

**Study the Prevalence of Diabetic Kidney
Disease as a Cause for Starting Dialysis in
Ain Shams University Hospital**

Thesis

Submitted for partial fulfillment of master degree in

Internal Medicine

By:

Dalia Mahmoud Alwakel

M.B.Ch.

Faculty of medicine Ain Shams University

Under supervision of

Prof. Dr. Iman Ibraheim Sarhan

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

Prof. Dr. Osama Mahmoud

*Professor of internal Medicine and Nephrology
Faculty of medicine Ain Shams University*

Dr. Ahmed Yousef Emam

*Lecturer of internal Medicine and Nephrology
Faculty of medicine Ain Shams University*

**Faculty of Medicine
Ain Shams University
2015**



بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

وقل زدني علماً

صدق الله العظيم

سورة طه آية (114)





Acknowledgement

First of all, all gratitude is due to **God** almighty for blessing this work, until it has reached its end, as a part of his generous help, throughout my life.

Really I can hardly find the words to express my gratitude to **Prof. Dr. Iman Ibraheim Sarhan**, Professor of Internal Medicine and Nephrology, faculty of medicine, Ain Shams University, for his supervision, continuous help, encouragement throughout this work and tremendous effort he has done in the meticulous revision of the whole work. It is a great honor to work under his guidance and supervision.

I would like also to express my sincere appreciation and gratitude to **Prof. Dr. Osama Mahmoud**, Professor of internal Medicine and Nephrology, faculty of medicine, Ain Shams University, for his continuous directions and support throughout the whole work.

Really I can hardly find the words to express my gratitude to **Dr. Tamer El-Saed**, Lecturer of internal Medicine and Nephrology, Faculty of Medicine, Ain Shams University for his continuous directions and meticulous revision throughout the whole work, I really appreciate their patience and support.

I owe much to **Dr. Ahmed Yousef Emam**, Lecturer of internal Medicine and Nephrology, Faculty of medicine Ain Shams University for his continuous guidance, encouragement during the progress of this work and direct supervision.

Last but not least, I dedicate this work to my family, whom without their sincere emotional support, pushing me forward this work would not have ever been completed.



Dalia Mahmoud Alwakel

Contents

List of Abbreviations	i
List of Tables	iv
List of Figures	v
Introduction and Aim of the Work.....	1
Review of Literature	4
* Risk Factors of End-Stage Renal Disease	4
* Diabetic Nephropathy	20
Patient and Methods	79
Results	81
Discussion	91
Summary and Conclusion	98
Recommendation	100
References	101
Arabic Summary	--

List of Abbreviations

ACE	: Angiotensin-converting enzyme inhibitors .
ACR	: Urinary albumin/creatinine ratio
ADVANCE	: The Action in Diabetes and Vascular Disease: PreterAx and DiamicroN MR Controlled Evaluation .
AGEs	: Advanced glycation end products.
ARBs	: Angiotensin II receptor blockers.
ANA	: antinuclear antibody.
CD 36	: Cluster of differentiation 36.
CDC	: Centers for disease control and prevention.
CKD	: Chronic kidney disease.
CTGF	: Connective tissue growth factor.
DCCT	: Diabetes Control Complications Trial.
DKD	: Diabetic kidney diseases.
DM	: Diabetes mellitus.
DN	: Diabetic nephropathy.
DNA	: Deoxyribonucleic acid.
DPP4	: Dipeptidyl peptidase 4.
ECM	: Extracellular matrix.
eGFR	: Estimated glomerular filtration rate.
ESRD	: End stage renal disease.
FIELD	: Fenofibrate Intervention and Event Lowering in Diabetes.
FSGS	: Focal segmental glomerulosclerosis
GCC	: Gulf cooperation council.

List of Abbreviations (Cont.)

