Correlation between adiponectin level and the degree of fibrosis in patients with NAFLD

Thesis

Submitted for Partial Fulfillment of Master Degree in Internal Medicine

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2020

بسم الله الرحمن الرحيم

قالوا

سبحانك لا علم لنا
إلا ما علمتنا إنك أنت
العليم الحكيم

صدق الله العظيم

سورة البقرة الآية: ٣٢

Acknowledgment

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

I'd like to express my respectful thanks and profound gratitude to Prof. Dr. Tarek Mohammed Youssef, *Professor of Internal Medicine Gastroenterology and Hepatology Unit Faculty of Medicine, Ain Shams University for his keen guidance, kind supervision, valuable advice and continuous encouragement, which made possible the completion of this work.*

I am also delighted to express my deepest gratitude and thanks to Dr. Manal Sabry Mohamed, *Assistant Professor of Internal Medicine Gastroenterology and Hepatology Unit Faculty of Medicine, Ain Shams University, for her kind care, continuous supervision, valuable instructions, constant help and great assistance throughout this work.*

I am deeply thankful to Dr. Ahmed El-Metwally Ahmed, *Lecturer of Internal Medicine Gastroenterology and Hepatology Unit Faculty of Medicine, Ain Shams University, for his great help, active participation and guidance.*

Esraa Ebrahim Abdullah Khalifah

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List of Abbreviations

Abb.	Full term
2hPP	2 hours postprandial
ACC	Acetyl-CoA Carboxylase
Adipo R1	Adiponectin receptor 1
Adipo R2	Adiponectin receptor 2
ALT	Alanine Aminotranferase
AMP	Adinosine Mono-Phosphate
AMPK	Adenosine Monophosphate-activated Protein Kinase
APRI	AST Platelet Ratio Index
ASK-1	Apoptosis Signal-regulating Kinase-1
AST	Aspartate Aminotransferase
ATP	Adinosine Tri-Phosphate
BMI	Body Mass Index
CBC	Complete blood count
CCL	C-C chemokine Legand
CCR	C-C chemokine Receptor
CPT-1	Carnitine Palmitoyl Transferase-1
CT	Computed Tomography
CTGF	Connective Tissue Growth Factor
CVD	Cardiovascular Diseases
ER	Endoplasmic Reticulum
FBS	Fasting blood sugar
FFA	Free Fatty Acids
FIB-4	Fibrosis-4
FL	Fatty Liver
FLI	Fatty Liver index
FXR	Farnesoid X Receptor
G-6-Pase	Glucose-6-Phosphatase
GGT	Gamma Glutamyl Transferase

List of Abbreviations Cont...

Abb.	Full term
GGT	Gamma Glutamyl Transferase
GLP-1	Glucagon-like peptide-1
HAART	Highly Active Anti-Retroviral Therapy
Hb A1C	Glycosylated Hemoglobin
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCC	Hepatocellular Carcinoma
HCV	Hepatitis C virus
HCV-Ab	Hepatitis C Virus antibody
HDL-C	high-density lipoprotein cholesterol
HMW	High Molecular Weight
HSC	Hepatic Stellate Cells
Hs-CRP	High-sensitivity C-Reactive Protein
HTN	Hypertension
IL	Interlukin
INR	International neutralization ration
IR	Insulin Resistance
IR	Insulin Resistance
JAK	Janus kinase
kb	Kilobases
KCs	Kupffer Cells
kDa	Kilo Dalton
LMW	Low Molecular Weight
LOXL-2	Lysyl Oxidase Like-2
LT	Liver Transplantation
MCP-1	Monocyte Chemoattractant Protein-1
MMP-1	matrix metalloproteinase-1
MMW	Medium Molecular Weight
MPO	Myeloperoxidase

List of Abbreviations Cont...

Abb.	Full term
MRE	Magnatic Resonance Elastography
MRI	Magnatic Resonance Imaging
NAFLD	Non-Alcoholic Fatty Liver Disease
NAS	NAFLD activity score
NASH	Non-Alcoholic Steato-Hepatitis
NFS	NAFLD Fibrosis Score
NF-κB	Nuclear Factor-kappa B
OCA	Obeticholic acid
OSA	Obstructive Sleep Apnea
PAI-1	Plasminogen Activator Inhibitor-1
PCO	Polycystic Ovarian disease
PDGF	Platelet Derived Growth Factor ()
PEPCK	Phosphoenolpyruvate Carboxykinase
PPAR-α	Peroxisome Proliferator Activated Receptor alpha
PTP1B	Protein Tyrosine Phosphatase 1B
RBP-4	Retinol Binding Protein-4
ROS	Reactive Oxygen Species
SAF	Steatosis Activity Fibrosis score
SEL	Selonsertib
SOCS-3	Cytokine Signaling-3
SREBP-1c	Sterol Regulatory Element Binding Protein-1c
STAT	signal transducer and activator of transcription
T2DM	Type 2 Diabetes Mellitus
TE	Transient Elastography
TG	Triglycerides
TGF	Tumor Growth Factor
TGF-β1	Transforming Growth Factor-beta 1

List of Abbreviations Cont...

