

# بسم الله الرحمن الرحيم





# شبكة المعلومات الجامعية التوثيق الالكتروني والميكرو فيلم





# 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





# بعض الوثائق الأصلية تالفة







بالرسالة صفحات  
لم ترد بالأصل





# **A STUDY OF FETUIN A IN FATTY LIVER (NAFLD) WITH AND WITHOUT CHRONIC KIDNEY DISEASE**

*Thesis*

*Submitted For Partial Fulfillment Of Master Degree In  
Internal Medicine*

Presented by

**Ahmed Ezzat Ibrahim Ahmed**  
(M.B., B.Ch)

Supervised by

**Prof. Dr. Mohamed Aly Marei Makhoul**

*Professor of Internal Medicine  
Faculty of Medicine, Ain Shams University*

**Dr. Ahmed Magdy Fateh Allah**

*Faculty of Medicine, Ain Shams University  
Lecturer of Internal Medicine*

**Dr. Ghada Abdelrahman Ahmed**

*Lecturer of Internal Medicine  
Faculty of Medicine, Ain Shams University*

**Faculty of Medicine  
Ain Shams University**

**2020**

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

قالوا

لسبحانك لا علم لنا  
إلا ما علمتنا إنك أنت  
العليم العظيم

صدق الله العظيم

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 Aly Marei Makhoulf**, Professor of Internal Medicine, 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 **Dr. Ahmed Magdy Fateh Allah**. Lecturer of Internal Medicine, Ain Shams University, for his kind supervision, indispensable advice and great help in this work.*

*I wish to express my great thanks and gratitude to **Dr. Ghada Abdelrahman Ahmed**, Lecturer of Internal Medicine, Ain Shams University, for her 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

<i>Subjects</i>	<i>Page</i>
• List of Abbreviations .....	I
• List of table .....	III
• List of Figures .....	IV
• Introduction .....	1
• Aim of the Work.....	3
• Review of literature: .....	
Chapter 1: Non-alcoholic fatty liver disease.....	4
Chapter 2: Fetuin-A.....	37
• Patients And Methods.....	60
• Results.....	69
• Discussion.....	81
• Summary .....	88
• Conclusion .....	92
• Recommendations .....	94
• References .....	95
• Arabic Summary .....	-

---

## LIST OF ABBREVIATIONS

<b>2 hr PP</b>	: Two Hour Post Prandial
<b>AASLD</b>	: American Association for The Study of Liver Disease
<b>AHSG</b>	: Alpha 2-Heremans Schmid Glycoprotein
<b>ALT</b>	: Alanin Aminotransferase
<b>AMPK</b>	: Activated Protein kinase
<b>AST</b>	: Aspartate Aminotransferase
<b>BCP</b>	: Binding Basic Calcium Phosphate
<b>BMI</b>	: Body Mass Index
<b>BP</b>	: Blood Pressure
<b>CaxP</b>	: Calcium-Phosphorus Product
<b>CCr</b>	: Creatinine Clearance
<b>CESD</b>	: Cholesterol Ester Storage Disease
<b>CKD</b>	: Chronic Kidney Disease
<b>CRF</b>	: Chronic Renal Failure
<b>CRP</b>	: C-Reactive Protein
<b>DNL</b>	: De Novo Lipogenesis
<b>EASL</b>	: European Association For The Study of Liver
<b>ELF</b>	: Enhanced Liver Fibrosis
<b>ESRD</b>	: End-Stage Renal Disease
<b>EVs</b>	: Extracellular Vesicles
<b>FBS</b>	: Fasting Blood Sugar
<b>FFA</b>	: Free Fatty Acid
<b>FFA</b>	: Free Fatty Acid
<b>FGF-21</b>	: Fetuin-A, Fibroblast Growth Factor-21
<b>FLI</b>	: Fatty Liver-Index
<b>GFR</b>	: Glomerular Filtration Rate
<b>GGT</b>	: Gamma-Glutamyl Transferase
<b>GLP-1</b>	: Glucagon-like peptide-1
<b>GLUT4-</b>	: Glucose Transporter-4
<b>GNG</b>	: Gluconeogenesis
<b>GSK-3</b>	: Glycogen Synthase Kinase-3
<b>HBV</b>	: Hepatitis B Virus
<b>HCC</b>	: Hepatocellular Carcinoma
<b>HCV</b>	: Hepatitis C Virus
<b>HD</b>	: Hemodialysis
<b>HDL</b>	: High-Density Lipoprotein
<b>HOMA-IR</b>	: Homeostasis Model
<b>HR</b>	: Heart Rate
<b>HRG</b>	: Histidine-Rich Glycoprotein

