Discussion on the risk factors of developing cardiovascular diseases (CVD) after the kidney transplantation

Kai Wang*, Qing-shan Qu, Shu-zhai Miao, Yanxuan Zhang and Xin Jing
Department of Organ Transplantation, People's Hospital of Zhengzhou, Zhengzhou City, Henan Province, PR China

Abstract: To discuss the risk factors of developing cardiovascular disease (CVD) after the kidney transplantation. Retrospective analysis on the data of 1106 patients who had been underwent kidney allotransplantation in People's Hospital of Zhengzhou from July, 2010 to Dec, 2014 and conformed to the inclusion criteria was taken. Cox proportional hazard model was used to analyze the risk factors of developing CVD after the kidney transplantation. 7 days, 1 month, 3 months, 6 months and 12 months before and after the operation, the data collection and following-up visits were respectively arranged. 12 months after the operation, the following-up visits were arranged once a half year until the end of March, 2014. 216 (19.5%) patients developed CVD after the kidney transplantation. Among them, 47 (4.2%) patients developed CVD within the first three months after the operation, which accounted for 26.8% in the CVD patients; 125 (11.3%) patients developed CVD within the first one year after the operation, which accounted for 47.9% in the CVD patients. 51 (4.6%) patients died after the operation. Among them, 19 (2.7%) patients died of CVD, which accounted for 37.3% in the whole died patients. Multiple factors analysis revealed that the following were the risk factors to develop CVD after the kidney transplantation: The age of receptors was greater than 50 (OR=2.39, 95%CI 1.15-3.60); The receptors had diabetes before the surgery (OR=3.18, 95%CI 1.56-6.42); The receptors had CVD medical history before the surgery (OR=3.85, 95%CI 2.15-7.54); The primary diseases of receptors were diabetic nephropathy (DN) (OR=2.12, 95%CI 1.14-3.98); The preoperative dialysis time was greater than 12 months(OR=1.27, 95%CI 0.98-1.38); The postoperative serum creatinine of the receptors was greater than 200 μmol/L (OR=2.78, 95%CI 1.35~4.53); The delayed graft failure (DGF) occurred (OR=1.24, 95%CI 1.02~1.42); Acute rejection appeared(AR)(OR=2.98, 95%CI 1.56~5.72); Renal allograft dysfunction appeared (OR=4.86, 95%CI 3.15~7.78). The morbidity of CVD is high after the kidney transplantation and the risk factors are diversified. That revising or excluding relevant risk factors may lower the morbidity of developing CVD and is in favor of the long-term survival for the transplanted kidney.

Keywords: Kidney transplantation; cardiovascular disease (CVD); risk factors.

INTRODUCTION

The postoperative cardiovascular disease (CVD) mainly contains angina caused by ischemic heart disease (IHD), acute myocardial infarction (AMI), arrhythmia, heart failure and blood vessel diseases of brain with 10 times morbidity and mortality than common people. The dead patients caused by CVD accounts for 40% in the whole dead patients who died within the first year after the kidney transplantation (Meier-Kriesche *et al*., 2004). The existing risk factors in the common people that can cause atherosclerosis contain smoking, male, advanced age, hypertension, diabetes, hyperlipidemia, obesity and other traditional risk factors. Those are risk factors of developing CVD after the kidney transplantation at the same time. In addition, the preoperative dialysis time, renal ischemia time, DGF, renal allograft dysfunction, acute rejection and long-term usage of immunosuppressor are deemed to be closely related to the occurring of CVD after the kidney transplantation. On account of lacking prospective study on the kidney transplantation recipients at present, the viewpoints about the risk factors of developing CVD after the kidney transplantation still can not come to an agreement. Under this circumstance, on the basis of the study on common people, the clinical features of kidney transplantation are combined with the large samples data to retrospectively analyze and evaluate the risk factors of developing CVD after the operation.

