Ain Shams University
Facutly of Medicine
Nephrology Department

Hepatic Dysfunction In Renal Transplant Recipients

Thesis

Submitted By
Ahmed Moustafa Taha Mohamed
(M.B.B.Ch, Dip.)

In partial fulfillment of Master Degree in
Nephrology

SUPERVISED BY

Prof. Dr. Essam Mohamed Khedr
Prof. of Internal medicine and nephrology
Ain Shams faculty of medicine

Prof. Dr. Ahmed Aziz Abd El Nabi
Prof. of Internal medicine and nephrology
Ain Shams faculty of medicine

Dr. Sahar Mahmoud Shawky
Assist. Prof. of Internal medicine and nephrology
Ain Shams faculty of medicine

2012

Acknowledgment

To **GOD**, I owe all thanks and gratitude, for giving me help and power to complete this work.

Special thanks to **Prof. Dr. Essam Mohamed Khedr** , professor of internal medicine and nephrology, faculty of medicine, Ain Shams University, for his support, guidance, positive attitude and assurance, working with him caused me a real pleasure.

I'm deeply thankful and grateful to **Prof. Dr. Ahmed Aziz Abd El Nabi**, professor of internal medicine and nephrology, faculty of medicine, Ain Shams University, for his patience, continuous support, and help, invaluable expert and scientific guidance.

I'm so grateful and thankful to **Dr. Sahar Mahmoud Shawky** assistant professor of internal medicine and nephrology, faculty of medicine, Ain Shams University, she offered me an unrelenting support, beside her friendly kind attitude and endless patience and guidance, which add to me a lot both in science and character, without her support this work would have never been realized.

To my parents and parents-in-law, who contained me with love, kindness.

At last, but not least, I would like to thank my dear wife for her love, courage, patience, and constant support.

Contents

Abbreviations Table

AIDS	Acquired immune deficiency syndrome
ALG	Antilymphocyte globulin
ALT	Alanine aminotransferases
AST	Aspartate aminotransferase
ATG	Anti thymocyte globulin
ATP	Adenosine triphosphate
ATT	Antituberculous treatment
AZT	Azathioprine
BPAR	Biopsy Proven Acute Rejection
CAN	Chronic allograft nephropathy
CFT	Complement Fixation Test
CMV	Cytomegalovirus
CsA	Cyclosporine A
CT	Computed tomography
CTP	Child-Turcotte-Pugh
CTP	Child-Turcotte-Pugh score
DEAFF	Detection of early antigen fluorescent foci
DM	Diabetes mellitus
EBV	Epstein-Barr virus
ELISA	Enzyme-linked immunosorbent assay
ETVR	End of treatment virological response
FK-506	Tacrolimus
G-CSF	Granulocyte colony-stimulating factor
GFR	Glomerular filtration rate
GFR	Glomerular Filtration Rate
GIT	Gastrointestinal tract
GM-CSF	Granulocyte-macrophage colony-stimulating factor
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C Virus
HEL	Human embryo lung
HHV	Human Herpes Virus

HIV	Human immune deficiency virus
HSV	Herpes simplex virus
IFT	Indirect immunofluorescence test
IgG	Immunoglobulin G
IgM	Immunoglobulin M
JASN	Journal of American Society of Nephrology
LD	Lactate dehydrogenase
LFTs	Liver Function Tests
MELD	Model for End-Stage Liver Disease
MMF	Mycophenolate mofetil
NAFLD	nonalcoholic fatty liver disease
NASH	nonalcoholic steatohepatitis
NODAT	New Onset Diabetes After Transplantation
NRH	Nodular regenerative hyperplasia
PCR	Polymerase chain reaction.
PTDM	Post transplant Diabetes Mellitus
RIA	Radioimmunoassay
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SVR	Sustained virological response
TH0	T Helper 0 cells
TH2	T Helper 2 cells
UNOS	United Network for Organ Sharing
VZV	Varicella zoster Virus

Tables

Figures

Introduction

Renal transplantation has become the treatment of choice for most patients with end-stage renal disease. Marked improvements in early graft survival and long-term graft function have translated into kidney transplantation being a more cost-effective alternative to dialysis **(Bradley, 2010).**

Liver disease has emerged as an important cause of morbidity and mortality in renal transplant recipients. Liver insufficiency is the cause of death in up to 28% of long-term survivors after renal transplantation **(Gheith et al, 2007).**