---

## *List of Abbreviations*

---

<b>IGFs</b>	: Insulin-Like Growth Factors
<b>IRS-1</b>	: Insulin Receptor Substrate Proteins
<b>KNG</b>	: Kininogen
<b>LAL</b>	: Lysosomal Acid Lipase
<b>LDL</b>	: Low-Density Lipoprotein
<b>MAPK</b>	: Mitogen-Activated Protein Kinase
<b>MetS</b>	: Metabolic Syndrome
<b>MRE</b>	: Magnetic Resonance Elastography
<b>NAFLD</b>	: Non- Alcoholic Fatty Liver Disease
<b>NASH</b>	: Nonalcoholic Steatohepatitis
<b>NICE</b>	: National Institute for Health and Care Excellence
<b>PI3-K</b>	: Phosphatyl Inositol 3-Kinase
<b>PKB</b>	: Protein Kinase B
<b>PNPLA3</b>	: Patatin-Like Phospholipase Domain-containing Protein 3
<b>RBS</b>	: Random Blood Sugar
<b>RR</b>	: Respiratory Rate
<b>SNPs</b>	: Single-Nucleotide Polymorphisms
<b>SNPs</b>	: Several Single Nucleotide Polimorphisms
<b>T2DM</b>	: Type 2 Diabetes Mellitus
<b>VCTE</b>	: Vibration Controlled Transient Elastography
<b>VLDL</b>	: Very Low-Density Lipoprotein
<b>WHO</b>	: World Health Organization
<b>WHO</b>	: World Health Organization



## LIST OF TABLE

<i>Tab. No.</i>	<i>Subject</i>	<i>Page</i>
<b>Table (1)</b>	Comparison between the four studied groups regarding patient characteristics	70
<b>Table (2)</b>	Comparison between the four studied groups regarding Serum Feutin-A	71
<b>Table (3)</b>	Correlation between serum Feutin-A & all studied variables in all studied participants “Cases & Controls”	73
<b>Table (4)</b>	Correlation between serum Feutin-A & all studied variables in Group I “Adult Normal Controls”	74
<b>Table (5)</b>	Correlation between serum Feutin-A & all studied variables in Group II “Adult Patients with NAFLD”	75
<b>Table (6)</b>	Correlation between serum Feutin-A & all studied variables in Group III “Adult Patients with CKD & NAFLD”	76
<b>Table (7)</b>	Correlation between serum Feutin-A & all studied variables in Group IV “Adult Patients with CKD”	77
<b>Table (8)</b>	Diagnostic Accuracy of Feutin-A regarding differentiation between cases and controls	79
<b>Table (9)</b>	Best cut off point of serum Feutin-A for differentiation between cases and controls	80

## LIST OF FIGURES

<i>Fig. No.</i>	<i>Subject</i>	<i>Page</i>
<b>Fig. (1)</b>	Image obtained from a human liver biopsy stained with hematoxylin and eosin.	8
<b>Fig. (2)</b>	The key metabolic players and the major pathogenic pathways involved in NAFLD.	14
<b>Fig. (3)</b>	Non-alcoholic fatty liver disease (NAFLD): a multisystem disease. Reported associations between NAFLD and various human diseases.	16
<b>Fig. (4)</b>	Schematic structure of type 3 cystatins.	40
<b>Fig. (5)</b>	Cartoon of human fetuin-A/ $\alpha$ 2-HS glycoprotein showing cystatin-like domains 1 and 2 and a third unrelated domain in green, yellow, and blue shading, respectively.	41
<b>Fig. (6)</b>	There is an inverse correlation between serum fetuin-A levels and adiponectin in patients with stable cardiovascular disease.	43
<b>Fig. (7)</b>	The action of insulin receptor.	46
<b>Fig. (8)</b>	Comparison of serum fetuin-A levels in chronic kidney disease cases in relation to creatinine clearance.	48
<b>Fig. (9)</b>	Comparison of serum CaxP levels in chronic kidney disease cases in relation to creatinine clearance.	48
<b>Fig. (10)</b>	Scatter diagram of serum fetuin-A versus high-sensitivity C-reactive protein in chronic kidney disease cases.	48
<b>Fig. (11)</b>	With caloric excess, there is fatty acid excess and insulin resistance fueling hepatic triacylglycerol synthesis and steatosis.	59
<b>Fig. (12)</b>	Comparison between the four studied groups regarding Serum Fetuin-A	72
<b>Fig. (13)</b>	Correlation between serum Fetuin-A & BMI among studied participants	78
<b>Fig. (14)</b>	ROC Curve Displaying Diagnostic Accuracy of Fetuin-A regarding differentiation between cases and controls	79