Thereby, the potential high-risk patients of CVD can be fast found during clinical treatment and implemented the intervene treatment, which is beneficial for improving the survival of recipients or the transplant kidneys. This survey retrospectively analyzes on the data and following-up records of 1161 patients who had been underwent the kidney transplantation because of the end stage of renal disease(ESRD) in the 309th hospital of Chinese People's Liberation Army from May 1st, 2009 to Nov 30th, 2013 and discusses the risk factors of developing CVD after the kidney transplantation.

MATERIALS AND METHODS

Inclusion criteria and collected contents

The inclusion criteria and collected contents in data of cases. Inclusion criteria: age>18; transplantation patients without multiple-organs combined transplantation; kidney transplantation without blood type incompatibility. The

**Corresponding author:* e-mail: zmby519@163.com

collected contents in data of cases included: the age, gender, weight, idiopathic kidney diseases and preoperative dialysis time of recipients; with or without medical histories of hypertension, hyperlipidemia, diabetes and cardiovascular events before or after the operation; postoperative immunosuppressor programs, treatment conditions of hypertension drugs, fasting blood-glucose level, serum creatinine level, blood fat level, blood ciclosporin level, with or without proteinuria, with or without acute rejection, with or without cytomegalovirus infection, with or without DGF and with or without renal allograft dysfunction (Qin *et al*., 2013). All the data of cases and following-up records were registered in the Chinese Scientific Registry of Kidney Transplantation (CSRKT). In line with the *Guidelines on Prevention and Treatment of Blood Lipid Abnormality in Chinese Adults (2007)*, the diagnostic criteria for dyslipidemia were that if the examination for venous blood conformed to any one of the following items, the blood lipid would be affirmed to be abnormal (Xu *et al*., 2008): serum low density lipoprotein (LDL-C)>4.14 mmol/L (160mg/dl); serum high density lipoprotein (HDL-C)<1.04mmol/L (40mg/dl); total cholesterol (TC)>6.22mmol/L (240mg/dl); triglyceride (TG)>2.26 mmol/L (200mg/dl). In this survey, the FPG was regarded as the basis to define the new-onset post-transplant diabetes mellitus (PTDM), and the specific definitions were that (Li *et al*., 2010): without diabetes before the operation, with FPG ≥7.0 mmol/L or with normal FPG but the patients were treated with insulin or oral hypoglycemic drugs after excluding postoperative acute glucose metabolism disturbance.

The present study had been written approved by the Clinical Ethic Committee of the People's Hospital of Zhengzhou. And informed consent was obtained from all patients.

Research incidents and grouping of cases

The CVD after the kidney transplantation contained the following clinical symptoms or diagnose (Fellström, 2001): ischemic heart disease (IHD): angina, myocardial infarction (MI), arrhythmia, cardiac failure, coronary artery revascularization or death caused by heart ischemia; Incidents of blood vessel of brain: embolism and cerebral hemorrhage caused by cerebral thrombosis; left ventricular hypertrophy, congestive heart failure and cardiomyopathy; atherosclerosis diseases of surrounding blood vessels. All the cases were divided into two groups on the basis of developing CVD or not developing CVD after the kidney transplantation: cases developing CVD was divided into Group A; cases not developing CVD was divided into Group B (control group). The main research incidents referred to whether patients developed CVD or not after the operation. The minor research incidents referred to the survival statements of the patients or the transplanted kidney after the operation.

STATISTICAL ANALYSIS

The software SPSS 10.0 was adopted to analyze. The normal distribution measurement data were expressed by x±s. The comparison between the two groups was analyzed by one-way analysis of variance. The comparison between the enumeration data were examined by χ^2.The Cox proportional hazard model was adopted to proceed the multiple-factors analysis. $P<0.05$ meant that the differences had statistical significance.