GBM	: Glomerular basement membrane
GLP1R	: Glucagon like peptide 1 receptor.
HIV	: Human Immunodeficiency Virus.
HOPE	: Heart Outcomes Prevention Evaluation.
ICAM-1	: Intracellular adhesion molecule-1.
IDNT	: Irbesartan in Diabetic Nephropathy Trial .
Ig AN	: Immunoglobulin A nephropathy .
Ig G	: Immunoglobulin G.
Ig M	: Immunoglobulin M.
IL	: Interleukin.
JAK	: Janus kinases.
KSA	: kingdom of Saudi Arabia.
KDOQI	: Kidney disease outcomes quality initiative
L-FABP	: Urinary L-type fatty acid binding protein.
L-PGDS	: Lipocalin-Type Prostaglandin D2 Synthase.
MCP-1	: monocyte Chemoattractant protein-1
MDRD	: Modification of Diet in Renal Disease.
mRNA	: Messenger ribonucleic acid.
MGN	: Membranous glomerulonephritis
MPGN	: Membranoproliferative glomerulonephritis
MMP-2	: Matrix metalloproteinase-2.
NADPH	: Nicotinamide adenine dinucleotide phosphate-oxidase.
NICE	: National Institute for health and clinical Excel.
NSAID	: Non steroidal anti inflammatory drug.
NF-kB	: Nuclear factor-kB.
PA	: Plasminogen activator.
PAI-1	: Plasminogen activator inhibitor-1 .
PFD	: Pirfenidone .
PKC	: Protein kinase C.
PKC-a	: Protein kinase C-a.
PKC-b1	: Protein kinase C-b1 .

List of Abbreviations (Cont.)

PKC-b2	: Protein kinase C-b2.
PYD	: Pyridoxamine
RAAS	: Renin-angiotensin-aldosterone system.
RAGEs	: Receptors for advanced glycation products .
RBX	: Ruboxistaurin.
RCT	: Randomized controlled trials.
RF	: rheumatoid factor.
ROS	: reactive oxygen species.
SCr-II	: Scavenger receptor II .
SLE	: Systemic lupus erythematosus
SSA	: Sub-Saharan Africa.
STAT	: Signal transducer and activator of transcription .
T2DM	: Type 2 diabetes mellitus.
TGF-b	: Transforming growth factor-b .
TNF-a	: Tumor necrosis factor-a .
TNFR1	: Tumor necrosis factor receptor 1.
TNFR2	: Tumor necrosis factor receptor 2.
UAE	: Urinary albumin excretion.
UACR	: Urinary albumin/creatinine ratio
UKPDS	: United Kingdom Prospective Diabetes Study.
Urinary CTGF	: Urinary connective tissue growth factor.
UK	: United Kingdom.
USA	: United States of America.
UTI	: Urinary tract infection.
USRDS	: United States Renal Data System.

List of tables

<i>Table</i>	<i>Title</i>	<i>Page</i>
1	Treatment of hypertension in CKD according to the nature of kidney disease	11
2	Glomerular classification of DN	34
3	A new classification of Diabetic Nephropathy2014: a report from Joint Committee on Diabetic Nephropathy	45
4	The kidney Disease management according to CKD stages	48
5	Kidney disease improving global outcomes ACR categories	49
6	Screening recommendations for microvascular complications of diabetes mellitus	51
7	Biomarker of glomerular injury implicated in diabetic kidney disease	61
8	Urinary biomarkers for early detection of DKD	64
9	Common oral anti- diabetes agents used in type 2 diabetes in the UK and doses adjustments in CKD	66
10	Novel therapy of DN	78
11	Descriptive data	81
12	Etiology of ESRD in Ain Shams university hospital 2004-2013	83
13	Total prevalence of DN as a cause of ESRD in Ain Shams university hospitals 2004-2013	84
14	DN prevalence per year	85
15	Ultrasound of ESRD in Ain Shams university hospital (2004-2013)	88
16	Biopsy of ESRD patients in Ain Shams university hospital (2004-2013)	89
17	Immunology of ESRD patients in Ain Shams university hospital (2004-2013)	90

