



شبكة المعلومات الجامعية
التوثيق الإلكتروني والميكروفيلم

بسم الله الرحمن الرحيم



HANAA ALY



شبكة المعلومات الجامعية
التوثيق الإلكتروني والميكروفيلم



شبكة المعلومات الجامعية التوثيق الإلكتروني والميكروفيلم



HANAA ALY



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 تغييرات



يجب أن

تحفظ هذه الأقراص المدمجة بعيدا عن الغبار



HANAA ALY



Role Of Circulating Ectodysplasin A as a Biomarker in Non-alcoholic Fatty Liver Disease

A Thesis

*Submitted for the Partial Fulfillment of the Requirements of Master
degree In Gastroenterology and hepatology*

By

Ahmed Hafez Ezzat El-Sayed Ali

M.B.B.CH

Supervisors

Prof. Moataz Mohamed Sayed

*Professor of Internal Medicine & Gastroenterology
Faculty of Medicine - Ain Shams University*

Prof. Manal Sabry Mohamed

*Assistant Professor of Internal Medicine & Gastroenterology
Faculty of Medicine Ain Shams University*

Prof. Ahmed Mohamed ElGhandour

*Assistant Professor of Internal Medicine & Gastroenterology
Faculty of Medicine Ain Shams University*

*Faculty of Medicine
Ain Shams University*

2021

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

قالوا

لسبب انك لا تعلم لنا
إلا ما علمتنا إنك أنت
العليم الكبير

صدقة الله العظيم

سورة البقرة الآية: ٣٢

Acknowledgement

First, thanks to Allah, most merciful and compassionate. Without the help of Allah, nothing could be done.

*I would like to express my sincere gratitude and deep appreciation to **Prof. Moataz Mohamed Sayed** Professor of Internal medicine & Gastroenterology, Faculty of Medicine, Ain Shams University, for his continuous scientific guidance. Words cannot adequately express my great thanks and gratitude to him.*

*I am delighted to express my deep gratitude and sincere thanks to **Prof. Manal Sabry Mohamed** Assistant Professor of Internal medicine & Gastroenterology, Faculty of Medicine Ain Shams University, Faculty of Medicine, Ain Shams University, for her great help, endless support, and kind supervision throughout the period of work.*

*I am greatly indebted to, **Prof. Ahmed Mohamed ElGhandour** Assistant Professor of Internal medicine & Gastroenterology, Faculty of Medicine, Ain Shams University, for his continuous interest, helpful cooperation, and effective advice throughout the entire work. He guided me patiently, provided me generously with his valuable experience, which kept me on the right way.*

Ahmed Hafez Ezzat El-Sayed Ali.

List of Contents

Title	Page No.
List of Tables.....	I
List of Figures	III
List of Abbreviations.....	IV
Introduction	1
Aim of the Work	4
Review of Literature	5
Patients and Methods.....	60
Results.....	67
Discussion	86
Summary & Conclusion.....	94
References	98
الملخص العربي.....	1

List of Tables

Table No.	Title	Page No.
Table 1:	Components of the metabolic syndrome and their measurement threshold as defined by the American Heart Association	10
Table 2:	Histological and ultrasonographic grading of hepatic steatosis	22
Table 3:	weight loss percentages and impact on NAFLD	34
Table 4:	Comparison between the two studied groups according to demographic data and clinical data.....	67
Table 5:	Comparison between the two studied groups according to anthropometric criteria	69
Table 6:	Comparison between the two studied groups according to biochemical parameters	71
Table 7:	Comparison between the two studied groups according to CBC	73
Table 8:	Comparison between the two studied groups according to liver function....	75
Table 9:	Comparison between the two studied groups according to Ectodysplasin A	78
Table 10:	Agreement (sensitivity, specificity) Ectodysplasin A to detect its relation to the incidence and severity of non alcoholic Fatty Liver Disease patients group	79
Table 11:	Agreement (sensitivity, specificity) for GGT to predict NAFLD cases	81
Table 10:	Correlation between ascitic fluid Endocan and different parameters in the SBP group.....	66
Table 11:	Correlation between ascitic fluid Endocan and different parameters in Non-SBP group	72

