

RELATIONSHIP BETWEEN SERUM FETUIN –A LEVELS AND DEVELOPMENT OF DIABETIC FOOT

Thesis

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

Presented by

Mohamed Abdelmoneim Elmikawy

M.B.,B.CH.

Supervised by

Prof. Dr. Nermin Ahmed Sheriba

Professor of Endocrinology and Metabolism

Faculty of Medicine – Ain Shams University

Dr. Yara Mohamed Eid

Assistant Professor of Endocrinology and Metabolism

Faculty of Medicine – Ain Shams University

Dr. Ahmed Mohamed Bahaa Eldin

Lecturer of Endocrinology and Metabolism

Faculty of Medicine – Ain Shams University

Faculty of Medicine

Ain Shams University

2017

ACKNOWLEDGMENTS

In the beginning I have to thank Allah who gave me power and strength to carry out this work.

It is a great pleasure to express my sincere gratitude and highest appreciation to Prof. Dr. Nermin Sheriba, Professor of Endocrinology and metabolism, Faculty of Medicine Ain Shams University under whose guidance and constant supervision this work has been prepared. Actually, more and above words fail to cope with her overwhelming kindness and moral support that was a great help to me.

I would like to express my sincere gratitude to Dr. Yara Eid, Assistant Professor of Endocrinology and metabolism, Faculty of Medicine Ain Shams University for her generous help, valuable suggestions and keen supervision and great effort to achieve this work.

My deepest appreciations are to Dr. Ahmed Bahaa Eldin Lecturer of Endocrinology and metabolism, Faculty of Medicine, Ain Shams University, for her considerable help and continuous guidance.

List of Contents

	Page No.
LIST OF ABBREVIATIONS	I
LIST OF TABLES	IV
LIST OF FIGURES	VI
INTRODUCTION AND AIM OF WORK	1
REVIEW OF LITERATURE	4
CHAPTER 1: Diabetic Foot.....	4
1-Introduction	4
2- Complications of Diabetes	4
3-Definition of diabetic foot	5
4- Epidemiology of diabetic foot disease	6
5- Etiopathogenesis of diabetic foot lesions ...	6
6- Peripheral Vascular Disease in Diabetes ...	10
7-Evaluation of diabetic foot	11
8- Clinical assessment of Diabetic foot	14
9- Management of Diabetic foot	28
CHAPTER 2: Fetuin A.....	41
1- Introduction	41
2- Structure of fetuin-A	41
3- Regulators of hepatic Fetuin-A expression	42
4-Clinical context of fetuin-A	43
5- High level of fetuin A	51

6-Low levels of fetuin A	53
7-Biological Functions of Fetuin-A	55
CHAPTER 3: Macrovascular Complication Of Diabetes	58
1-Introduction	58
2- Pathophysiology and causative mechanisms	59
3- Peripheral arterial disease with diabetes.....	62
4- Diagnosis of PAD	64
5- Risk factor modification	66
6- Management	67
MATERIALS AND METHODS	68
RESULTS	77
DISCUSSION	91
SUMMARY And CONCLUSION	102
RECOMMENDATIONS	106
REFERENCES	107
ARABIC SUMMARY	

List of Abbreviations

Albumin:creatinine ratio	(ACR)
Angiotensin-converting-enzyme	(ACE)
Ankle Brachial Index	(ABI)
Basic calcium phosphate	(BCP)
Cerebrovascular accidents	(CVAs)
Charcot Neuropathy	(CN)
Complete blood count	(CBC)
Coronary kidney disease	(CKD)
Coronary vascular disease	(CVD)
C-reactive protein	(CRP)
End stage renal disease	(ESRD)
Erythrocyte sedimentation rate	(ESR)
Estimated glomerular filtration rate	(eGFR)
Glucose transporter-4	(GLUT4)
Glycogen synthase kinase	(GSK-3)
Glycohemoglobin	(HbA1c)
Hepatocellular carcinoma cell line genome	(HepG2)
High mobility group protein B1	(HMGB1)
Hyperbaric oxygen	(HBO)

Insulin receptor substrate	(IRS)
Insulin receptor substrate proteins	(IRS-1)
Lipopolysaccharide	(LPS)
Low-density lipoprotein	(LDL)
Lower extremity amputations	(LEA)
Matrix metalloproteinases	(MMP)
Methicillin-resistant staphylococcus aureus	(MRSA)
Mitogen-activated protein kinase	(MAPK)
Myocardial infarction	(MI)
National Institute for Health and Care Excellence	(NICE)
Negative pressure wound therapy	(NPWT)
Nicotinamide adenine dinucleotide phosphate	(NADP)
Nitric oxide	(NO)
Peripheral arterial disease	(PAD)
Peripheral vascular disease	(PVD)
Phosphatidyl inositol 3-kinase	(PI3-K)
Polymerase chain reaction	(PCR)
Protein kinase B	(PKB)
Protein kinase C	(PK-C)

Pulse-volume recording	(PVR)
Reactive oxygen species	(ROS)
Recombinant platelet derived growth factor	(PDGF)
Relative risk	(RR)
Removable Cast Walkers	(RCW)
Tissue growth factors	(TGFs)
Total Contact Cast	(TCC)
Ultrasonic duplex scanning	(UDS)
Vascular calification	(VCs)
Vascular smooth muscle cells	(VSMCs)
α2-Heremans-Schmid glycoprotein	(Ahsg)

