



# **Evaluation of Fetuin-A Level and Valvular Calcification in Prevelant Hemodialysis Patients**

*Thesis Submitted for Partial Fulfillment of Master  
Degree in Internal Medicine*

***BY***

**Mohamed Hussien Ghaly**

*M.B.B.Ch*

*Under Supervision of*  
**Prof. Dr./ Essam Mohamed Khedr**

*Professor of Internal Medicine and Nephrology  
Faculty of Medicine - Ain Shams University*

**Dr. /Ahmed Shaban Serag El Deen**

*Lecturer of Internal Medicine and Nephrology  
Faculty of Medicine - Ain Shams University*

**Dr./ Mohamed Tarif Hamza**

*Lecturer of Clinical Pathology  
Faculty of Medicine - Ain Shams University*

**Faculty of Medicine**

**Ain Shams University**

**2015**



# Acknowledgment

- ✎ All praise are to **Allah** and all thanks. He has guided and enabled me by his mercy to fulfill this thesis, which I hope to be beneficial for people.
- ✎ I would like to express my deepest gratitude and sincere appreciation to **Prof. Dr. Essam Mohamed Khedr**, Professor of internal medicine and nephrology, Faculty of medicine, Ain Shams University for his encouragement, his kind support and appreciated suggestions that guided me to accomplish this work.
- ✎ I am also grateful to, **Dr. Ahmed Shaban Serag El Deen**, Lecturer of internal medicine and nephrology Faculty of medicine, Ain Shams University, who freely gave his time, effort and experience along with continuous guidance through out this work.
- ✎ A lot of thanks are extended to **Dr. Mohamed Tarif Hamza**, Lecturer of clinical pathology, Faculty of medicine, Ain Shams University for performing the laboratory measurements and fulfilling the biochemical part in this study.
- ✎ Special thanks and great appreciations to **Dr. Abdel Wahab Mohamed Sabry**, consultant of Cardiology in the National Institute of Urology and Nephrology, for his great effort in performing the echocardiography for all the enrolled patients in this study.
- ✎ Finally, I would like to express my profound gratitude to **Dr. Ashraf Donia**, Head of Nephrology Department in the National Institute of Urology and Nephrology, as well as my professors and colleges in the National Institute of Urology and Nephrology for their support, advice, encouragement and help in performing this study.

✎ **Mohamed Hussien Ghaly**



 **To**

**My Family** for their warm affection,  
patience, encouragement, and  
for always being there when I  
needed them

 **To**

My fiancée and the future wife  
**Marwa** for always supporting,  
helping and encouraging me in  
performing the study

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

قَالَ

سَبِّحْكَ لَا إِلَهَ إِلَّا مَا عَلَّمْتَنَا إِنَّكَ أَنْتَ  
الْعَلِيمُ الْعَظِيمُ

صدق الله العظيم

سورة البقرة الآية: ٣٢

## Contents

Subjects	Page
• List of Abbreviations.....	I
• List of tables.....	V
• List of figures.....	VIII
• Introduction .....	1
• Aim of the Work.....	6
• Review of literature	
- <b>Chapter (1):</b> Cardiovascular Risk Factors in ESRD...	7
- <b>Chapter (2):</b> Vascular Calcification and Uremia.....	39
- <b>Chapter (3):</b> Fetuin-A.....	78
• Subjects and Methods.....	105
• Results .....	111
• Discussion.....	137
• Conclusion .....	167
• Recommendations.....	169
• References .....	171
• Arabic summery	

## List of Abbreviations

<b>ACE</b>	: Angiotensin convertin enzyme
<b>ADMA</b>	: Asymmetric dymethyl arginine
<b>AGEs</b>	: Advanced glycation end products
<b>AHSG</b>	: $\alpha_2$ -Heremans and Schmid glycoprotein
<b>ALP</b>	: Alkaline phosphatase
<b>AoC</b>	: Thoracic aorta calcification
<b>APP</b>	: Acute Phase Protien
<b>AS</b>	: Aortic stenosis
<b>ATP III</b>	: Third Adult Treatment Panel
<b>BBB</b>	: Blood brain barrier
<b>BCP</b>	: Basic calcium phosphate
<b>BMI</b>	: Body mass index
<b>BMP</b>	: Bone morphogenetic protein
<b>BP</b>	: Blood pressure
<b>Ca</b>	: Calcium
<b>CAC</b>	: Coronary artery calcification
<b>CAD</b>	: Coronary arteryt disease
<b>CAII</b>	: Carbonic anhydrase II
<b>Cbfa 1</b>	: Core binding factor a-1
<b>CHD</b>	: Coronary heart disease
<b>CIMT</b>	: Carotid artery intima-media thickness
<b>CKD</b>	: Chronic kidney disease
<b>CKD–</b>	: Chronic kidney disease–mineral bone
<b>MBD</b>	disease
<b>CPPs</b>	: Calciprotein particles

