بسم الله الرحمن الرحيم

MONA MAGHRABY

شبكة المعلومات الجامعية

التوثيق الالكتروني والميكروفيلم

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شبكة المعلومات الجامعية

التوثيق الإلكتروني والميكروفيلم

جامعة عين شمس

التوثيق الإلكتروني والميكروفيلم

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Role of Activin A as a novel marker for diagnosis and evaluation of nonalchoholic fatty liver disease

Thesis
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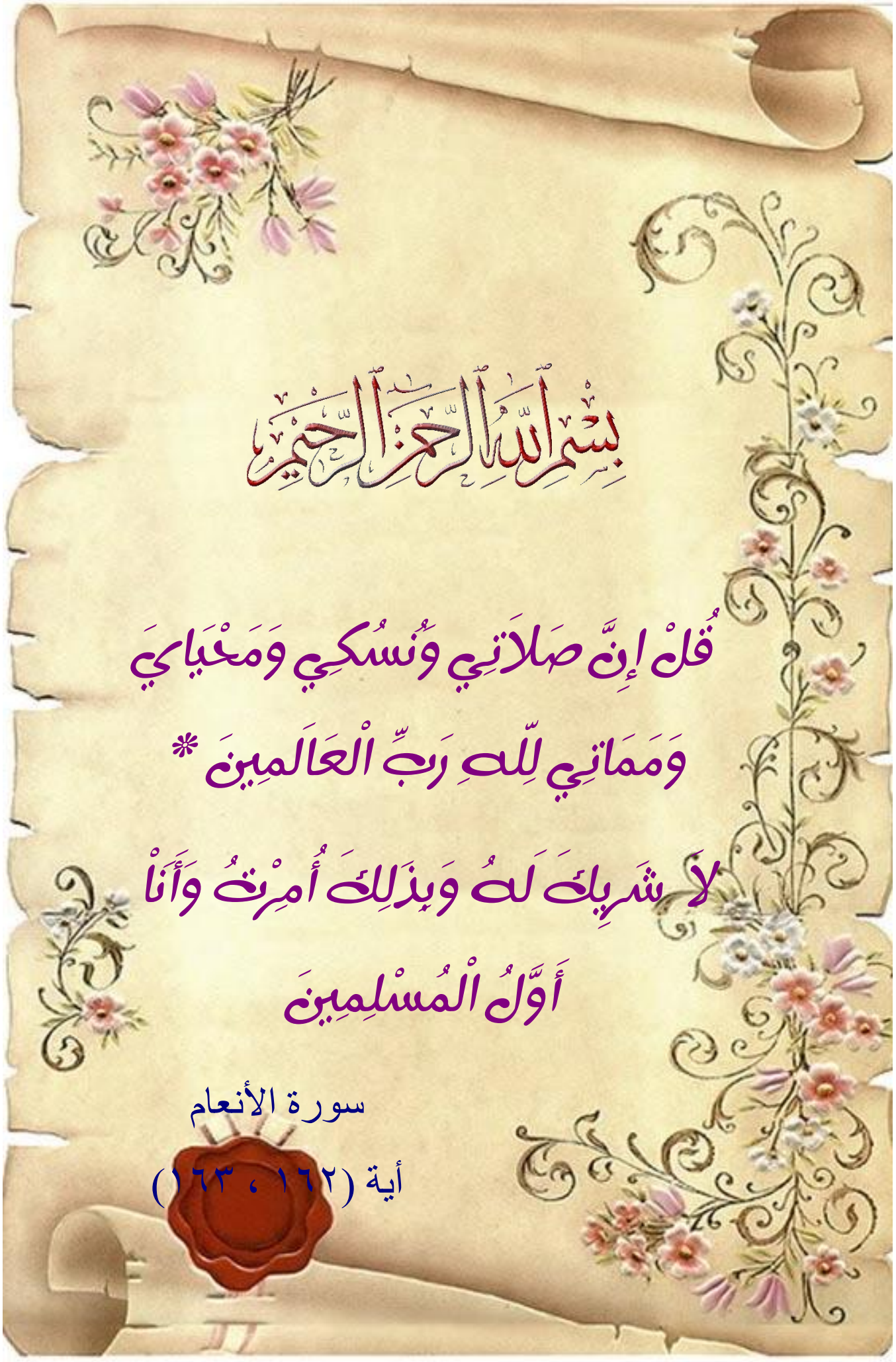
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List of abbreviations

