

Risk Factors Profile and Cardiovascular Events in Solid Organ Transplant Recipients

Ahad J Ghods

Division of Nephrology and Transplantation, Hasheminejad Kidney Hospital, Tehran University of Medical Sciences, Tehran, Iran

Keywords. kidney transplantation, cardiovascular diseases, risk factors, organ transplantation

By advances in surgical techniques, success in prevention and treatment of transplant-related infections, and introduction of new immunosuppressive drugs, the patient and graft survival rates in solid organ transplant recipients has steadily and remarkably improved. It has been shown that the longer the transplant patients survival rate, the more saturation with cardiovascular risk factors and the greater risk of cardiovascular mortality. Currently, cardiovascular disease is the primary cause of death after kidney transplantation and is among the three most common causes of death after heart and liver transplantation. Over the past decades, because of risk factor reduction, mortality from coronary artery disease has substantially decreased in the general population. Recent studies suggest that risk factors reduction also significantly decreases cardiovascular events and deaths in solid organ transplant recipients.

IJKD 2012;6:9-13
www.ijkd.org

INTRODUCTION

Over the past decades, organ transplantation has been used increasingly for the treatment of patients with end-stage organ failure and has become the treatment of choice for many patients with end-stage kidney, liver, heart, or lung disease. Only in 2008, a total of 28 330 solid organ transplantations were carried out in the United States.¹ The most common organ transplantation was kidney transplants ($n = 16\,821$), followed by liver ($n = 6301$), heart ($n = 2176$), lung ($n = 1554$), kidney-pancreas ($n = 861$), pancreas alone ($n = 396$), intestine ($n = 188$), and heart-lung ($n = 33$) transplants.¹ Obviously, in the same year, similar numbers of transplants were also performed in Europe plus other countries of the world. The main reason for such increasing number of transplants around world is continuous improvements in patient and graft survival rates that leads to increasing number of candidates for solid organ transplantation.

According to the most recent data of the Scientific Registry of Transplant Recipients patient survivals have improved in all solid organ transplantations.²

Patient survival after 5 years of transplantation has remarkably increased in kidney transplant recipients and has reached over 90% and over 80% in living and deceased donor kidney transplantations, respectively. There have also been significant improvements in patient survival in liver and heart transplant recipients. In heart transplant recipients, the 5-year patient survival has reached 74% and in liver transplant recipients, patient survival after 5 years of transplantation has reached 75% and 72% for living donor and deceased donor liver transplantation, respectively. However, there has been modest increase in patient survival in lung, intestine, and heart-lung transplant recipients. Five-year patient survival has reached 55% in intestine transplant recipients and to 53% and 49% after lung and heart-lung transplantation, respectively.²

The main reasons for improving patient and graft survival rates during the past decades have been advances in surgical techniques, success in prevention and treatment of transplant-related infections, increasing public awareness, and introduction of new immunosuppressive drugs.

However, as the number of patient deaths due to surgical complications, transplant-related infections, and immunological graft losses has decreased resulting in prolongation of life expectancy after transplantation, solid organ transplant recipients have been faced with a greater risk of mortality that is cardiovascular death. Today, cardiovascular disease has become one of the leading causes of death in solid organ transplant recipients.

Currently, cardiovascular diseases are the primary cause of death after kidney transplantation and are among the three most common causes the death after heart transplantation and liver transplantation.³⁻⁷ However, cardiovascular diseases only account for approximately 10% of deaths in lung transplant recipients.^{5,8} Cardiovascular mortality rate is lower among lung transplant recipients because the length of survival is lower after lung transplantation compared with length of survival after kidney, heart, or liver transplantations. This is an established fact that the longer the transplant patient survival rate, the more saturation with cardiovascular risk factors and the greater risk of cardiovascular mortality.^{3,9}

This review will mainly focus on the high prevalence of risk factors and cardiovascular events in kidney transplant recipients. Then, it will briefly describe that these risk factors and cardiovascular events has also increased remarkably in liver and heart transplant recipients.

