Cardiovascular Disease in Post Renal Transplant recipients

Essay submitted for partial fulfillment
of
Master Degree of Internal Medicine

By

Noha Elsayed Elsadaany
M.B.B.Ch
Ain Shams University

Supervised by

Prof . Dr. Mohamad Mahmoud Abd Elghany
Professor of Internal Medicine and Nephrology
Faculty of Medicine
Ain Shams University

Dr . Heba Wahid Mohamed El Said
Lecturer of Internal Medicine and Nephrology
Faculty of Medicine
Ain Shams University

Faculty of Medicine
Ain Shams University
2008-2009

Introduction

Cardiovascular diseases (CVD) in transplant recipients accounts for 35%-50 of all causes of mortality in transplant recipients.

Risk factors for CVD are multiple and include ; non traditional risk factors unique to patients with chronic kidney disease and transplantation risk factors related to transplantation and immunosuppressive medications . Aggressive treatment of all cardiac risk factors should be performed **(David D. Douglas *et al., 2008)*** .

Hypertension is prevalent in renal-transplant recipients and is associated with graft loss, congestive heart failure, ischemic heart disease, and death. Anemia, presents in 15 to 25 percent of renal-transplant recipients, is a risk factor for left ventricular enlargement, congestive heart failure and death. Diabetes, smoking, hyperlipidemia, and hyperhomocysteinemia all have adverse cardiac and renal consequences, as they do in patients with chronic renal insufficiency and those receiving dialysis.

In short; aggressive blood-pressure control, early use of angiotensin-converting–enzyme inhibitors, aggressive management of anemia, aggressive lipid control, tight control of diabetes, and lowering of homocysteine levels are likely to have a profound effect on the outcomes of transplantation and should be addressed in clinical trials **(Claudio Rigatto, M.D. et al 2002*).***

Some of the traditional risk factors for cardiac disease and death such as hypertension, obesity, left ventricular hypertrophy (LVH), diabetes, hyperlipidemia,chronic allograft nephropathy, and hyperhomocysteinemia are more common in renal transplant recipients . This may be due to persistence of a problem that predated transplantation or may result from renal insufficiency or the use of immunosuppressive medications . Other potential risk factors for heart disease are emerging such as evidence of inflammation (elevated C-reactive protein [CRP] and fibrinogen) ; cardiac markers (troponins, B-type natriuretic protein [BNP], and N-terminal pro-BNP) ; and other factors, such as lipoprotein (a) , elevated (calcium x phosphate) product, and cardiac calcifications **(Rachel Becker-Cohen *et al ., 2006)***.

Research efforts and resources now are being invested in studying the causes and treatment strategies of CVD in adult transplant recipients(Levey AS et al ., 1998).

The aim of work

1 – To review pre transplant risk factors for cardiovascular diseases and acquired post transplant (specific)risk factors concerning renal transplantation .

2- To design a protocol, guidelines and recommendations to deal with these risk factors before and after renal transplantation **.**

Acknowledgment

First and above all, all thanks to Allah who granted me the power to accomplish this work.

I would like to express my sincerest gratitude and appreciation to ***Prof. Dr . Mohammed Mahmoud Abd El Ghany*** *Professor of internal medicine and nephrology, Faculty of Medicine. Ain Shams University, who not only added to the value of the work being my supervisor but also encouraged and challenged me throughout this academic work.*

My deep thanks and appreciation to ***Dr. Heba Waheed El-Said*** *, for her guidance, encouragement and her keen supervision and valuable remarks.*

I'm deeply grateful to all my family members for their unlimited financial & moral support not only throughout this work, but throughout my life.