List of Tables

Table 12: Correlation between and Ectodysplasin A and different parameters in group I (NAFLD)	82
Table 13: Correlation between Ectodysplasin A and FLI, APRI, Fib4 score in group I (NAFLD)	83
Table 14: Correlation between and Ectodysplasin A (%) and Glucose and cholesterol in group I (NAFLD).....	84
Table 15: Correlation between Ectodysplasin A and Liver Enzymes in group I (NAFLD).....	85

List of Figures

Figure No.	Title	Page No.
Figure 1:	Diagram of processes contributing to the pathogenesis of NAFLD and progression to cirrhosis.	11
Figure 2:	Diagram illustrating processes leading to triglyceride accumulation in hepatocytes leading to steatosis	12
Figure 3:	Overview of factors involved in the modulation of cellular epigenome ..	17
Figure 4:	Association of NAFLD with cardiovascular diseases, extrahepatic malignancy, surgical complications, and various other diseases.....	18
Figure 5:	Comparison between the two studied groups according to DM.....	68
Figure 6:	Comparison between the two studied groups according to WC.....	70
Figure 7:	Comparison between the two studied groups according to BMI.....	70
Figure 8:	Comparison between the two studied groups according to HbA1c.....	72
Figure 9:	Comparison between the two studied groups according to platelets	74
Figure 10:	Comparison between the two studied groups according to liver enzymes	76
Figure 11:	Comparison between the two studied groups according to albumin and ALP	77
Figure 12:	Comparison between the two studied groups according to Ectodysplasin A.....	78
Figure 13:	ROC curve for Ectodysplasin A to detect its relation to the incidence and severity of non alcoholic Fatty Liver Disease patients group.....	79
Figure 14:	ROC curve for GGT to predict NAFLD cases	81

List of Abbreviations

Abbreviation	Full name
NAFLD	nonalcoholic fatty liver disease
HS	hepatic steatosis
HCC	hepatocellular carcinoma
NASH	non-alcoholic steatohepatitis
MetSyn	metabolic syndrome
ROS	reactive oxygen species
MAFLD	metabolic associated fatty liver disease
NAFL	nonalcoholic fatty liver
DM2	type 2 diabetes
IR	insulin resistance
US-FLI	US-Fatty Liver Indicator
SCFAs	short-chain fatty acids
VLDL	very-low-density lipoprotein
SNPs	single-nucleotide polymorphisms
CDCA	chenodeoxycholic acid
CA	cholic acid
ASBT	apical sodium-dependent bile acid transporter
GWAS	genome-wide association studies
ALD	alcohol-related liver disease
FFA	free fatty acid
PNPLA3	patatin-like phospholipase domain-containing protein 3
TM6SF2	transmembrane 6 superfamily member 2
TNF-α	tumor necrosis factor α
IL-1β	interleukin-1β
CVD	cardiovascular diseases
ANA	anti-nuclear-antibodies

List of Abbreviations

SMA	smooth muscle antibodies
AMA	anti-mitochondrial antibodies
CHC	chronic hepatitis C
IGF	insulin growth factor
FLI	fatty liver index
FIB-4	fibrosis-4
NFS	NAFLD fibrosis score
ELF	enhanced liver fibrosis
VCTE	vibration-controlled transient elastography
PDFF	proton density fat fraction
TE	Transient Elastography
NPV	negative predictive value
PPV	positive predictive value
VCTE	Vibration-controlled transient elastography
MRE	Magnetic resonance elastography
MD	Mediterranean Diet
NICE	National Institute for Health and Care Excellence
HE	hepatic encephalopathy
LT	liver transplantation
WHO	World Health Organization
IL-4	interleukin-4
GCKR	glucokinase regulator
SECs	sinusoidal endothelial cells
HSCs	hepatic stellate cells
HSD17B13	hydroxysteroid 17β- dehydrogenase
WLM	western lifestyle model
TLR-4	tolllike receptor 4

Introduction

Nonalcoholic fatty liver disease (NAFLD) is chronic liver condition characterized by Insulin resistance, type 2 diabetes and fat accumulation in the liver that may cause hepatic inflammation and progressive scarring leading to nonalcoholic steatohepatitis (NASH) and irreversible liver damage (cirrhosis) (**Dharmalingam and Yamasandhi, 2018**) .