## *List of Abbreviations*

---

<b>CRF</b>	: Chronic renal failure
<b>CRP</b>	: C-reactive protein
<b>CT</b>	: computed tomography
<b>CVD</b>	: Cardiovascular disease
<b>DAMPs</b>	: Damage-associated molecular patterns
<b>DM</b>	: Diabetes mellitus
<b>EN- RAGE</b>	: Extracellular newly identified RAGE- binding protein
<b>ESRD</b>	: End stage renal disease
<b>FGF-23</b>	: Fibroblast growth factor-23
<b>FMC</b>	: Fetuin mineral complexes
<b>FRS</b>	: Framingham Risk Score
<b>GFR</b>	: Glomerular filtration rate
<b>GLA</b>	: Glutamic acid
<b>GLUT-1</b>	: Glucose transporter gene-1
<b>HA</b>	: Hydroxyapatite
<b>HD</b>	: Hemodialysis
<b>HDL</b>	: High density lipoprotein
<b>HDL-C</b>	: High density lipoprotein - cholesterol
<b>HF:</b>	: Heart failure
<b>Hgb</b>	: Hemoglobin
<b>HMGB1</b>	: High-mobility group box protein 1
<b>HTN</b>	: Hypertension
<b>IDL</b>	: Intermediate-density lipoprotein
<b>IFN-<math>\gamma</math></b>	: Interferon gamma
<b>IL</b>	: Interleukin
<b>i-PTH</b>	: Intact parathormone

---

## *List of Abbreviations*

---

<b>kD</b>	: Kilo Dalton
<b>LDL</b>	: Low density lipoprotein
<b>LDL-C</b>	: Low density lipoprotein- cholesterol
<b>Lp(a)</b>	: Lipoprotein a
<b>LVH</b>	: Left ventricular hypertrophy
<b>MAC</b>	: Mitral annular calcification
<b>MCAo</b>	: Middle cerebral artery occlusion
<b>MGP</b>	: Matrix Gla protein
<b>MI</b>	: Myocardial infarction
<b>MIA</b>	: Malnutrition, inflammation, and atherosclerosis
<b>MMP-9</b>	: Metalloproteinase-9
<b>MMPs</b>	: Metalloproteinases
<b>NTPPPH</b>	: Nucleoside triphosphate pyrophosphohydrlase
<b>OPG</b>	: Osteoprotegerin
<b>OPN</b>	: Osteopontin
<b>PAMPs</b>	: Pathogen associated molecular patterns
<b>PDGF</b>	: Platelet-derived growth factor
<b>PEW</b>	: Protein energy wasting
<b>Pit-1</b>	: Sodium-dependent phosphate co-transporter
<b>PO4</b>	: Phosphorus
<b>PP</b>	: Pyrophosphate
<b>PTH</b>	: parathyroid hormone
<b>PTHrP</b>	: PTH-related peptide
<b>PTX3</b>	: Pentraxin 3
<b>PWV</b>	: Pulse wave velocity

---

IV

## *List of Tables*

<b>Table No</b>	<b>Title</b>	<b>Page</b>
<b>Table (1)</b>	Estimating risk for men & women by ATP III hard CHD risk score (2002).	16
<b>Table (2)</b>	CVD Points for women by Framingham General CVD risk score (2008).	18
<b>Table (3)</b>	CVD Risk for women by Framingham General CVD risk score (2008).	19
<b>Table (4)</b>	CVD Points for men by Framingham General CVD risk score (2008).	19
<b>Table (5)</b>	CVD Risk for men by Framingham General CVD risk score (2008).	20
<b>Table (6)</b>	Demographic and clinical characteristics of the patients.	111
<b>Table (7)</b>	Biochemical parameters of the patients.	113
<b>Table (8)</b>	Pearson correlation coefficient and it statistical significance between Fetuin A and selected quantitative variables.	115