## Abstract

**Background:** Obesity and insulin resistance are known risk factors for both chronic kidney disease (CKD) and nonalcoholic fatty liver disease (NAFLD). Further studies identify mechanisms common to both diseases linked through an inter-organ communication orchestrated by fetuin-A and adiponectin. **Aim of the Work:** to determine the serum level of Fetuin A in cases of non- alcoholic fatty liver disease (NAFLD), as compared to normal controls. Also, as a main objective, is to determine the serum level of Fetuin A in cases of chronic kidney disease (CKD), as compared to normal controls, and try to correlate it to the severity of the disease. **Patients and Methods:** This cross sectional cohort study was conducted on 80 persons divided into 4 groups: Group I: Includes 20 Healthy adult normal controls, Group II: Includes 20 adult patients with NAFLD, Group III: Includes 20 adult patients with CKD & NAFLD and Group IV: Includes 20 adult patients with CKD. **Results:** We detected that there is statistically significant difference between the four studied groups regarding Weight, Height & BMI ( $P<0.05$ ). However there is a statistically insignificant difference between the four studied groups regarding Age & Gender ( $P>0.05$ ). That there is statistically significant difference between the four studied groups regarding Serum Fetuin-A ( $P<0.05$ ). There is statistically significant positive correlation between Serum Fetuin-A & (Weight, BMI, Systolic BP, Urea, Creatinine, Sodium, Calcium, Phosphorous, Cholesterol, Triglyceride, LDL, ALT, AST, FBS, 2hr PP & RBS); In addition to that there is a statistically significant negative correlation between Serum Fetuin-A & (Height, HDL & Albumin) ( $P<0.05$ ). There is statistically significant negative correlation between Serum Fetuin-A & (HDL) in Group I “Adult Normal Controls” ( $P<0.05$ ). The results revealed a statistically significant positive correlation between Serum Fetuin-A & (FBS); In addition to that there is a statistically significant negative correlation between Serum Fetuin-A & (Diastolic BP) ( $P<0.05$ ). We detected that there is statistically significant positive correlation between Serum Fetuin-A & (FBS), (2 hr PP)(RBS), Serum urea & Creatinine and potassium.; In addition to that there is a statistically significant negative correlation between Serum Fetuin-A & (Diastolic BP) and (Systolic BP) ( $P<0.05$ ). We detected that there is statistically significant positive correlation between Serum Fetuin-A & (LDL, Calcium, Triglyceride & Creatinine); In addition to that there is a statistically significant negative correlation between Serum Fetuin-A & (HR) ( $P<0.05$ ). **Conclusions:** Fetuin-A is a glycoprotein in the liver and a potent inhibitor of vascular calcification in the blood circulation in patients with chronic renal failure and end-stage kidney failure.

**Key words:** Fetuin A, Fatty Liver, NAFLD, chronic kidney disease



## INTRODUCTION

Fetuin-A, also called Alpha 2-Heremans Schmid Glycoprotein, is a multifunctional plasma agent that has been proven in animal and human studies. It plays a role as a physiological inhibitor of insulin receptor tyrosine kinase associated with insulin resistance and a negative acute phase reactant. It also regulates bone remodeling and calcium metabolism being an important inhibitor of calcium salt precipitation and vascular calcifications. (*Wojtysiak, et al., 2010*)

Due to secretion of Fetuin-A mainly by the liver, it may be a marker of liver function and predictor of mortality in patients with cirrhosis and other complications. (*Dabrowska, et al., 2015*)

The associations between high Fetuin-A and metabolic syndrome as well as its hepatic manifestation: nonalcoholic fatty liver disease (NAFLD) and atherogenic lipid profile have been well proven. Furthermore, obesity is a risk factor for chronic kidney disease (CKD) and nonalcoholic fatty liver disease (NAFLD). Further studies identify mechanisms common to both diseases linked through an inter organ communication orchestrated by Fetuin-A and Adiponectin. (*Makhlouf, et al., 2018*)

In the renal field, Fetuin-A has principally been studied as an inhibitor of ectopic calcium deposition, yet Fetuin-A is also an important promoter of insulin