Diagnostic value of circulating immunogenic cell death biomarker, soluble receptor of advanced glycation end product (sRAGE) in patient with Hepatocellular Carcinoma (HCC)

Thesis

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By

Yasmin Sedek Hussien Elghaziry

M.B., B.Ch., & MsC

Faculty of medicine-Ain shams university

Supervised by

Prof. Fawzyia Hassan Abu Ali

Professor of Internal Medicine, Allergy and Clinical Immunology
Faculty of Medicine, Ain Shams University

DR. Rasha Yousef Shahin

Assistant Professor of Internal Medicine, Allergy and Clinical Immunology
Faculty of Medicine, Ain Shams University

DR. Asmaa Saber Mostafa

Assistant Professor of Internal Medicine, Allergy and Clinical Immunology
Faculty of Medicine-Ain Shams University

Faculty of Medicine
Ain Shams University
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List of Abbreviations

A1ATD	Alpha1 antitrypsin deficiency
AASLD	The American Association for the Study of Liver Diseases
AFP	Alpha-fetoprotein
AGEs	Advanced glycation end products
AIH	Auto Immune Hepatitis
AJCC	American Joint Committee on Cancer
ALT	Alanine Aminotransferase
ANOVA	One-way analysis of variance
AST	Aspartate Aminotransferase
AUC	The area under the ROC curve
Aβ	Amyloid beta peptide
BCLC	The Barcelona Clinic Liver Cancer
CLD	Chronic liver disease
CLIP	The Cancer of the Liver Italian Program score
cRAGE	Cleaved receptor of advanced glycation end product
CT	Computed tomography
DM	Diabetes millitus
EBRT	External-beam Radiation Therapy
ECOG	Eastern Cooperative Oncology Group
ECS	Endothelial cells
ELISA	Enzyme Linked Immunosorbent Assay
EPO	Erythropoietin
ERS	Estrogen receptors
esRAGE	Endogenous secretory receptor of advanced glycation end product
FAH	Fumarylacetoacete hydrolase
FDG	Fluorodeoxyglucose
FLR	Future liver remnant
FNAB	Fine-needle aspiration biopsy
HBV	Hepatitis B Virus
HBVsAg	Hepatitis B surface antigen
HBx	Hepatitis B X gene
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HDV	Hepatitis D virus
HH	Hemochromatosis
HMGP1	High-mobility group protein box-1
INR	International normalized ratio

LDL	Low-density lipoprotein
LT	Liver Transplantation
MELD	Model for End Stage Liver Disease
MRI	Magnetic resonant imaging
NAFLD	Non Alcoholic Fatty Liver Disease
NF-KB	nuclear factor kappa B
OCS	Oral contraceptives
OD	Optical density
PDGFR	Platelet derived growth factor family receptor
PET	Positron emission tomography–computed tomography
PS	Performance Scale
PT	Prothrombin Time
PT	Partial Thromboplastin Time
RAGE	Receptor for advanced glycation end products
RFA	Radiofrequency ablation
ROC	Receiver-operating characteristic
ROS	Reactive oxygen species
SHARP	Study of Heart and Renal Protection
Srage	soluble receptor for advanced glycation end products
TACE	Transarterial chemotherapy embolization
TAE	Transarterial embolization
TARE	Transarterial radioembolization
TIPS	Transjugular intrahepatic portosystemic shunt
TNM	Tumor, Node, Metastasis
UICC	The Union Internationale Contre le Cancer
VEGF	Vascular endothelial growth factor

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Introduction

Introduction

Hepatocellular carcinoma (HCC) is considered the most common type of liver cancer nowadays, actually fifth in place, and comes in third place worldwide as regards mortality rate in cancer patients in general. Among the well known risk factors that predispose to HCC are chronic infection with hepatitis C (HCV) or hepatitis B (HBV), excessive alcohol consumption, exposure to aflatoxin B, obesity and nonalcoholic steatohepatitis (NASH) due to diabetes **(McGlynn et al., 2011)**

Chronic liver patients at the stage of extensive fibrosis or cirrhosis are most prone to develop HCC. Close and accurate monitoring of such patients is mandatory to allow proper detection and management as soon as possible aiming for a quick eradication of the disease **(Raphael et al., 2012).**

Advanced glycation end products (AGEs), group of heterogeneous irreversible adducts, result from process of non-enzymatic glycation of nucleic acids, proteins and lipids **(Singh et al., 2001).** AGEs target to accelerate inflammatory reaction when they conjugate with their full-length membrane bound receptor, receptor for advanced glycation

end products, well known as RAGE **(Hyogo and Yamagishi., 2008).**

RAGE belongs to the immunoglobulin family and structurally is considered as a multiligand receptor. Generation of reactive oxygen products and proinflammatory cytokine occur as a result of AGE binding to the ligand receptor through initiation of cell signaling pathways **(Riehl et al., 2009).**

Advanced glycation end products (AGEs) and their receptor (RAGE) system were recently found to be involved in various diseases due to the oxidative stress, inflammatory and thrombogenic reactions they elicit when engaged together. Among these diseases or disorders are cardiovascular disease, inflammatory and autoimmune disorders, neurodegenerative diseases, cancer growth, metastasis and of course diabetes **(Yamagishi et al., 2010).**

As the liver is the organ that catabolizes and gets rid of circulating AGEs **(Basta et al., 2011),** any damage to it, including liver cirrhosis and NASH, may lead to the deviation of the AGE-RAGE axis and may be a crucial turn point for liver carcinogenesis **(Hiwatashi et al., 2008).**

Interestingly, other isoforms of RAGE were detected, truncated soluble isoforms (sRAGE), and proved to have a cytoprotective action against the harmful binding effect of AGE and RAGE. These isoforms contain the RAGE extracellular domain only **(Basta et al., 2011).** One isoform is a result of the full-length receptor while the other form is due to proteolytic cleavage of RAGE **(Raucci et al., 2008).** Both forms are present in human serum and have ability to bind to ligands and also bind to free AGEs preventing harmful binding of ligands to surface RAGE, therefore providing a protective role against hepatocellular injury (**Sparvero et al., 2009).**

Aim of the Work

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To assess the diagnostic and predictive value of soluble receptor for advanced glycation end products in patients with HCC in comparison to patients with chronic liver disease.