Noha El sadaany

Cardiovascular Disease in Post Renal Transplant recipients

Cardiovascular diseases (CVD) in transplant recipients accounts for 35%-50 of all causes of mortality in transplant recipients. Risk factors for CVD are multiple and include ; non traditional risk factors unique to patients with chronic kidney disease and transplantation risk factors related to transplantation and immunosuppressive medications . Aggressive treatment of all cardiac risk factors should be performed . Hypertension is prevalent in renal-transplant recipients and is associated with graft loss, congestive heart failure, ischemic heart disease, and death. Anemia, presents in 15 to 25 percent of renal-transplant recipients, is a risk factor for left ventricular enlargement, congestive heart failure and death. Diabetes, smoking, hyperlipidemia, and hyperhomocysteinemia all have adverse cardiac and renal consequences, as they do in patients with chronic renal insufficiency and those receiving dialysis. In short; aggressive blood-pressure control, early use of angiotensin-converting–enzyme inhibitors, aggressive management of anemia, aggressive lipid control, tight control of diabetes, and lowering of homocysteine levels are likely to have a profound effect on the outcomes of transplantation and should be addressed in clinical trials . Some of the traditional risk factors for cardiac disease and death such as hypertension, obesity, left ventricular hypertrophy (LVH), diabetes, hyperlipidemia,chronic allograft nephropathy, and hyperhomocysteinemia are more common in renal transplant recipients . This may be due to persistence of a problem that predated transplantation or may result from renal insufficiency or the use of immunosuppressive medications . Other potential risk factors for heart disease are emerging such as evidence of inflammation (elevated C-reactive protein [CRP] and fibrinogen) ; cardiac markers (troponins, B-type natriuretic protein [BNP], and N-terminal pro-BNP) ; and other factors, such as lipoprotein (a) , elevated (calcium x phosphate) product, and cardiac calcifications . Research

efforts and resources should be invested in studying the causes and treatment strategies of CVD in adult transplant recipients.

So the aim of work is to review pre transplant risk factors for cardiovascular diseases and acquired post transplant(specific)risk factors concerning renal transplantation and to design a protocol, guidelines and recommendations to deal with these risk factors before and after renal transplantation as modifying these risk factors will reduce cardiovascular events , not only to improve the quality of life but also to offer extended life expectancy compared with dialysis.

List of abbreviations

ACE	***Angiotensin converting enzyme***
ADA	***American Diabetes Association***
ATP II	***Adult Treatment Panel II***
ATP III	***Adult Treatment Panel III***
ALERT	***Assessment of Lescol in Renal Transplantation trial***
AHA	***American Heart Association***
aPL	***Antiphospholipid antibodies***
ARB	***angiotensin receptor blocker***
ARIC study	***Atherosclerosis risk in communities study***
ASCVD	***Arteriosclerosis cardiovascular disease***
BMI	***Body mass index***
CABG	***Coronary bypass graft surgery***
CAD	***Coronary artery disease***
CAN	***Chronic allograft nephropathy***
CBVD	***Cerebrovascular death***
CD	***Cluster of differentiation***
CD30	***Cluster of differentiation***
CD40L	***CD40 ligand***
CHD	***Coronary heart disease***
CHF	***Congestive heart failure***
CKD	***Chronic kidney disease***
CMV	***Cytomegalovirus***
CNI	***calcineurin inhibitors***
CRP	***C-reactive protein***
CsA	***Cyclosporine***
CV	***Cardiovascular***
CVD	***Cardiovascular disease***
DASH	***Dietary Approaches to Stop Hypertension***
DIRECT study	***Diabetes Incidence after REnal Transplantation: Neoral C_2 ® monitoring versus Tacrolimus***
DM	***Diabetes mellitus***
DMMS	***Dialysis morbidity and mortality study***
ECF	***Extracellular fluid***
ECG	***Electrocardiogram***
EPO	***Erythropiotein***
ESA	***Erythropoiesis- stimulating agents***
ESRD	***End-stage renal disease***

FKBP FK	*Binding-protein*
Hb	*Heamoglobin level*
HLA	*Human leucocyte antigen*
HMG-CoA	*3-hydroxy-3-methylglutaryl coenzyme A*
IDL	*Intermediate density lipoprotein*
Ig	*Immunoglobulin*
ICG	*International consensus guidelines*
IVIG	*Intravenous immunoglobulins*
JNC VII	*Joint National Committee on Prevention, Detection, and evaluation of High Blood Pressure*
K/DOQI	*Kidney Disease Outcomes Quality Initiative*
LDL	*low density lipoprotein*
LVH	*Left ventricular hypertophy*
MACE	*Major adverse cardiac event*
MATRIX	*Management of Anemia in French Kidney Transplant Patients*
MTHFR	*Methylenetetrahydrofolate reductase*
MPG	*N-methylpurine- DNA glycosylase*
MMF	*Mycophenolate mofetil*
NCEP	*National Cholesterol Education Program*
NCEP III	*National Cholesterol Education Project Plan III*
NODAT	*New-onset diabetes after transplantation*
NRT	*Nicotine replacement therapy*
NKF-DOQI	*National Kidney Foundation's Disease Outcomes Quality Initiative*
PVD	*Peripheral vascular disease*
PTA	*Post transplantation anemia*
PTDM	*Post transplantation Diabetes mellitus*
RCT	*Randomized controlled trials*
RRT	*Rerenal replacement therapy*
RTR	*Renal transplant recipients*
SCr	*Serum creatinine*
sICAM-1	*Soluble intracellular adhesion molecule -1*
Th2	*T helper cell 2*
tHcy	*Total homocysteine*
t PA	*Tissue plasminogen activator*
USRD	*U.S. Renal Data System*
UNOS	*United Network for Organ Sharing*
VLDL	*Very-low-density lipoprotein*
WW	*Weight Watchers*

