Study of visfatin level in patients with non-alcoholic fatty liver disease and its role in progression to non-alcoholic steatohepatitis

A Thesis Submitted for partial fulfillment of master degree in Internal Medicine

By

Ahmed Zaher Abdel Ghafar Aly

M.B.B.Ch.

Supervised by

Dr. Khaled Abdel Hameed Mohamed

Professor of Internal Medicine, Gastroenterology & Hepatology – Ain Shams University

Dr. George Safwat Riad

Assistant professor of Internal Medicine, Gastroenterology & Hepatology – Ain Shams University

Dr. Hany Aly Hussein

Assistant professor of Internal Medicine, Gastroenterology & Hepatology – Ain Shams University

2018

Abstract: Nonalcoholic fatty liver disease (NAFLD) includes a wide range of liver clinico-pathological conditions, starting from pure fatty steatosis up to nonalcoholic steatohepatitis (NASH), which may develop to cirrhosis, liver failure and hepatocellular carcinoma (HCC). NAFLD has become by far the commonest chronic liver disease (CLD) in the United States, accounting for a steadily increasing percentage of CLD cases over the last quarter century. Aim of the work: To evaluate serum visfatin level as a novel non-invasive marker for non-alcoholic fatty liver disease and its role in progression to non-alcoholic steatohepatitis. **Patients and methods:** This case control study was conducted at The Gastroenterology and Hepatology Unit, Department of Internal Medicine, Ain Shams University on 60 adult Egyptian patients with non-alcoholic fatty liver disease and 30 control healthy subjests during the period from march 2017 to September 2017**. Results:** Serum visfatin levels were significantly increased in patients with NAFLD when compared to healthy controls. In addition, visfatin levels decreased when NASH was diagnosed. However, it was still significantly higher than in healthy subjects. **Recommendation:**Further studies are needed to evaluate relationship between visfatin and NAFLD and its role in progression to NASH.

Key words: NAFLD, NASH, Serum visfatin

بسم الله الرحمن الرحيم

وقل اعملوا

فسيرى الله عملكم

ورسوله والمؤمنون

صدق الله العظيم

سورة التوبة آية ١٠٥

Acknowledgment

To **Allah**, everything in life is resumed. In this work, Allah has helped me a lot. Allah offered me what I didn't know and what I have to know. So, before I begin the acknowledgment, I must kneel thanking Allah who inspired me, took my hand and provided me with power, patience and guidance.

It gives me honor to express my deep gratitude to prof. **Dr. Khaled Adbel Hameed Mohamed**, Professor of *Internal Medicine, Gastroenterology&Hepatology – Ain Shams University*, who provided the basis for this work, for his supervision and for enriching me with her vast experience.

I would like to say that words are not enough to express my sincere gratitude to my supervisor **Dr. George Safwat Riad**, assistant Professor of *Internal Medicine, Gastroenterology & Hepatology – Ain Shams University*. for his kind supervision and continuous guidance throughout the course of this research.

I would like to express my deepest thanks and appreciation tomy supervisor**Dr. Hany Aly Hussein**, assistant Professor of *Internal Medicine, Gastroenterology & Hepatology – Ain Shams University*, for endless help in the clinic, providing me with an ideal and inspiring research environment and enriching me with continuous support.

DEDICATION

To my Family

Forhelpingmealotthroughoutthis workbytheirsupportandtime.

Contents

List of Tables

List of Figures

List of Abbreviations

Symbol	Abbreviation
11 β-HSD 1	11 β-hydroxysteroid dehydrogenase type 1
5αR	5-α. reductase
AAR	AST/ ALT ratio
ACE	Angiotensin converting enzyme inhibitors
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AMPK	Adenosine monophosphate-activated protein kinase
ANA	Anti-nuclear antibodies
apoB	Apolipoprotein B
APRI	Age/platelet ratio index
ARBs	Angiotensin receptor blockers
ARFI	Acoustic radiation force impulse imaging
AST	Aspartate aminotransferase
AUROC	Area under the receiver operating characteristics curve
BMI	body mass index
CBC	Complete blood picture
CC	Cryptogenic cirrhosis
CK18	Cytokeratin-18
CLD	Chronic liver disease
CSF	Cerebro-spinal fluid
CT	Computed tomography
CYP2E1	Cytochrome P450 2E1.

Symbol	Abbreviation
DAG	Diacylglycerol
DGAT2	Diacylglycerol O-acyltransferase 2
DNL	De novo lipogenesis
DPP-4	Dipeptidyl Peptidase-4 inhibitors
EASL	European Association for the study of the liver
ELF	European liver fibrosis
ER	Endoplasmic reticulum
FFAs	Free fatty acids
FGF21	Fibroblast growth factor 21
FIB-4	Fibrosis-4
FLI	Fatty liver index
GCs	Glucocorticoids
GGT	Gamma glutamyltranspeptidase
GIP	Glucose dependent insulinotropic polypeptide
GLP-1	Glucagon-like peptide-1
GLUT	Glucose transporter
HCC	Hepatocellular carcinoma
HDL	High density lipoproteins
HFD	High-fat diet
HOMA	Homeostasis Model of Assessment
HPCs	Hepatic progenitor cells
HTN	Hypertension
Ikk-β	Inhibitor of nuclear factor Kappa-B kinase subunit beta.