NASH is a common manifestation of liver cell injury of various etiologies and of metabolic disorders of fatty acid metabolism. It is a chronic liver condition and can progress to cirrhosis and end-stage liver disease. As the most aggressive form of NAFLD, NASH carries the highest risk for adverse outcomes (**Lindenmeyer and McCullough, 2018**).

Fatty liver not associated with alcohol consumption is now recognized as possibly the most common cause of chronic, asymptomatic liver enzyme elevation in the United States and Europe (**Paschos and Paletas, 2009**). NASH patients may be asymptomatic or present with mild abdominal pain (**Bedogni et al., 2005**).

The liver damage observed in NASH has been well described even though the pathogenesis of the disease remains uncertain. Macrovesicular and/or microvesicular steatosis, ballooning degeneration of hepatocytes, lobular inflammation and, occasionally, cirrhosis characterize the histology of this condition. Steatosis is observed in acinar zone 3, along with zone 3 Mallory bodies and/or acinar zone 3 sinusoidal fibrosis. Morphologically,

the mitochondria are swollen, and paracrystalline inclusion bodies can be visualized using electron microscopy (**Brown and Kleiner, 2016**).

The diagnosis of NASH requires additional morphological evidence of hepatic injury, ranging from inflammation and hepatocellular ballooning to Mallory's hyaline and fibrosis, the latter ranging from minimal to cirrhosis. The histological features of NAFLD/NASH are identical to those of alcoholic liver injury (**Dharmalingam and Yamasandhi, 2018**).

As a result, there has been increased recognition of the need to assess and closely monitor individuals for risk factors of components of NAFLD and NASH, as well as the severity of these conditions using biomarkers. Biomarkers can be used as unbiased differential indicators of illness onset, aid in the classification of a diseased or non-diseased state, provide the ability to stage disease progression and/or offer insight into its relative severity. An individual's risk of developing a disorder may also be obtained from biomarker research. As such, a prognostic indicator could be used for risk stratification of the general population. In addition to identifying illnesses, the efficacy of clinical or therapeutic interventions aimed toward these disorders may also be obtained (**Califf, 2018**).

There is no shortage of biomarkers and predictive models of NASH and advanced fibrosis; however, none of these noninvasive modalities can completely replace liver biopsy at this time (**Zhou et al., 2019**).

Ectodysplasin A (EDA) is a protein that in humans is encoded by the EDA gene. Ectodysplasin A is a transmembrane protein of the TNF family which plays an important role in the development of ectodermal

tissues such as skin in humans. It is recognized by the ectodysplasin A receptor (**Kere et al., 1996**).

Additionally, Ectodysplasin A (EDA) considered as a new hepatokine, may be involved in energy metabolism (**Neuman et al., 2014, Yang et al., 2019**). Literature showed increased levels of hepatic and secreted EDA in steatosis (**He et al., 2017**). Increased levels of hepatic and secreted EDA were detected in steatosis, *in vivo* and *in vitro*. Steatosis was ameliorated by EDA knockdown *in vitro*, while intrahepatic triglycerides content and liver enzymes were improved *in vivo*. Furthermore, knockdown of EDA upregulated lipolytic genes and suppressed lipogenic genes. Studies revealed associations between circulating EDA and higher odds of NAFLD, while circulating EDA presented a practicable performance to identify NAFLD (**Yang et al., 2019**). This study aims to evaluate serum EDA in nonalcoholic fatty liver disease (NAFLD) in human.