List of Tables

List of Figures

List of Contents

Title	Page

Cardiovascular diseases in chronic kidney disease patients

Cardiovascular diseases in chronic kidney disease patients

Cardiovascular disease (**CVD**) is the most common cause of death in patients with chronic kidney disease (**CKD**) and end-stage renal disease (**ESRD**). The clinical epidemiology of CVD in CKD is challenging due to a prior lack of standardized definitions of CKD, inconsistent measures of renal function, and possible alternative effects of 'traditional' CVD risk factors in patients with CKD. These challenges add to the complexity of the role of renal impairment as the cause or the consequence of cardiovascular disease
(**K. Kundhal, C.E. Lok et al ., 2005**).

The Incidence and Prevalence of CVD in CKD (NKF-DOQI CKD Stages 1-4):

•***Incidence***

Only one prospective study has determined the incidence of CVD in a non-ESRD cohort without CVD at baseline, followed 147 patients for 10 years and found an incidence of CVD events (myocardial infarction, ischemic stroke) of 41% in men and 19% in women (**Jungers et al.,1997**).

The incidence of myocardial infarction was three times higher in men with CKD than in the general male population in all age groups. The same was true for women until age 65 years, after which the difference became less marked. The mean glomerular filteration rate (**GFR**) was

31 ml/min at the time of the events. In a prospective cohort of non-ESRD patients that included congestive heart failure (**CHF**) as part of its CVD outcomes, found, in a patient subset, that 7.4% with no previous CVD developed new cardiac disease (**Levin et al., 2001**).

This is consistent with a population study of approximately 16,000 patients atherosclerosis risk in communities study (**ARIC study**) where the incidence of de novo cardiovascular events was 4.8% (8.3 events/1,000 person-years) if the patient was in stage 2 CKD and 9.3% (16.8/1,000 person years) if in stage 3-4 CKD (**Manjunath G et al., 2003**).

In a study of 6,223 people in the Framingham study, 18% of men and 20% of women with renal impairment already had CVD . The incidence rate of cardiovascular events (coronary artery disease "**CAD**", CHF, ischemic stroke) was 21.3/1,000 patient-years for men and 25.6/1,000 patient-years for women with stage 3 CKD. This contrasts with 18.5 and 11.0 per 1,000 patient-years in men and women, respectively, with a lower serum creatinine (**SCr**) (**Culleton BF, 1999**).

In a Canadian cohort of pre-ESRD patients with known baseline CVD, who were followed for a median of 23 months, 35% developed a new event, worsening CVD, or were hospitalized for cardiac disease (**Levin A et al ., 2001**).

In the ARIC study, the incidence of recurrent events over a mean duration of 6.2 years was 20.4% (38.1

events/1,000 person years; stage 2 CKD) and 28.4% (60.8/1,000 person years; stage 3-4 CKD)(**Manjunath G et al ., 2003**).

•***Prevalence***

The Framingham Heart Study found the prevalence of CVD in people with renal impairment (SCr 136-265 µmol/l in men and 120-265 µmol/l in women) to be 64% higher compared with individuals with lower SCr values (**Culleton BF et al.,1999**).

A population-based study of 1.12 million people found a prevalence in patients with GFR <60 ml/min (CKD stage 3 or less) of 14.9% with CAD, 6.8% cerebrovascular death (**CBVD**), 5.0% peripheral vascular disease(**PVD**) and 7.1% with CHF (**Go AS et al., 2004**).

In a Canadian multi-center prospective cohort of 313 pre-ESRD patients, the prevalence of all CVD was 38% **.** The prevalence of left ventricular hypertophy (**LVH**) has been found to increase with a decline in renal function. Indeed, large population-based studies consistently find a high prevalence of CVD **(levin A et al., 2001**).

Conversely, in a study of 14,527 people with known CAD (diagnosed myocardial infarction) 33.6% had stage 3 or greater CKD (**Navekar NS et al ., 2004**).