Elevation of the levels of the hepatic transaminases associated with discrete alterations in hepatic function is common post transplant and is usually a transient and self-limiting manifestation of drug toxicity. More severe manifestations of liver disease may require further investigation and modification of the immunosuppressive regimen (**William et al, 2005).**

Viral infection is an important cause of hepatic complications Post transplantation **(Ojo et al, 1998).**

Hepatitis C virus (HCV) infection is currently the major cause of chronic liver disease following kidney transplantation. The presence of HCV infection has been found to negatively affect the morbidity and mortality rates in patients on dialysis, in spite of that, it seems that kidney transplantation is a reasonable treatment option after a careful pretransplant evaluation **(Einollahi , 2010).**

Alanine transferase is a good marker of histologic hepatic lesion in HCV-infected Renal Transplant patients and, therefore, liver biopsy can be avoided in patients with persistently normal Alanine transferase **(Perez et al, 2005).**

HCV (Hepatitis C virus) infected transplant recipients with abnormal liver function have inferior survival rates. HCV infection in renal transplants is associated with greater rates of proteinuria and Chronic allograft nephropathy **(Mahmoud et al, 2004).**

HBV (Hepatitis B virus) related liver complications can present as de novo infection, acute flare in patients with chronic infection, chronic hepatitis, cirrhosis, or

hepatocellular carcinoma. The adverse impact of HBV infection on clinical outcomes has been reported by different investigators **(Tak Mao Chan ,2010).**

HBV infection decreased patient survival earlier than HCV and that HCV decreased graft survival more significantly than HBV. Both HBV and HCV were associated with rapid progression of chronic allograft nephropathy. HBV was the strongest risk factor for mortality compared with HCV, acute rejection episode, diabetes mellitus, or other hazardous factors **(Ingsathit , et al, 2007).**

Renal transplant patients infected concomitantly with HBV and HCV present a significantly lower long-term patient survival (**Corrêa et al, 2003).**

Herpes simplex viral hepatitis should be considered in immunocompromised persons with elevated serum transaminases without evidence of fulminant hepatic necrosis **(Duckro et al, 2006).**

Infection due to cytomegalovirus (CMV) is the most frequent opportunistic infection following renal transplantation. It is usually asymptomatic.

Cytomegalovirus disease causes fever, leucopenia, thrombocytopenia and slightly elevated transaminases **(Pérez-Valentín et al, 2002).**

Hepatotoxicity induced by immunosuppressants is difficult to evaluate since these drugs are sometimes used to treat liver diseases, or in combination with other drugs that can also cause hepatotoxicity, In addition, immunosuppressant therapy can favor the development of infections, which by themselves can cause liver damage, or reactivate latent chronic viral hepatitis **(Toscano et al, 2010).**

In a study using regimen of immunosuppression in renal transplantation composed of cyclosporine or (tacrolimus), mycophenolate , and steroid immunosuppression , in 50% of all patients serum alanine transferase (ALT) was elevated, There were more alanine transferase increases in patients on cyclosporine more than those who were on tacrolimus **(Kahu et al, 2005).**

Dose-dependent cyclosporine-induced hepatic dysfunction was observed early post-transplant. Neither tacrolimus- nor sirolimus-associated hepatic dysfunction was dose-dependent. Hepatic dysfunction had no significant impact

on either patient or graft survival; however, this finding may be due to the relatively short duration of follow up **(Gheith et al, 2007).**

Azathioprine is a drug commonly used for the immunosuppression in renal transplantation. Hepatotoxicity is a rare, but important complication of this drug **(Romagnuolo et al, 1998).**

Mycophenolate mofetil is a good alternative agent in special situations like acute/chronic liver diseases with elevated transaminases **(Srivastava et al, 2004).**

Tuberculosis occurs at higher rates in renal transplant recipients than in the general population. It would be desirable to use isoniazid prophylaxis in renal transplant recipients at risk for reactivation of tuberculosis; yet many transplant centers do not routinely employ isoniazid prophylaxis because they perceive transplant recipients to be an enhanced risk of hepatotoxicity from isoniazid **(Antony et al, 1997).**

The Model for End-Stage Liver Disease (MELD)score is a numerical scale, ranging from 6 (less ill) to 40 (the most