KIDNEY TRANSPLANTS

It is well documented that patients with kidney failure, at all stages, are at a high risk of cardiovascular mortality. There are studies suggesting that patients with mild to moderate kidney failure experience a high rate of fatal and nonfatal cardiovascular events prior to reaching end-stage kidney disease. Go and coworkers conducted a study in a large, community-based population and observed an independent graded association between reduced estimated glomerular filtration rate and cardiovascular events. They showed that as estimated glomerular filtration rate decreases, the age-adjusted rate of death, cardiovascular events, and hospitalizations increases.¹⁰

Currently, cardiovascular diseases are the leading cause of death in patients with end-stage kidney disease, not only in those undergoing dialysis, but also in kidney transplant recipients. Sarnak and coworkers compared the annual cardiovascular

mortality in patients undergoing dialysis and in transplant recipients with that in the general population.¹¹ They showed that cardiovascular death rate is higher in dialysis patients for all age groups, especially for the young whose cardiovascular mortality is up to 100 times higher than that of the general population. The reason for such a high cardiovascular mortality is that patients with end-stage kidney disease are heavily saturated with cardiovascular risk factors. In dialysis patients and kidney transplant candidates, the prevalence of systemic hypertension, left ventricular hypertrophy, diabetes, and hypercholesterolemia have been reported to be 80%, 75%, 40%, and 25% respectively.³ After a successful kidney transplantation, the probability of cardiovascular mortality decreases compared with dialysis patients, but it does not reach the rate in general population. This is because many cardiovascular diseases risk factors do not disappear after a successful kidney transplantation. In addition, by taking immunosuppressive drugs that have diabetogenic and atherogenic potentials either preexisting cardiovascular disease risk factors are worsened or even new risk factors develops.³

According to several studies, the prevalence of cardiovascular disease risk factors increases or remains higher after kidney transplantation. The prevalence of systemic hypertension, diabetes, hypercholesterolemia, left ventricular hypertrophy, and obesity have been reported to present in 80%, 55%, 60%, 52%, and 32% of kidney transplant recipients, respectively. Several studies have also shown that the annual risk of cardiovascular death in kidney transplant recipients to be in the range of 3.5% to 5%, which is 50-fold higher than that in the general population.³

Aakhus and coworkers studied cardiovascular morbidity and mortality in 406 stable kidney transplant recipients during a 5 years' follow-up.¹² In this period, they recorded 88 deaths, 74% of the causes of which were cardiovascular events. They also showed that in all age groups, the annual rate of cardiovascular mortality was significantly higher in kidney transplant recipients compared with that in the general population. The comparison of baseline characteristics between survivors (n = 317) and nonsurvivors (n = 88) showed that the prevalence of cardiovascular risk factors such as ischemic heart disease, congestive heart failure, cerebrovascular disease, diabetes,

hypertension, high systolic blood pressure, high triglyceride levels, declined creatinine clearance, left ventricular hypertrophy, and sedentary life style were all significantly higher in nonsurvivor kidney transplant recipients. The authors studied predictors for cardiovascular events after kidney transplantation by using multivariable analysis and showed that predictors for death of ischemic heart disease were age, systolic blood pressure, high-density lipoprotein cholesterol, congestive heart failure, and diabetes mellitus. The predictors for major ischemic heart events were also the same plus total cholesterol levels and cerebrovascular diseases.¹²

Risk factors for cardiovascular events after a successful kidney transplantation has also been studied by Vanrenterghem and coworkers.¹³ In this study, the authors investigated the incidence of cardiovascular events and identified the main risk factors for cardiovascular complications and mortality in 2071 kidney transplant recipients. They showed that the incidence of cardiovascular events increases over time. According to this study, 75% of kidney transplant recipients were free from cardiovascular events at 10 years after transplantation; however, this rate decreased to 47% by 15 years posttransplantation. The important risk factors for cardiovascular events in kidney transplant recipients surviving more than 1 year after transplantation were male gender, older age, hypertension before transplantation, longer duration of dialysis, cardiovascular events before transplantation, posttransplant diabetes, corticosteroid therapy, and high serum triglyceride levels.¹³

Meier-Kriesche and coworkers used data of 58 900 kidney transplant recipients that were supplied by the United States Renal Data System and the Scientific Registry of Transplant Recipients, and they showed that decreased kidney function is a strong risk factor for cardiovascular death after kidney transplantation. In this study, a serum creatinine of more than 1.5 mg/dL at 1 year after transplantation was a strong risk factor for cardiovascular death. Risk of decreased kidney function was completely independent from other known risk factors.¹⁴

There are many known cardiovascular risk factors in kidney transplant recipients that can be divided into traditional and nontraditional risk factors.

Traditional risk factors are systemic hypertension, diabetes mellitus, hypercholesterolemia, congestive heart failure, left ventricular hypertrophy, cardiovascular events before transplantation, duration of dialysis, hypertriglyceridemia, obesity, smoking, anemia, and immunosuppressive drugs, and nontraditional risk factors include hyperhomocysteinemia, proteinuria, oxidative stress biomarkers, systemic inflammation biomarkers, lupus anticoagulant antibodies, advanced glycosylation end products.^{3,15-21} The discussion about each of these risk factors is beyond the scope of this review.

