INFULENCE OF GLYCEMIC CONTROL ON CARDIOVASCULAR EVENTS IN DIABETIC PATIENTS UNDER MAINTENANCE HEMODIALYSIS

MD Thesis Protocol

Submitted for the partial Fulfillment of the requirements of MD degree in nephrology

By

Abdelmoneem Ateya Hamada

MSc in Nephrology

SUPERVISORS

PROF.DR.ESSAM MOHAMED KHEDR

Professor of nephrology and internal medicine

Faculty of Medicine – Ain Shams University

PROF.DR.MAGDY M.SAED.ELSHARKAWY

Professor of nephrology and internal medicine

Faculty of Medicine – Ain Shams University

DR.SAHAR MOHAMED SHAWKY

Lecturer of nephrology and internal medicine

Faculty of Medicine – Ain Shams University

DR.WALID AHMED BICHARI

Lecturer of nephrology and internal medicine

Faculty of Medicine – Ain Shams University

AIN SHAMS UNIVERSITY

2015

ACKNOWLEDGEMENT

First and foremost thanks are due to **ALLAH** the beneficent and merciful of all.

I would like to express my deep gratitude and appreciation to ***PROF. PROF.DR. Essam Mohamed Khedr, Professor of nephrology and internal medicine, Faculty of Medicine, Ain Shams University***, for his continuous help and unlimited support.

I am greatly indebted and grateful to ***PROF. DR. Magdy M.Saed Elsharkawy, Professor of nephrology and internal medicine, Faculty of Medicine, Ain Shams University*** , for his continuous encouragement to bring this work to the attempted goal.

I'm also thankful to ***Dr. Sahar Mohamed Shawky, Lecturer of nephrology and internal medicine, Faculty of Medicine, Ain Shams University*** , for his help and advice.

Special appreciation is dedicated to ***Dr. Walid Ahmed Bichari, Lecturer of nephrology and internal medicine, Faculty of Medicine, Ain Shams University,*** for his valuable efforts.

Abdelmoneem Ateya Hamada

CONTENTS

LIST OF ABBREVIATIONS

ACCORD	Action to Control Cardiovascular Risk in Diabetes
ACEi	Angiotensin-Converting Enzyme inhibitors
ADMA	Asymmetric DiMethylArgenine
ADVANCE	Action in Diabetes and Vascular disease PreterAx and DiamicroN-MR Controlled Evaluation
AGE	Advanced glycation end products
AGE	Advanced glycation end products
ARB	Angiotensin receptor blockers
ASVD	Atherosclerotic Vascular Disease
AURORA	A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis Assey
BFD	BioFeedback Dialysis
BMI	Body Mass Index
BP	Blood pressure
C a x P	Calcium Phosphorus product
CABG	Coronary Artery By pass Graft
CAC	Coronary Artery Calcification
CAD	Coronary Artery Disease
CHARISMA	Clopidogril for High Atheroembolic Risk and Ischemic Stabilization Mangement and Avoidance
CHF	Congestive Heart Failure
CKD	Chronic kidney Disease
CKD - D	Chronic kidney Disease - Diabetes
CKD - ND	Chronic kidney Disease - Non Diabetes

CRF	Chronic Renal Failure
CRP	C-reactive protein
cTnl	cardiac Troponin I
cTnT	cardiac Troponin T
CV	CardioVascular
CVD	CardioVascular Disease
4 - D	Description and results of Deutsche Diabetes Dialysis Studies
DCCT	Diabetes Control and Complications Trial
DCOR	Dialysis Clinical Outcomes Revisited
DM	Diabetes Mellitus
DOPPS	Dialysis Outcomes and Practice Patterns Study
e-GFR	estimated Glomerular Filtration Rate
EBCT	Electron-beam CT scan
EDIC	Epidemiology of Diabetes Interventions and Complications
EPO	Prythropoetin
ESRD	End-Stage Renal Disease
FGF-23	Fibroblast growth factor 23
GFR	Glomerular Filtration Rate
Hb	Hemoglobin
HbAlC	Hemoglobin A1C
HD	Hemodialysis
HDL	High-Density Lipoprotein
HR	Hazard Ratio
iPTH	intact ParaThyroid Hormone
IDH	IntraDialytic liypotension
KDOQI	Kidney Disease Outcomes Quality Initiative
LDL	Low Density Lipoprotein