List of Tables

Table No.	Page No.
Table (1): Factors increasing the Risk of Diabetic Foot Ulceration and infection.....	14
Table (2): Interpretation of the results of Ankle-Brachial Index measurement. (ABI)...	16
Table (3): Medical History.	17
Table (4): Lower extremity diabetic foot exam...	19
Table (5): NICE guidance currently recommends that people with diabetes should be informed that risk Calculators give an estimate only.....	61
Table (6): Risk Factors and Treatment Goals for Patients with Diabetes and PAD.....	66
Table (7): Demographic and clinical variables of the studied groups	77
Table (8): Duration and type of foot lesion.....	78
Table (9): Duration of DM and use of oral hypoglycemic agents and insulin in the diabetic groups.....	79
Table(10): Comparison of laboratory variables in the studied groups	80
Table(11): Comparison of Fetuin A level in the studied groups.....	81

Table(12): Multivariable binary logistic regression model for predictors of diabetic foot lesions occurrence	83
Table(13): Comparison of the area under the ROC curves for discrimination between diabetics with or without diabetic foot using Fetuin A or the multivariable binary logistic regression model.....	84
Table(14): Correlation between Fetuin A level and relevant quantitative variables.	85

List of Figures

Fig. No.		Page
Fig (1):	Complications of diabetic foot.	9
Fig (2):	Show clinical and diagnostic approach to diabetic foot disorders.....	22
Fig (3):	The risk factors for amputation are multifactorial and similar to those for ulceration.....	24
Fig (4):	Charchot foot.....	26
Fig (5):	The diabetic foot services	37
Fig (6):	Charcot's Arthropathy	38
Fig (7):	Gangrene	38
Fig (8):	Bunion with Nail Changes	38
Fig (9):	Planter Infected Ulcer	38
Fig (10):	Hammer Toes	38
Fig (11):	Tinea Interdigitalies	39
Fig (12):	Self-Inspection.....	39
Fig (13):	Take care of Dry skin.....	39
Fig (14):	To see feet in mirror for redness, Swelling, ulcer or crack foot.....	39
Fig (15):	Cut the nails straight	39
Fig (16):	Removable cast walker	40

Fig. No.	Page
Fig (17): Scotchcast boot.....	40
Fig (18): Structure of Fetuin A	42
Fig (19): Increased Fetuin A in obesity and fatty liver	44
Fig (20): Insulin receptor pathways	45
Fig (21): Relationship of different levels of fetuin A with atherosclerosis	46
Fig (22): Fetuin A deficiency in ESRD.....	48
Fig (23): Fetuin A increases Insulin resistance and atherosclerosis.	52
Fig (24): Role of Fetuin A in inhibition of vascular calcification	54
Fig (25): Typical protocol for the diagnosis of peripheral arterial disease in patients with diabetes.....	65
Fig (26): Serum Fetuin A level in the control, DM, or DM with diabetic foot group	82
Fig (27): Type of foot lesions in the DM with diabetic foot group.....	82
Fig (28): Scatter plot for the correlation between age and serum fetuin A level. Fitted line represents local regression smoothing (LOESS) trend line.	86

Fig. No.	Page
Fig (29): Scatter plot for the correlation between serum fetuin A level and SBP. Fitted line represents local regression smoothing (LOESS) trend line.	87
Fig (30): Scatter plot for the correlation between serum fetuin A level and DBP. Fitted line represents local regression smoothing (LOESS) trend line.	87
Fig (31): Scatter plot for the correlation between serum fetuin A level and MAP. Fitted line represents local regression smoothing (LOESS) trend line.	88
Fig (32): Scatter plot for the correlation between HbA1c level and serum fetuin A level. Fitted line represents local regression smoothing (LOESS) trend line.	88
Fig (33): Scatter plot for the correlation between serum fetuin A and TAG levels. Fitted line represents local regression smoothing (LOESS) trend line.	89
Fig (34): Scatter plot for the correlation between serum fetuin A and HDL levels. Fitted line represents local regression smoothing (LOESS) trend line.	89
Fig (35): Scatter plot for the correlation between the duration of DM and serum fetuin A level. Fitted line represents local regression smoothing (LOESS) trend line.	90

INTRODUCTION

Serum fetuin-A is a multifunctional glycoprotein, which is exclusively secreted from hepatocytes in humans (**Denecke et al., 2003**).

An association between insulin resistance and type 2 diabetes in individuals with high serum fetuin-A levels was reported (**Stefan et al., 2008**).

Fetuin-A is an independent risk factor for developing diabetes (**Eraso et al., 2010**). Additionally, recent studies have emphasized that there may be an association between fetuin-A levels and peripheral arterial disease (PAD) (**Lorant et al., 2011**).

Diabetes mellitus (DM) is a common metabolic disorder .The most common form of diabetes is type 2 diabetes. These metabolic abnormalities lead to long-term damage of various organs, causing their dysfunction and failure. Diabetes-related micro-vascular complications are responsible for the majority of new cases of blindness, kidney failure (**American Diabetes Association, 2013**).

Diabetic foot is one of the major complications of diabetes and is the main reason for nontraumatic major

amputations (**ADA, 2013**). The common clinical features of diabetic foot include ulcers, foot deformity, infection, neuropathy, PAD, osteomyelitis, and gangrene (**Wagner, 1981**).

The risk of lower-extremity amputation is higher in patients with diabetes and PAD than in those without diabetes (**Jude et al., 2001**).

The role of fetuin-A and its involvement in patients with type 2 diabetes and PAD, who commonly suffer from advanced/systemic atherosclerosis, seems to be very complex and has not been fully understood as yet (**Kallio et al., 2003**).

Aim of the study

The aim of this study is to investigate the possible relationship between serum fetuin-A levels and the development of diabetic foot.