Studies in the general population have shown that because of risk factors reduction, mortality due to coronary artery disease has substantially decreased in the recent years. Now the question is whether reduction of cardiovascular risk factors in solid organ transplant recipients has also decreased cardiovascular events. Ford and coworkers conducted a study and showed that mortality from coronary heart disease in the United States has decreased substantially in recent decades.²² From 1980 through 2000, the age-adjusted death rate for coronary heart disease fell from 542.9 to 266.8 deaths per 100 000 population among men and from 263.3 to 134.4 deaths per 100 000 population among women, resulting in more than 340 000 fewer deaths from coronary heart disease in 2000. Approximately, 47% of this decrease was explained by the use of medical and surgical treatments and approximately 44% was attributed to changes in cardiovascular risk factors, including reduction in total cholesterol (24%), systolic blood pressure (20%), smoking prevalence (12%), and physical inactivity (5%). During this period, the prevalence of obesity and diabetes increased. As a result, these reductions were partially offset by the increase in the body mass index and the prevalence of diabetes by 8% and 10%, respectively.²² Pilmore and coworkers studied all patients in Australia and New Zealand with a functioning kidney transplant between 1980 and 2007 and examined trends in the cause and timing of all 2195 deaths recorded after kidney transplantation. They showed that cardiovascular events were the most common cause of death throughout all the time points examined; however, cardiovascular death rates significantly decreased by the period from 2005 to 2007 in the kidney transplant population.²³

LIVER, HEART, LUNG, AND HEART-LUNG TRANSPLANTS

As mentioned, the longer the solid organ transplant recipient survival rate, the more saturation with cardiovascular risk factors and the greater risk of cardiovascular mortality. In liver transplant recipients, patient survival after 5 years of transplantation has reached 75% and 72% in living donor and deceased donor liver transplantations, respectively. According to several epidemiologic studies, the prevalence of cardiovascular risk factors such as hypertension, hyperlipidemia, obesity, and diabetes significantly increases after liver transplantation.²⁴ This indicates that the rates of cardiovascular events and cardiovascular death also increase in liver transplant recipients. In some other studies, cardiovascular events range from 9.4% at 5 years to 25% at 10 years after liver transplantation.⁶ Cardiovascular death accounts for about 21% of deaths of liver transplant recipients surviving more than 3 years posttransplant. Cardiovascular death is the third leading cause of death, 22% of all late mortalities in liver transplant recipients.^{6,25,26}

According to the International Heart Lung Transplant Registry, the half life of heart transplant recipients has currently reached about 10 years. The prevalence rates of hypertension, kidney dysfunction, hyperlipidemia, diabetes, and cardiac allograft vasculopathy are reported to be 73.3%, 27.2%, 57.6%, 27.8%, and 7.8%, respectively, at 1 year after heart transplantation, which increases significantly to 97.4%, 38.3%, 93.3%, 38.6%, 51.9%, respectively at 10 years. Cardiovascular death is also among the three most common causes of death in heart transplant recipients.²⁷

