شبكة المعلومات الجامعية

التوثيق الإلكتروني والميكروفيلم

بسم الله الرحمن الرحيم

HANAA ALY

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جامعة عين شمس

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قسم

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

A Thesis

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By

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Ahmed Hafez Ezzat El-Sayed Ali.

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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**

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.