ActR	activin type II receptors
ALD	alcoholic liver disease
ALK	activin receptor-like kinase
ALT	alanine transaminase
BMI	body mass index
CCR	chemokine receptor
COX-2	cyclooxygenase-2
CPT	carnitine palmitoyltransferase
ECM	Extracellular matrix
EPA	eicosapentaenoic acid
FAS	fatty acid synthase
FSTL3	follistatinlike 3
GD	gestational diabetes
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HFF	hepatic fat fraction
HIV	human immunodeficiency virus
HTAG	hepatic triacylglycerol
IL6	Interlukin 6
iNOS	inducible nitric oxide synthase
IR	insulin resistance
MMP	matrix metalloproteinases
MRI	Magnetic resonance image
MS	metabolic syndrome
NAFL	non-alcoholic fatty liver
NAFLD	Non-alcoholic fatty liver disease
NASH	nonalcoholicstea to hepatitis
OSA	Obstructive sleep apnea
PBMC	peripheral blood mononuclear cells
PCOS	Polycystic ovarian syndrome
rtPCR	Reverse transcription polymerase chain reaction
T_2DM	type 2 diabetes mellitus
TGF	transforming growth factor
TIMPs	tissue inhibitor of MMPs
TNF	Tumor necrosing factor
TZDs	Thiazolidinediones

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ABSTRACT

Background: Nonalcoholic fatty liver disease (NAFLD) is a disease gaining increasing interest worldwide. It ranges from simple nonalcoholic steatosis to nonalcoholic steatohepatitis (NASH), is characterized by steatosis, inflammation and fibrosis, and may lead to liver cirrhosis and hepatocellular carcinoma. Nonalcoholic fatty liver disease shares common pathogenetic mechanisms with other components of the insulin resistance or metabolic syndrome, with adipokines playing a crucial role.

Aim of the Work: Recent studies suggest that activin A, a member of the transforming growth factor (TGF) superfamily, is involved in the pathogenesis of liver disorders. We sought to explore its possible role in non-alcoholic fatty liver disease (NAFLD).

Patients and Methods: This study is a comparative case control study. This study was carried out at outpatient's clinics of internal medicine department of Ain Shams University. **Target population: Group 1:** Including 35 patients with NAS (steatosis) with exclusion criteria of intake of hepatotoxic drugs. **Group 2:** Including 35 patients with fatty liver and elevated liver enzymes (NASH). **Group 3:** Including 20 patients as a control group.

Results: There was high statistically significant difference between the studied groups as regard weight and BMI. In the Steatosis group the mean Liver size was 13.97 (±1.29 SD) with range (12-16) cm, all the patients (100%) had enlarged- echogenic liver. In the NASH group the mean Liver size was 13.71 (±1.36 SD) with range (12-16) cm, all the patients (100%) had enlarged-echogenic liver. In the control group the mean Liver size was 9.85 (±1.5 SD) with range (8-12) cm, all the patients (100%) had Normal liver. There was high statistically significant difference between the studied groups as regard liver size. There was high statistically significant difference between the studied groups as regard ALT, AST, total and direct bilirubin, plts count and activin A, significant difference between the studied groups as regard Albumin. There was high statistically significant difference between the studied groups as regard APRI score, FIB-4. There was high correlation between Activin A and BMI, APRI score, FIB-4 and liver size with high significance ($p<0.001$). Using Activin A. it was shown that above 858.5, it can discriminate between NAFLD and non-NAFLD with level of sensitivity 100% and specificity 100%.

Conclusion: Serum activin A showed a trend towards progressive increase from controls, to SS and NASH patients, but the significance was lost after adjustment for measures of adiposity. Activin A was not independently associated with NASH or any specific hepatic lesion within NAFLD patients. Prospective studies are needed to confirm the hypothesis raised herein, before mechanistic studies attempt to elucidate mechanism and prove causality.

