بسم الله الرحمن الرحيم

MONA MAGHRABY

شبكة المعلومات الجامعية

التوثيق الالكتروني والميكروفيلم

MONA MAGHRABY

شبكة المعلومات الجامعية

التوثيق الإلكتروني والميكروفيلم

جامعة عين شمس

التوثيق الإلكتروني والميكروفيلم

قسم

نقسم بالله العظيم أن المادة التي تم توثيقها وتسجيلها
علي هذه الأقراص المدمجة قد أعدت دون أية تغيرات

يجب أن

تحفظ هذه الأقراص المدمجة بعيدا عن الغبار

MONA MAGHRABY

Role Of Circulating Vascular cell adhesion protein – 1 as a Biomarker In Non-alcoholic Fatty Liver Disease

Thesis

Submitted for partial fulfillment of Master's Degree in Gastroenterology and Hepatology

Presented by

Yasser Mohamed Ali Abdelhady Alsaid

M.B.B.CH, Faculty of Medicine- October 6 University

Supervised by

Prof. Dr. Mohamed Abd EL Moghny Mostafa

Professor of Internal Medicine and Gastroenterology

Faculty of Medicine, Ain Shams University

Prof. Dr. Ahmed Ali El Ray

Professor of Gastroenterology and Hepatology

Faculty of Medicine, October 6 University

Dr. Ahmed Samir Abd El Sadek

Asst. Professor of Internal Medicine and Gastroenterology

Faculty of Medicine, Ain Shams University

Dr. Khaled Abdl EL Hamid Rafat

Lecturer of Internal Medicine and Gastroenterology

Faculty of Medicine, Ain Shams University

Faculty of Medicine

Ain Shams University

2021

سورة البقرة الآية: ٣٢

Acknowledgement

First and foremost thanks to ALLAH, the Most Merciful.

I wish to express my deep appreciation and sincere gratitude to ***Prof. Dr. Mohamed Abd EL Moghny Mostafa,*** *Professor of Internal Medicine and Gastroenterology, Ain Shams University, for his close supervision, valuable instructions, continuous help, patience, advices and guidance. He has generously devoted much of his time and effort for planning and supervision of this study. It was a great honor to me to work under his direct supervision.*

I wish to express my great thanks and gratitude to ***Prof. Dr. Ahmed Ali El Ray,*** *Professor of Gastroenterology and Hepatology, October 6 University, for her kind supervision, indispensable advice and great help in this work.*

I wish to express my great thanks and gratitude to ***Dr. Ahmed Samir Abd El Sadek,*** *Asst. Professor of Internal Medicine and Gastroenterology, Ain Shams University, for his kind supervision, indispensable advice and great help in this work.*

I wish to express my great thanks and gratitude Dr. ***Khaled Abdl EL Hamid Rafat,*** *Lecturer of Internal Medicine and Gastroenterology, Ain Shams University, for his kind supervision, indispensable advice and great help in this work.*

Last and not least, I want to thank all my family, my colleagues, for their valuable help and support.

Finally I would present all my appreciations to my patients without them, this work could not have been completed.

Contents

List of Abbreviations

Abb.	Full term
ALD	Alcohol-related liver disease
AMA	Anti-mitochondrial antibodies
ANA	Anti-nuclear-antibodies
AOC3	Amine oxidase copper– containing 3
ASBT	Apical sodium-dependent bile acid transporter
CA	Cholic acid
CDCA	Chenodeoxycholic acid
CHC	Chronic hepatitis C
CVD	Cardiovascular diseases
ELF	Enhanced liver fibrosis
FIB-4	Fibrosis-4
FLI	Fatty liver index
FXR	Farnesoid X receptor
HCC	Hepatocellular carcinoma
HE	Hepatic encephalopathy
HSCs	Hepatic stellate cells
IGF	Insulin growth factor
IL-1β	Interleukin-1β
IL-4	Interleukin-4
IR	Insulin resistance
LT	Liver transplantation
MAFLD	Metabolic associated fatty liver disease
MCD	Methionine-choline–deficient
MD	Mediterranean Diet
MetSyn	Metabolic syndrome
MRE	Magnetic resonance elastography
NAFL	Nonalcoholic fatty liver
NAFLD	Nonalcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
NFS	NAFLD fibrosis score
NICE	National Institute for Health and Care Excellence
NPV	Negative predictive value
PDFF	Proton density fat fraction