List of Figures

<i>Fig.</i>	<i>Title</i>	<i>Page</i>
1	Recognized molecular mechanisms involved in pathogenesis of diabetic kidney disease	27
2	Schematic illustrations of some of the recognized pathways implicated in the pathogenesis of diabetic kidney disease	30
3	Flow chart for classifying DN	34
4	Pathology of DN	41
5	Algorithm for screening and initiation of treatment in diabetic nephropathy	52
6	Mechanism of tubulointerstitial damage in diabetes without urinary albumin	63
7	Effects of incretin based therapies on renal risk factors in T2DM	68
8	Prevalence of DM as a causes of ESRD in Ain Shams university hospitals 2004-2013	83
9	Change in prevalence of diabetes as etiology of ESRD over 10 years period (2004-2013)	86
10	Prevalence of diabetes as etiology of end stage renal diseasesae (ESRD) (2004-2013)	87

Introduction

End stage renal diseases (ESRD) is increasing worldwide. This condition is particularly serious in developing countries where health resources are inadequate (*Stengel, 2003*).

The prevalence of dialysis therapy for kidney failure is increasing much faster than population growth in most parts of the world, there has been a 165% increase in dialysis treatments for ESRD over the past two decades (*Hampton, 2014*). Worldwide, the number of patients receiving renal replacement therapy (RRT) is estimated at more than (1.4) million, with an annual incident rate growing to 8% (*Chieppati and Remuzzi, 2005*). The global prevalence of ESRD treated with dialysis for countries with universal dialysis access increased by 134% after adjusting for population growth and aging (*Hampton, 2014*).

The findings indicate that the significant growth in dialysis therapy is strikingly out of proportion to population growth for a majority of regions in the world (*Hampton, 2014*).

Various chronic diseases have detrimental effects on the kidneys. Rapidly rising global rates of chronic diseases portend a consequent rise in kidney failure or end stage renal disease (ESRD) (*Tomson and Bailey, 2011*).

Diabetes and hypertension remain the most commonly reported cause of ESRD (*Foley and Collins, 2007*). Glomerulonephritis is the third leading cause of ESRD, Overuse of over-the-counter pain medication or abuse of illegal drugs increases the risk of ESRD. Other diseases can lead to ESRD as kidney stones, polycystic kidney disease,

systemic lupus erythematosus, congenital nephrotic syndrome and atherosclerosis (**Feest, 2007**).

Diabetes is the largest single cause of ESRD in the United Kingdom; accounting for 30- 40% of all cases (**Sandra, 2005**).

Study conducted in Egypt showed that hypertension was responsible for (28%) of the cases of renal failure in Egypt. Other significant causes were: chronic Glomerulonephritis (16.6%), ESRD of unknown etiology (16.2%), obstructive uropathy (9.3%) and diabetic nephropathy (8.9%) (**Afifi and Kareem, 1999**).

Another cross sectional study in Egypt showed that the prevalence of diabetic nephropathy increased gradually from (8.9%) in 1996, to (14.5%) in 2001. average age of patients with diabetic nephropathy was significantly higher than other causes of patients with ESRD. Mortality was also significantly higher in diabetic patients with ESRD (**Afifi et al., 2004**).

Aim of the work

To identify the prevalence of diabetic kidney disease as a cause of starting dialysis in Ain Shams university hospital and to compare change of prevalence over past 10 years from (2004 to 2013).

Risk Factors of End-Stage Renal Disease

Chronic Kidney Disease (CKD):

The Glomerular filtration rate (GFR)

The Glomerular filtration rate (GFR) is considered the best measure to assess the kidney function. Normal GFR varies according to patient's age, sex, and body size. In young adults, the normal GFR is approximately 120ml per minute per 1.73 m² to 130 ml per minute per 1.73 m² and declines slightly with age (*Parera et al., 2005*).