---

## *List of Tables*

---

<b>Table No</b>	<b>Title</b>	<b>Page</b>
<b>Table (9)</b>	Demographic characteristics of hemodialysis patients cross to different levels of fetuin A.	119
<b>Table (10)</b>	Significance of biochemical measures in hemodialysis patients according cross different levels of fetuin A.	120
<b>Table (11)</b>	Demographic and clinical characteristics of the studied patients according to prescence or absence of valvular calcifications.	122
<b>Table (12)</b>	Biochemical measures of the studied patients according to prescence or absence of valvular calcifications.	123
<b>Table (13)</b>	Comparison between HD cases without evidence of calcified valves, those with calcified either aorta or mitral and those with both valves calcified according to demographic and clinical characteristics.	125
<b>Table (14)</b>	Comparison between HD cases without evidence of calcified valves, those with calcified either aorta or mitral and those with both valves calcified according to biochemical measures.	126

## *List of Tables*

<b>Table No</b>	<b>Title</b>	<b>Page</b>
<b>Table (15)</b>	Status of calcification cross tertiles of calcification.	128
<b>Table (16)</b>	A multiple logistic analysis with calcification of valves as a dependent variable and selected independent variables.	131
<b>Table (17)</b>	Correlation of FRS 1998 (chol) with the evaluated parameters.	132
<b>Table (18)</b>	Correlation of FRS 1998 (LDL) with the evaluated parameters.	133
<b>Table (19)</b>	Correlation of FRS ATP III with the evaluated parameters.	134
<b>Table (20)</b>	Correlation of FRS 2008 with the evaluated parameters.	135

*List of figures*

Figure Number	Title	Page
<b>Figure (1)</b>	Epidemiology of cardiovascular disease in haemodialysis patients.	7
<b>Figure (2)</b>	CHD score sheet for men in FRS 1998.	13
<b>Figure (3)</b>	CHD score sheet for women in FRS 1998.	14
<b>Figure (4)</b>	Risk factors for cardiovascular disease in patients with chronic kidney disease/end-stage renal disease.	29
<b>Figure (5)</b>	Diagrammatic representation of intimal and medial calcification.	43
<b>Figure (6)</b>	Medial compared with intimal calcification.	43
<b>Figure (7)</b>	Involvement of factors modulating vascular calcification in the process of atherosclerosis via inflammation.	51
<b>Figure (8)</b>	Pathogenic mechanisms of vascular calcification.	52
<b>Figure (9)</b>	Major mechanisms of vascular calcification.	52

---

## *List of Figures*

---

<b>Figure Number</b>	<b>Title</b>	<b>Page</b>
<b>Figure (10)</b>	Pathways potentially involved in aortic valve calcific degeneration associated with ESRD.	53
<b>Figure (11)</b>	Schematic of human smooth muscle cell mineralization regulated by inorganic phosphate ion mediated by sodium-dependent phosphate co-transporter (Pit-1).	55
<b>Figure (12)</b>	Pit-1 is found to be upregulated by certain inducers such as calcium, BMP-2 and PDGF.	56
<b>Figure (13)</b>	Effects of calcium and phosphate on VSMC mineralization.	57
<b>Figure (14)</b>	Proposed role of elevated phosphate (Pi) in osteochondrogenic phenotype change and matrix mineralization in vascular SMC.	57
<b>Figure (15)</b>	Echocardiogram of the heart in the parasternal long-axis view. This image shows a densely calcified aortic valve, with the crosses indicating the hinge points of the valve in the cardiac skeleton.	72

## *List of Figures*

<b>Figure Number</b>	<b>Title</b>	<b>Page</b>
<b>Figure (16)</b>	Protein structure and posttranslational modification of fetuin-A.	80
<b>Figure (17)</b>	Inhibitory effect of fetuin-A on insulin receptor (IR) by direct noncompetitive interaction with IR.	85
<b>Figure (18)</b>	Mechanism of inhibition of ectopic calcification by fetuin-A.	88
<b>Figure (19)</b>	Protective roles of fetuin-A in ischemic injury and sepsis.	101
<b>Figure (20)</b>	Comparison of serum fetuin-A levels ( $\mu\text{g/ml}$ ) in the group of hemodialysis patients and the group of healthy subjects.	114
<b>Figure (21)</b>	Correlation between fetuin-A and age in HD patients.	117
<b>Figure (22)</b>	Correlation of serum fetuin-A levels ( $\mu\text{g/ml}$ ) with serum albumin (g/dl) in the HD group.	117
<b>Figure (23)</b>	Relationship of serum fetuin-A levels ( $\mu\text{g/ml}$ ) with serum hsCRP mg/dl) in the HD group.	118