Abb.	Full term
PPV	Positive predictive value
SCFAs	Short-chain fatty acids
SECs	Sinusoidal endothelial cells
SIBO	Small intestinal bacterial overgrowth
SMA	Smooth muscle antibodies
T2D	Type 2 diabetes
TE	Transient Elastography
THV	Terminal hepatic venule
TNF-α	Tumor necrosis factor α
VAP-1	Vascular adhesion protein-1
VCAM-1	Circulating vascular cell adhesion protein – 1
VCTE	Vibration-controlled transient elastography
VCTE	Vibration-controlled transient elastography
VLDL	Very-low-density lipoprotein
WHO	World Health Organization
WLM	Western lifestyle model

List of Table

List of Figures

INTRODUCTION

As a result of the obesity pandemic, non-alcoholic fatty liver disease (NAFLD) has become the most common cause of chronic liver disease worldwide. NAFLD is the hepatic manifestation of obesity and a precursor of and independent risk factor for type 2 diabetes ***(Yki-Jarvinen. 2014), (Lonardo et al., 2015).***

NAFLD comprises a spectrum of disease that ranges from hepatocellular steatosis without necro-inflammation (NAFL) to non-alcoholic steatohepatitis (NASH), fibrosis, cirrhosis and even hepatocellular carcinoma. In addition, NAFLD is an independent risk factor for cardiovascular disease, with recent studies unequivocally showing an increased cardiovascular mortality in NAFLD patients ***(Ekstedt et al., 2015), (Angulo et al., 2015).***

The global prevalence of NAFLD and NASH is around 25% and 3%, respectively, although this rises to an estimated 90% and 25%, respectively, in severely obese patients ***(Younossi et al., 2016), (Vernon G et al., 2011).*** Liver biopsy is still considered as the gold standard for the diagnosis of NASH and the assessment of disease activity and fibrosis, although it has important disadvantages such as its high cost, invasive nature and the risk of sampling error ***(EASL guidelines 2016).***

This has inspired the search for non-invasive disease markers, including both serum biomarkers and imaging methods. Nevertheless, there are currently no non-invasive markers that can adequately distinguish NAFLD from NASH ***(Machado et al., 2013).***

Similarly, while many markers have shown an acceptable accuracy for the exclusion of advanced fibrosis/cirrhosis (F3-F4) ***(McPherson et al., 2013),*** the identification of advanced disease is less accurate, and the distinction between significant (⩾ F2) or any (⩾ F1) fibrosis versus no fibrosis remains difficult ***(Guha et al., 2008).***

The latter represents an unmet need, as recent guidelines recommend a closer follow-up of patients with significant fibrosis ***(EASL guidelines 2016),*** and the long-term prognosis of patients with fibrosis, even F1, is worse compared to NAFLD patients without fibrosis ***(Angulo et al., 2015).***

Neoangiogenesis is increased in NASH patients and correlates with the severity of fibrosis ***(Kitade et al., 2009).***

Endothelial dysfunction and pathological angiogenesis in turn predispose the liver to further injury as they increased intrahepatic vascular resistance, distorted the sinusoidal microvascular architecture, modulated leukocyte infiltration and caused local tissue hypoxia ***(Coulon S et al., 2013), (Francque et al., 2012) ,(Lefere et al., 2016).***

Indeed, both processes seem to be early events that precede the development of inflammation and fibrosis ***(Pasarin et al., 2011)*** and further substantiate the links between NAFLD and cardiovascular disease ***(Francque et al., 2016).***

Vascular cell adhesion molecule-1 or CD106 is a 110 kDa transmembrane glycoprotein member of the immunoglobulin gene superfamily ***(Osborn et al., 1989)***.

It was first described as a cytokine-inducible endothelial adhesion molecule. It can bind to leukocyte integrin very late antigen-4 (VLA-4) to recruit leucocytes to sites of inflammation. Thus, VCAM-1 stimulates adhesion of lymphocyte and monocytes to the surface of the vascular endothelium. In addition, eosinophils and basophils, but not neutrophils, can bind to endothelial cells via VCAM-1/VLA-4 interaction.

This adhesion molecule is expressed primarily on endothelial cells; however, other cell types, both vascular and nonvascular cells, are also capable of expressing VCAM-1. New insights and diagnostic improvements in NAFLD such as transient elastography and FibroScan are trending.

However, focusing on noninvasive, cheap, and useful biomarkers in clinical practice is mandatory. In this way, the role of circulating biomarkers related to endothelial dysfunction and the severity of underlying liver disease

need to be investigated. It is suggested that there is a role of VCAM-1 stimulating adhesion of lymphocyte and monocytes to the surface of the vascular endothelium. VCAM-1 is not investigated thoroughly in different stages of liver diseases, such as NAFLD ***(Lefere et al., 2017)***.