadi et al., 2005).***

Surveillance of patients at highest risk for developing HCC (i.e., patients with cirrhosis) is an important strategy that can potentially decrease the HCC related mortality rate ***(Sangiovanni et al., 2004).***

Alpha-fetoprotein (AFP) is a serum marker that is most widely used for diagnosis as well as surveillance of HCC. However, AFP levels may be normal in up to 40% of patients with HCC, particularly during the early stages of HCC. Furthermore, elevated AFP levels may be seen in patients with cirrhosis or exacerbations of chronic hepatitis. Prospective studies evaluating the performance characteristics of AFP for HCC surveillance reported