Keywords: Activin A - Nonalchoholic Fatty Liver Disease

Introduction

Non-alcoholic fatty liver disease (NAFLD) is emerging as one of the mostcommon causes of abnormal liver function, and in the Western world the estimated prevalence is reported to be about 20% **(Bjornsson and Angulo, 2007).**

Histologically, NAFLD is a spectrum of disease ranging from simple steatosis (i.e., fat accumulation) of the liver to nonalcoholicstea to hepatitis (NASH) with inflammation and fibrosis and subsequently, extensive fibrosis and NASH-associated cirrhosis characterizing the most advanced forms of NASH, while NASH implies a risk of progressive liver disease **(Ekstedt et al., 2006),** simple steatosis might be regarded as a benign condition **(Dam-Larsen et al., 2004).**

NAFLD involves the accumulation of triglycerides in hepatocytes, necrosis, and apoptosis of these cells, accompanied by inflammatory and fibrogenic responses within the liver, potentially leading to the development of cirrhosis. The two-hit model summarizes the important early metabolic events leading to fat accumulation and subsequently hepatocellular necrosis and inflammation in NASH **(Day and James, 1998).**

Based on the two-hit model, it is of major importance to identify factors that could trigger hepatic fat accumulation as well as mediators that could promote the hepatic transition from simple steatosis to NASH. The metabolic syndrome with obesity, dyslipidemia, and insulin resistance (IR) is frequently associated with NAFLD **(Marchesini et al., 2003).**

Although these conditions, as well as inflammation and oxidative stress **(Seki et al., 2002),** may predispose to NAFLD development, the mechanisms that underlie hepatic fat accumulation and triggering of hepatocyte injury and hepatic fibrosis in NASH are still largely unknown. In particular, little is known about the mediators that could trigger the extensive hepatic fibrogenic response in certain individuals with NAFLD, leading to advanced NASH. Activin A is a member of the transforming growth factor (TGF)-bsuper family **(de Caestecker, 2004)** and was originally described as an inducer of follicle- stimulating hormone release **(Ling et al., 1986).**

More recently, activin A has been recognized as a multifunctional cytokine expressed in a wide range of cells and tissues with roles in regulation of wound repair, cell differentiation, apoptosis, and inflammation, and growing evidence implicates activin A in the pathogenesis of various inflammatory disorders such as rheumatoid arthritis, inflammatory bowel disease, and atherosclerosis**(Werner and Alzheimer, 2006).**

Studies also suggest that activin A could be involved in the pathogenesis of various liver disorders such as acute liver injury, chronic viral hepatitis, and certain hepatic malignancies **(Rodgarkia-Dara et al., 2006),** recently we demonstrated an involvement of activin A in NAFLD **(Yndestad et al., 2009).** In this chapter, after a general introduction to NAFLD and activin A biology, we elaborate a potential pathogenic role of activin A in the development and progression of NAFLD.

Aim of The Work

Recent studies suggest that activin A, a member of the transforming growth factor (TGF) superfamily, is involved in the pathogenesis of liver disorders. We sought to explore its possible role in non-alcoholic fatty liver disease (NAFLD).

Chapter (1)

Non-Alcoholic Fatty Liver Disease

I. INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is an umbrella term and encompasses the simple deposition of adipose tissue in the liver to more progressive steatosis with associated hepatitis, fibrosis, cirrhosis, and in some cases hepatocellular carcinoma (HCC). For the sake of terminology, NAFLD is comprised of non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH). NAFL is characterized by steatosis of the liver, involving greater than 5% of parenchyma, with no evidence of hepatocyte injury. Whereas, NASH is defined by histologic terms, that is a necroinflammatory process whereby the liver cells become injured in a background of steatosis. Although the natural history of NAFLD remains incompletely characterized, what is clear from the published data is a risk of progression to cirrhosis and HCC (**Lebeaupin et al., 2018).**

However, whether there is a clear progression of NAFL to NASH is under active investigation, but early evidence suggests this could be the case. In terms of epidemiology, several studies have tried to quantify the true worldwide incidence of NAFL/NASH; however, due to extreme variations in study parameters and available testing, a clear and reliable occurrence rate is not currently available. With that being said, estimates have been posited suggesting the incidence of NAFLD to be 20%-30% in Western countries and 5%-18% in Asia. It is no surprise that the prevalence of NAFLD is increasing worldwide with each passing year,