In lung transplant recipients, the length of patient survival is lower compared to liver and heart transplant recipients. According to the registry, the half life for lung transplant recipients has reached about 5 years. Cardiovascular risk factors only modestly increase in these patients and cardiovascular death accounts for less than 10% of all causes. The same is true for heart-lung transplant recipients that have lower patient survival rates (half life of about 3 years) and modest increase in cardiovascular risk factors. In these patients, infection and graft failure are still the leading causes of death.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Organ Procurement and Transplantation Network/ Scientific Registry Transplant Recipients. 2008 Annual Report. Available from: <http://optn.transplant.hrsa.gov/data/annualreport.asp>
2. Organ Procurement and Transplantation Network/ Scientific Registry Transplant Recipients. 2009 Annual Report. Available from: <http://optn.transplant.hrsa.gov/data/annualreport.asp>
3. Ojo AO. Cardiovascular complications after renal transplantation and their prevention. *Transplantation*. 2006;82:603-11.
4. Aker S, Ivens K, Grabensee B, Heering P. Cardiovascular risk factors and diseases after renal transplantation. *Int Urol Nephrol*. 1998;30:777-88.
5. Trulock EP, Edwards LB, Taylor DO, Boucek MM, Keck BM, Hertz MI. Registry of the International Society for Heart and Lung Transplantation: twenty-third official adult lung and heart-lung transplantation report--2006. *J Heart Lung Transplant*. 2006;25:880-92.
6. Guckelberger O, Mutzke F, Glanemann M, et al. Validation of cardiovascular risk scores in a liver transplant population. *Liver Transpl*. 2006;12:394-401.
7. Rabkin JM, Corless CL, Rosen HR, Olyaei AJ. Immunosuppression impact on long-term cardiovascular complications after liver transplantation. *Am J Surg*. 2002;183:595-9.
8. Sekine Y, Waddell TK, Matte-Martyn A, et al. Risk quantification of early outcome after lung transplantation: donor, recipient, operative, and post-transplant parameters. *J Heart Lung Transplant*. 2004;23:96-104.
9. De Vito Dabbs A, Song MK. Risk profile for cardiovascular morbidity and mortality after lung transplantation. *Nurs Clin North Am*. 2008;43:37-53; vi.
10. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med*. 2004;351:1296-305.
11. Sarnak MJ, Levey AS, Schoolwerth AC, et al. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. *Circulation*. 2003;108:2154-69.
12. Aakhus S, Dahl K, Wideroe TE. Cardiovascular disease in stable renal transplant patients in Norway: morbidity and mortality during a 5-yr follow-up. *Clin Transplant*. 2004;18:596-604.
13. Vanrenterghem YF, Claes K, Montagnino G, et al. Risk factors for cardiovascular events after successful renal transplantation. *Transplantation*. 2008;85:209-16.
14. Meier-Kriesche HU, Baliga R, Kaplan B. Decreased renal function is a strong risk factor for cardiovascular death after renal transplantation. *Transplantation*. 2003;75:1291-5.

15. Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. *Am J Kidney Dis.* 1998;32:S112-9.
16. Aakhus S, Dahl K, Wideroe TE. Cardiovascular morbidity and risk factors in renal transplant patients. *Nephrol Dial Transplant.* 1999;14:648-54.
17. Abbott KC, Hypolite IO, Hshieh P, Cruess D, Taylor AJ, Agodoa LY. Hospitalized congestive heart failure after renal transplantation in the United States. *Ann Epidemiol.* 2002;12:115-22.
18. De Lima JJ, Gowdak LH, de Paula FJ, et al. Treatment of coronary artery disease in hemodialysis patients evaluated for transplant—a registry study. *Transplantation.* 2010;89:845-50.
19. Simmons EM, Langone A, Sezer MT, et al. Effect of renal transplantation on biomarkers of inflammation and oxidative stress in end-stage renal disease patients. *Transplantation.* 2005;79:914-9.
20. Ducloux D, Ruedin C, Gibey R, et al. Prevalence, determinants, and clinical significance of hyperhomocyst(e)inaemia in renal-transplant recipients. *Nephrol Dial Transplant.* 1998;13:2890-3.
21. Humar A, Kerr SR, Ramcharan T, Gillingham KJ, Matas AJ. Peri-operative cardiac morbidity in kidney transplant recipients: incidence and risk factors. *Clin Transplant.* 2001;15:154-8.
22. Ford ES, Ajani UA, Croft JB, et al. Explaining the decrease in U.S. deaths from coronary disease, 1980-2000. *N Engl J Med.* 2007;356:2388-98.
23. Pilmore H, Dent H, Chang S, McDonald SP, Chadban SJ. Reduction in cardiovascular death after kidney transplantation. *Transplantation.* 2010;89:851-7.
24. Mells G, Neuberger J. Reducing the risks of cardiovascular disease in liver allograft recipients. *Transplantation.* 2007;83:1141-50.
25. Fouad TR, Abdel-Razek WM, Burak KW, Bain VG, Lee SS. Prediction of cardiac complications after liver transplantation. *Transplantation.* 2009;87:763-70.
26. Appleton CP, Hurst RT, Lee KS, Reuss C, Hentz JG. Long-term cardiovascular risk in the orthotopic liver transplant population. *Liver Transpl.* 2006;12:352-5.
27. International Society of Heart and Lung Transplantation. Heart/Lung Registries. Available from: <http://www.isHLT.org/registries/slides.asp?slides=heartLungRegistry>

Correspondence to:

Ahad J Ghods, MD, FACP
 Division of Nephrology and Transplantation Unit, HashemiNejad
 Kidney Hospital,
 Vanak Sq, Tehran 19697, Iran
 Tel: +98 21 22 00 99 88
 Fax: + 98 21 22 00 65 61
 E-mail: ahad.ghods@gmail.com

Received August 2011

Archive of SIB