LV	Left ventricular
LVEF	Left Ventricular Ejection Fraction
LVH	Left ventricular hypertrophy
MBF	Myocardial blood flow
MI	Myocardial Infarction
MICS	Malnutrition-Inflammation- Cachexia Syndrome
NHANES	National Health And Nutrition Examination Survey
NODAD	New-onset diabetes after initiation of hemodialysis
OR	Odd Ratio
PD	Peritoneal dialysis
PROACTIVE	PROspective PioglitAzone Clinical Trial In macro Vascular Events
PTCA	Percutaneous Transluminal Coronary Angioplasty
PTH	Parathyroid hormone
RAAS	Renin-Angiotensin-Aldosterone System
RBCs	Red Blood Cells
RR	Relative Risk
RWMA	Regional Wall Motion Abnormalities
SBP	Systolic Blood Pressure
SF	Serum Fructosamine
ST	ST segment of ECG
su	Sulfonylurea
TID	Thrice Intermittent Dialysis
TNT	Treating to New Targets
TZD	Thiazolidinedione
UF	Ultra Filtrate
UKPDS	United Kingdom Prospective Diabetes Study
URR	Urea Reduction Ratio
USRDS	US Renal Data System

VADT	Veterans Affairs Diabetes Trial
VALIANT	VALsartan In Acute myocardial iNfarcTion
VC	Vascular Calcification
WBCs	White Blood Cells

List Of Tables

List Of Figures

INTRODUCTION

The link between diabetes mellitus (DM), end-stage renal disease (ESRD) and hemodialysis (HD) has many faces. DM is the most common cause of ESRD worldwide, accounting for 44.2% of ESRD patients in the US Renal Data System (USRDS) in 2005 ***(National Institute of Diabetes and Digestive and Kidney Diseases, 2005).*** On the other hand, there is a high incidence of new-onset diabetes after initiation of hemodialysis (NODAD) as shown in USRDS which is associated with significantly higher mortality compared to those who did not develop NODAD ***(Salifu et al., 2010)*** .

However, data are scarce on how diabetes should best be treated in patients in ESRD. It is known that blood glucose levels need to be well controlled in these patients; but in ESRD, both uremia and dialysis can complicate glycemic control by affecting the secretion, clearance, and peripheral tissue sensitivity of insulin. Several factors, including uremic toxins, may increase insulin resistance in ESRD, leading to a blunted ability to suppress hepatic gluconeogenesis and regulate peripheral glucose

utilization. In type 2 diabetes without kidney disease, insulin resistance leads to increased insulin secretion. This does not occur in ESRD because of concomitant metabolic acidosis, deficiency of 1,25 dihydroxy vitamin D, and secondary hyperparathyroidism ***(Shrishrimal et al., 2009).*** In addition, the dextrose concentration in the dialysate can affect glucose control. In general, dialysates with lower dextrose concentrations are used and may be associated with hypoglycemia ***(Kovesdy et al., 2008).***

In monitoring glycemic control, the importance of hemoglobin A1C (HbA1C) has also been well established ***(Chiasson et al., 2003).*** In hemodialysis patients with diabetes, however, some have reported that HbA1C was significantly associated with survival ***(Oomichi et al., 2006; Kalantar-Zadeh et al., 2007; Kovesdy et al., 2008)***, whereas others have reported that it was not ***(Okada et al., 2007; Fukuoka et al., 2007).***

In another study, ***Tsujimoto et al., (2009)*** investigated the impact of glycemic control on the emergence of cardiovascular disease (CVD) in diabetic patients who were on maintenance hemodialysis in a prospective observational study. They concluded that in diabetic hemodialysis patients, poor glycemic

control is a significant, independent predictor of the emergence of CVD, indicating the importance of careful management of glycemic control in hemodialysis patients.

In fact, poor glycemic control is associated with the development of comorbidities such as coronary artery disease and myocardial infarction (MI) in the general population ***(Gaede et al., 2003).*** It has been shown that these are predisposing conditions for sudden cardiac death. Furthermore, glycemia is known to influence the electrolyte balance, the function of potassium and calcium channels, and sympathetic activity, all relevant in the arrhythmogenesis of patients with kidney failure ***(Ritz and Wanner, 2008).***

Furthermore, hyperglycemia has been shown to play a significant role in the development of microangiopathy, endothelial dysfunction, ***(Scognamiglio et al., 2005)*** and impaired myocardial vasodilator function, ***(Srinivasan et al., 2005)*** which contribute to cardiac microvessel disease and structural heart disease ***(Fang et al., 2003).*** It has been reported that hyperglycemia induced excess generation of highly reactive

free radicals, causing oxidative stress, and inflammatory cytokines ***(Johansen et al., 2005).***

AIM OF WORK

The present study aims to evaluate the status of glycemic control in diabetic patients undergoing hemodialysis. In addition, we prospect to identify the risk factors associated with poor glycemic control and the subsequent morbidities with particular emphasis on cardiovascular complications.