ESRD has many causes that varies from one patient to another. The key risk factors for chronic kidney disease are the increasing age of the population, diabetes mellitus and hypertension. The most common causes include the following (*Myrray et al., 2007*).

- Diabetes mellitus.
- Uncontrolled hypertension can damage the kidneys over time.
- Glomerulonephritis
- Polycystic kidney disease is an example of a hereditary cause of chronic kidney disease.
- Medications such as the use of some analgesics regularly over long durations of time can cause analgesic nephropathy and kidney damage.
- Atherosclerosis leading to ischemic nephropathy, can cause kidney damage.
- Obstruction of the urinary tract by stones or cancer or enlargement of the prostate may cause kidney damage.

- Obese American people have up to a seven times greater risk of kidney failure than non obese people, suggesting that obesity should be considered a risk factor for ESRD (**Hyman, 2006**).

Risk Factors of ESRD:

Diabetes Mellitus:

A study was conducted in UK showed that ESRD is common. The main risk factor for impaired kidney function is diabetes mellitus. About (30%) of patients with diabetes develop some degree of diabetic nephropathy. In addition, a follow-up study conducted in South Africa showed that diabetes mellitus is a major risk factor of ESRD (**Keeton et al., 2004**).

A study demonstrated that the high prevalence (13%) of ESRD among adult American population is due to the rise in the number of people with diabetes and hypertension (**Moeller et al., 2002**). A Case control study conducted in USA confirmed that kidney stones increased the risk of chronic kidney disease especially interstitial nephritis, diabetic nephropathy, and hypertension. Chronic kidney disease is frequently seen among patients with kidney stones, an estimated percent of (10% - 15%) of patients eventually develop chronic kidney failure (**Vupputuri et al., 2004**). Both hypertension and diabetes mellitus were main risk factors for increasing incidence of ESRD in black men in USA. Studies showed that (30- 40%) of all patients with diabetes develop nephropathy, ESRD, and necessitating dialysis or kidney transplantation (**Chi-yuan et al., 2009**).

A study conducted in Egypt showed that hypertension was responsible for (28%) of the cases of renal failure in

Egypt. Other significant causes were: chronic Glomerulonephritis (16.6%), ESRD of unknown etiology (16.2%), obstructive uropathy (9.3%), and diabetic nephropathy (8.9%) (**Afifi et al., 1999**). Another cross sectional study conducted in Egypt in order to determine the prevalence of diabetic nephropathy as a cause of ESRD showed that the prevalence of diabetic nephropathy increased gradually from (8.9%) in 1996 to (14.5%) in 2001. average age of patients with diabetic nephropathy was significantly higher than other causes of patients with ESRD. Mortality was also significantly higher in diabetic patients with ESRD (**Afifi et al., 2004**).

In Saudi Arabia, (KSA) diabetes mellitus is becoming a major medical problem. This has been more evident over the last decade or so as a result of dramatic changes in life-style of the Saudi population. A study done at the King Fahd Hospital of the University, Al-Khobar, diabetic nephropathy accounted for 27.9% of cases of ESRD (**Al-Jiffri et al., 2003**). Also Cross sectional study conducted in Saudi Arabia to determine epidemiology and causes of ESRD showed that dialysis patients increase in the (KSA). Patients' average age was (55) years. Main causes of (ESRD) include diabetic nephropathy(28%), hypertension(24%), unknown (23%) and obstructive uropathy (8%) (**Shaheen and Al-Khader, 2005**).

In Jordan, a study about epidemiology of dialysis patient showed that prevalence of hemodialysis was (312) person per million population. ESRD incidence in 2002 was (111) person per million population. Diabetes mellitus was leading cause of hemodialysis (33.4 %) (**Batieha et al., 2007**). Another study conducted in Jordan confirmed that diabetes mellitus was the major leading cause of ESRD (29.2% of cases), followed by hypertension (18.4%) and glomerulonephritis (12.3%), obstructive uropathy (4.1%)