Significance of the Ratio between Insulin-Like Growth Factor-1 and Insulin-Like Growth Factor-Binding Protein-3 as a Predictive Marker of Insulin Resistance in Chronic Hepatitis C Patients

Thesis

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Abstract:

Back ground: Hepatitis C virus (HCV) infection is a worldwide disease that induces a range of chronic liver disease sequelae and metabolic abnormalities including insulin resistance and hepatic steatosis. Recent studies showed a lower level of serum insulin-like growth factor-1 (IGF-1) or a decrease in the IGF-1/IGF-binding protein-3 (IGFBP-3) ratio in patients in patients with diabetes mellitus as well as in patients with hepatic steatosis. As both hepatic steatosis and insulin resistance were two common phenomena in patients with chronic HCV.

Objective: to assess the significance of the ratio between insulin-like growth factor-1 (IGF-1) and insulin-like growth factor–binding protein-3 (IGFBP-3) in non-diabetic patients with hepatitis C virus and insulin resistance.

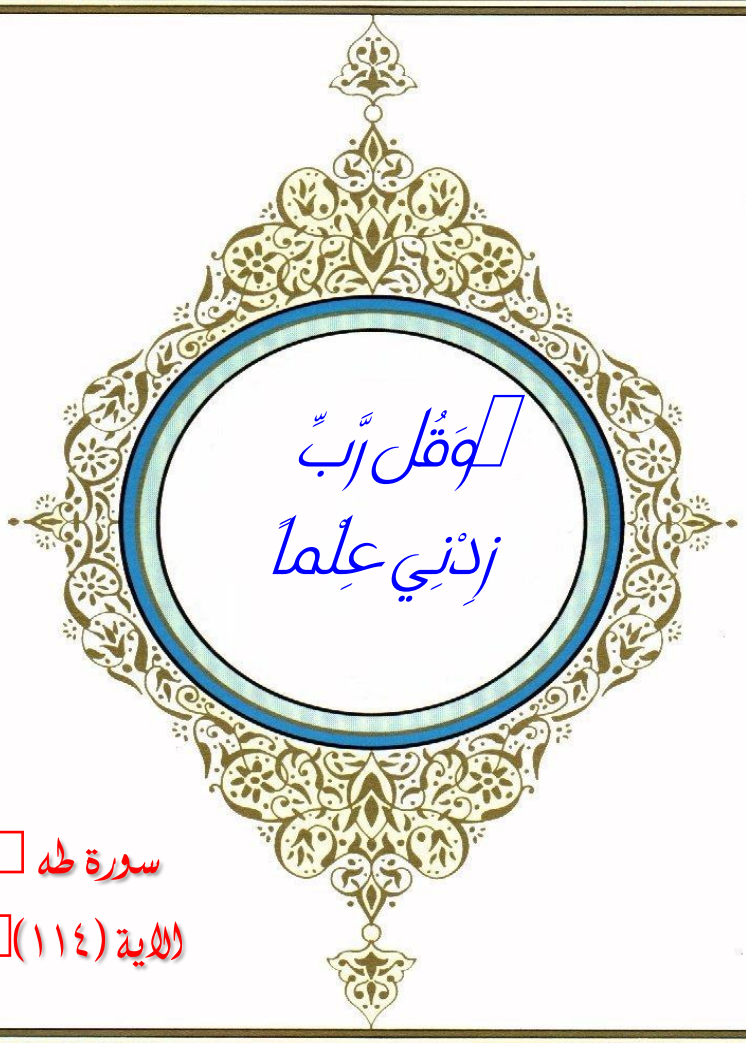
Patients and methods: in this case-control study, 30 non-diabetic patients were selected with HCV-related chronic liver disease and insulin resistance which is determined by the homeostasis model for assessment of insulin resistance (HOMA-IR) method (HOMA-IR $\geq$ 2.5) and 30 healthy volunteers matched in age and sex were selected as a control group. IGF-1 and IGFBP-3 were assessed in the cases and controls using the commercially-available ELISA kits. Insulin resistance was determined using HOMA-IR calculation.

Results: Chronic hepatitis C was more associated with insulin resistance and low IGF-1/IGFBP-3 ratio levels. Child-Pugh score (which is known to be used for assessment of the degree of liver decompensation) in our thesis was statistically correlated to HOMA-IR and IGF-1/IGFBP-3 ratio, illustrating the fact that the more insulin resistance, the more hepatic dysfunction.

Conclusion: Decrease in IGF-1/IGFBP-3 ratio level is a good predictive marker of insulin resistance and deterioration of liver functions in HCV-related chronic liver disease.

Keywords: IGF-1/ IGFBP-3 ratio, chronic hepatitis C, insulin resistance, HOMA-IR.