Symbol	Abbreviation
IL-6	Interleukin-6
IL-l β	Interleukin l-beta
IR	Insulin Resistance
IRS	Insulin receptor substrates
JNK1	Jun N-terminal kinase 1
LAP	Lipid Accumulation Product
LDL	Low density lipoprotein
LPS	Lipopolysaccarides
MCP1	Monocyte chemoattracted protein-1.
MMPs	Matrix metalloproteinases
MRE	Magnetic resonance elastography
MRI	Magnetic resonance imaging
MRS	Magnetic resonance spectroscopy
MTP	Microsomal transfer protein
NAFLD	Non-alcoholic Fatty Liver Disease
NAMPT	Nicotinamide phosphoribosyltransferase
NAS	NAFLD activity score
NASH	Non-alcoholic Steatohepatitis
NF-κB	Nuclear factor kappa B
NHANES	National Health and Nutrition Examination Survey
NICE	National Institute of Health and Care Excellence
NPV	Negative predictive value
PBEF	Pre B cell Colony Enhancing Factor

Symbol	Abbreviation
PI3K	Phosphoinositide 3-kinase
PIVENS	Pioglitazone versus Vitamin E versus placebo for the treatment of non-diabetic patients with NASH
PKB	Protein kinase B
PKCε	Protein kinase Cε
PPARγ	Peroxisome-proliferator activated receptor gamma
ROS	reactive oxygen species
RTE	Real-time shear wave elastography
SNPs	Single nucleotide polymorphisms.
SOCS	Suppressors of cytokine signalling
SREBP-1c	Sterol regulatory element binding protein-1c
T2DM	Type 2 diabetes mellitus
TE	Transient elastography
TGF-β	Transforming growth factor beta.
TIMPs	Tissue inhibitors of metalloproteinases
TNF-α	Tumor necrosis factor-alpha
TZDs	Thiazolidinediones
US	Ultrasonography
VAT	Visceral adipose tissue
VEGF	Vascular endothelial growth factor
VLDL	Very low density lipoprotein
WAT	White Adipose Tissue
ω-3 PUFAs	ω-3 polyunsaturated fatty acids

Introduction

Non-alcoholic fatty liver disease (NAFLD) is a common cause of cirrhosis and liver-related morbidity and mortality. It is already considered the hepatic manifestation of metabolic syndrome. The prevalence of NAFLD is increasing worldwide due to the alterations in lifestyle and the epidemic of obesity and insulin resistance(IR). Accumulation of visceral adipose tissue(VAT) and the development of IR seem to be pivotal to the steatohepatitis (NASH) and concomitant fibrosis **(Verrijken A et al.,2010).**

Adipose tissue acts as a store of energy and an active endocrine organ. Adipokines (adipocytokines)–agents secreted primarily by adipocytes–modulate lipid and glucose metabolism and insulin sensitivity **(Marra F and Bertolani C, 2009).** In addition to their well-established role in controlling adipose tissue physiology, adipokines have been shown to be involved in regulation of the inflammatory response, angiogenesis and fibrogenesis. As a result, adipokines together with insulin resistance seem to play a distinct role in the pathogenesis of NAFLD **(Polyzos SA, Kountouras J and Zavos C, 2009).**

Visfatin was recently identified as a protein expressed in visceral adipose tissue visfatin, an adipokine isolated by **Fukuhara et al. (2005)**, corresponds to a protein identified previously as pre-B cell colony-enhancing factor, a 52 kDa cytokine expressed, and secreted by lymphocytes. The biological role of visfatin is not entirely understood,

but several studies indicated glucose lowering and insulin mimicking/-sensitizing effects of visfatin **(Fukuhara A et al., 2005).**

Visfatin is proposed as important proinflammatory mediator, however, conflicting results have been reported on the potential link between NAFLD and visfatin **(Gaddipati R et al., 2010).** Serum visfatin level is significantly associated with NAFLD/NASH that is in line with previous studies **(Wozniak SE et al., 2009).** Notably elevation in circulating visfatin is parallel to the pancreatic beta cell dysfunction in diabetics **(Lopez-Bermejo A et al., 2006)**. Likewise, serum visfatin was correlated with systemic IR and development of metabolic syndrome **(Esteghamati A et al., 2012).** The purpose of the present study is to investigate the serum visfatin levels in patients with NAFLD and NASH.