Abb.	Full term
TIMP-1	tissue inhibitor of metalloproteinases-1
TNF	Tumor Necrosis Factor
tPAI-1	Total Plasminogen Activator Inhibitor-1
TZDs	Thiazolidinediones
US	Ultrasonography
USE	Ultrasound Elastography
VDR	Vitamin D Receptor
VLDL	Very Low Density Lipo-protien
VLDL	very-low-density lipoprotein
WC	Waist Circumference
α-SMA	Alpha Smooth Muscle Actin

ABSTRACT

Background: Non-alcoholic Fatty Liver Disease (NAFLD) is one of the most prevalent chronic liver diseases particularly in Egypt. It is defined as accumulation of lipids inside the hepatocytes, in absence of other etiologies of hepatic damage. It is frequently associated with obesity, diabetes mellitus and metabolic syndrome.

Objective: To find out the correlation between the degree of liver fibrosis in Non-alcoholic Fatty Liver Disease patients and their serum Adiponectin level as a future non-invasive method for assessment of liver fibrosis to substitute liver biopsy to avoid its hazardous complication. Also to study the correlation between diabetes mellitus as well as obesity and serum Adiponetctin level.

Patients and Methods: 50 patients were selected to participate in our study based on our inclusion criteria. They were recruited from the Internal Medicine department, Gastro-intestinal clinic in Al-Demerdash Hospital using a convenient sampling method. Diagnoses of NAFLD (Non-alcoholic fatty liver disease) was confirmed by laboratory markers (AST, ALT, Lipid profile), ultrasound as well as fibroscan examination.

Results: Analyzing adiponectin levels showed that -besides its significant correlation with BMI, hypertension, diabetes mellitus and dyslipidemia- it was significantly lower in high grade fibrosis group compared to low grade fibrosis group with P-value of (0.000) and a cutoff value for stage 3/4 fibrosis of about 2.31μg/ml which marked a promising hope of adeponictin being of protective value against liver fibrosis. However, more studies performed on populations of different sizes and characteristics are recommended to allow more accurate generalization of the results and hopefully exploring a new horizon for the follow up and treatment of patients with chronic liver disease especially NAFLD.

Conclusion: Adiponectin is an abundant adipocyte-derived protein with well-established anti-atherogenic, insulin-sensitizing and anti-inflammatory properties. The liver is a major target organ for adiponectin especially in fatty liver diseases and this adipocytokine has the ability to control many liver functions including metabolism, inflammation and fibrosis. Both serum levels and hepatic adiponectin receptor expression are decreased in NAFLD. Therefore, either adiponectin itself or adiponectin-inducing agents might be of key therapeutic interest in the near future in the treatment of NAFLD.

Keywords: Nonalcoholic fatty liver disease, hepatic stellate cells, adenosine monophosphate-activated protein kinase

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) represents a spectrum of disorders characterized by macrovescicular hepatic steatosis occurring in individuals without a relevant alcohol consumption. It is a complex metabolic condition in which both lifestyle and genetic factors have a pathogenic role and has been increasingly recognized as a major cause of liver-related morbidity and mortality ***(Satapathy and Sanyal, 2015).***

Moreover, NAFLD has been convincingly associated with the metabolic insulin-resistance syndrome; most patients are overweight or frankly obese, with altered glucose regulation, dyslipidemia, and raised blood pressure, all contributing to the disorder ***(Lucero et al., 2017).***

Insulin resistance, through the inhibition of lipid oxidation and increased fatty acid and triglycerides synthesis, is believed to be a key factor in the development of fatty liver. Moreover, insulin resistance states, such as obesity and diabetes, are also characterized by elevated expression and production of several cytokines; of particular interest are cytokines produced by adipose tissue, the so-called adipokines (adiponectin, leptin, resistin), NFα, TGFβ and PAI-1. Their role in the development of diabetes and other obesity complication has been suggested ***(Zhao et al., 2014).***

Adiponectin, a 28 kDa protein adipocytokine, is mainly produced and secreted into the circulation by white adipose tissue. The primary function of adiponectin is the regulation of carbohydrate and lipid metabolism. However, the full extent of its biological action remains to be elucidated, with a variety of effects on different cell and tissue types, including its immune modulatory, anti-inflammatory, and anti-fibrotic properties ***(Udomsinprasert et al., 2018).***

Regarding its protective effects, adiponectin regulates hepatic stellate cells (HSCs) proliferation, as well as migration, and induces their apoptosis through the activation of adenosine monophosphate-activated protein kinase (AMPK). Moreover, adiponectin can attenuate HSC activation and suppress the expression of pro-fibrogenic genes, including collagen Ⅰ, transforming growth factor-beta 1 (TGF-β1), and alpha-smooth muscle actin (α-SMA), leading to the inhibition of liver fibrogenesis. With such potent effects on HSCs against liver fibrosis, adiponectin may be developed as a novel therapeutic agent in liver fibrosis. As it can be detected in the circulation and exerts its effects on various cells, it may have prognostic and diagnostic value for several human diseases. Interestingly, hypo-adiponectinemia has been documented as highly prevalent in patients with NAFLD and liver fibrosis, thereby establishing the possible influence of adiponectin levels in the development and progression of liver fibrosis ***(Zhang et al., 2019).***