بسم الله الرحمن الرحيم



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صَدَقَ اللهُ العَظِيم

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Abb.		Full term
ALT	:	Alanine aminotransferase
ANOVA	:	Analysis of variance
AST	:	Aspartate transaminase
AGE	:	Atazanavir (ATV)
BUN	:	Blood Urea Nitrogen
BMI	:	Body Mass Index
CDC	:	Centers for Disease Control and Prevention
CTP score	:	Child-Turcotte-Pugh Score
CHC	:	Chronic Hepatitis C
CLD	:	Chronic Liver Disease
CBC	:	Complete blood count
DMNI	:	Damanhur Medical National Institute
DM	:	Diabetes mellitus
ELISA	:	Enzyme-linked immunosorbent assay
EHM	:	Extra-hepatic manifestation

Abb.		Full term
FBG	:	Fasting blood glucose
FFAs	:	Free Fatty Acids
GH-IGF-I	:	Growth hormone Insulin-like growth factor-1 axis
GLUT	:	Glucose Transporter
GH	:	Growth hormone
HB	:	Hemoglobin
HBsAg	:	Hepatitis B surface antigen
HBV	:	Hepatitis B virus
HCV-NS Proteins	:	Hepatitis C virus Non-Structural Proteins
HCV	:	Hepatitis C virus
HCC	:	Hepatocellular carcinoma
HDL	:	High-density lipoprotein
HOMA-IR	:	Homeostasis Model for Assessment of Insulin Resistance
HRS	:	Hepatorenal syndrome
HIV	:	Human immunodeficiency virus
IGf-1/IGFBP-3 ratio	:	Insulin-like growth factor-1 to Insulin like growth factor binding protein-3 ratio

Abb.		Full term
INR	:	International normalized ratio
IGFBP-3	:	Insulin like growth factor binding protein-3
IGFBPs	:	Insulin like growth factor binding proteins
IRS	:	Insulin receptor substrate
IR	:	Insulin resistance
IGF-1	:	Insulin-like growth factor-1
IL-1	:	Interleukin-1
IL-6	:	Interleukin-6
IDUs	:	Intravenous drug users
LSD	:	Least Significant Difference
LPL	:	Lipoprotein lipase
LPV	:	lopinavir
LDL	:	Low-density lipoprotein
MELD	:	Model For End-Sage Liver Disease
MVPA	:	Moderate- and Vigorous-Intensity Physical Activity
N	:	Number

Abb.		Full term
NIDDM	:	Non-insulin-dependent diabetes mellitus
NS5A	:	Nonstructural protein 5A
OSA	:	Obstructive Sleep Apnea
OVs	:	Oesophageal Varices
OGTT	:	Oral glucose tolerance test
PTT	:	Partial Thromboplastin Time
PCR	:	Polymerase chain reaction
PAI-1	:	Plasminogen activator inhibitor type -1
PCOS	:	Polycystic Ovary Syndrome
PI	:	Protease inhibitor
PP2-A	:	Protein Phosphatase 2-A
PT	:	Prothrombin time
RIA	:	Radio-Immunoassay
ROS	:	Reactive Oxygen Species
RTV	:	Ritonavir
RNA	:	Ribonucleic Acid
SBP	:	Spontaneous bacterial peritonitis
SSPG	:	Steady-state plasma glucose
SSPI	:	Steady-state plasma insulin

Abb.		Full term
SOCS3	**:**	Suppressor of cytokine signaling-3
SVR	**:**	Sustained virological response
IST	**:**	The insulin suppression test
QUICKI	**:**	The Quantitative Insulin Sensitivity Check Index
TGF-β	**:**	Transforming growth factor-β
TNF	**:**	Tumor necrosis factor
VLDL	**:**	Very-Low-Density Lipoprotein
WBCs	**:**	White blood cells
WHO	**:**	World Health Organization

Introduction

Chronic liver disease is frequently associated with insulin resistance which is known as a pathophysiological feature of hepatogenous diabetes. There are many theories illustrating the pathophysiology of hepatogenous insulin resistance and diabetes including hepatic parenchymal cell damage, porto-systemic shunting and hepatitis C virus (HCV). **(*Kawaguchi et al., 2011*)**

Recent studies from various parts of the world stated that chronic HCV infection (CHC) is associated with many metabolic disorders such as non-insulin-dependent diabetes mellitus (NIDDM) and they reported that between 13% and 33% of patients with chronic hepatitis C (CHC) have diabetes mellitus (DM). Insulin resistance (IR) or pre-diabetes is a common feature of disturbed carbohydrate metabolism in chronic liver disease with or without cirrhosis. **(*Dai et al., 2015*)**

IGF-1 is a single chain peptide that has a similar molecular structure to pro-insulin. Although IGF-1 is synthesized widely, most of the circulating IGF-1 is derived from the liver. ***(Su et al., 2010)***