RESULTS

Among the 1161 cases, 33 cases belonged to the second time for kidney transplantation, 4 cases belonged to the third time for kidney transplantation, 8 cases belonged to combined liver-kidney transplantation, 2 cases belonged to combined pancreas-kidney transplantation, 8 cases were less than 18 years old. By excluding the above-mentioned 55 cases, the left 1106 cases were divided into the two groups. The following-up periods were 343.9±304.9 d, the ages of recipients were 40.7±11.3 years old, the body mass indexes (BMI) were 22.55±3.47 kg/m^2, and 779 cases (70.43%) were male recipients. Before the kidney transplantation, 1012 cases (91.50%) were underwent hemato dialysis, 4 cases were underwent peritoneal dialysis, and 90 cases had no dialysis treatment histories, The preoperative dislysis periods were 520.7±602.2 d. 131 cases (11.84%) kidney transplantation were donated by living donors, 975 cases (88.16%) kidney transplantation were donated by died donors, the cold ischemia time of donor kidney was 8.37±3.65 h, and the warm ischemia time was 5.07±2.09min. In the primary diseases that could cause ESRD, 870 cases (78.67%) were chronic glomerulonephritis patients, 105 cases (9.49%) were diabetic nephropathy patients, and other cases that included interstitial nephritis, polycystic nephropathy, hypertensive nephropathy and other nephropathy of undetermined origin accounted for 11.84%. 1049 recipients (94.85%) had hypertension before the kidney transplantation, 223 recipients (20.16%) had diabetes before the operation, 113 recipients (10.21%) had CVD before the operation and 18 cases in 113 recipients had cerebral infarction. Before the kidney transplantation, 479 cases were examined the TC and TG level, and 7 cases of them ended up with TC>6.22 mmol/L, 46 cases (9.6%) of them ended up with TG>2.26 mmol/L. The records about LDL and HDL value were only 35 cases. All the patients adopted the Sanlian immunosuppressant projects. Among the whole patients, 1025 cases (92.68%) adopted projects that contained mycophenolate mofetil plus ciclosporin/tacrolimus plus hormone, 68 cases (7.32%) adopted projects that contained mizoribine plus ciclosporin/tacrolimus plus hormone.

The main and minor research incidents

Among 1106 recipients, 216 cases (19.5%) developed

deadly or non-deadly CVD after the kidney transplantation. Among the 216 cases, 153 cases (13.8%) had ischemic heart diseases, 33 cases (3.0%) had cerebrovascular diseases, 19 cases had left ventricular hypertrophy, 6 cases had congestive heart-failure, 5 cases had blood vessels atherosclerosis in carotid artery and renal artery. 47 cases (4.2%) developed CVD within the first three months after the operation in total and 125 cases (11.3%) developed CVD 1 year after the operation, which respectively accounted for 26.8% and 47.9% of the total postoperative CVD patients. 271 cases (24.5%) developed delayed graft failure (DGF). 157 cases developed acute reaction and 119 cases (75.8%) in 157 cases developed the acute reaction within three months after the operation. 108 (9.8%) transplanted kidneys lost functions and 67 cases of them came up dysfunction within three months after the operation and 89 cases of them came up 1 year after the operation, which respectively accounted for 62.0% and 82.4% of the total kidneys dysfunction patients. 51 cases (4.6%) died and 19 cases (2.7%) of them died of CVD and accounted for 37.3% of the total death patients. 21 cases died of infectious diseases, 5 cases died of malignant tumors, 10 cases died of transplanted kidneys dysfunction and other patients died of disseminated intravascular coagulation, alveolar haemorrhage syndromes, gastrointestinal tracts complication and other diseases. Among the 51 death patients, 33 cases died within three 3 months after the operation and 47 cases died within 1 year after the operation, which respectively accounted for 64.7% and 92.2% of the total death patients. 6 cases developed CVD and lost kidney functions at the same day. Therefore, the possibility that CVD maybe the pathogenesis to cause kidney dysfunction could not be excluded. Hence the 6 cases did not be listed into the Cox proportional hazard model.

Analysis on the risk factors of CVD

Group A had 216 cases and group B had 890 cases. After the comparison for the clinical data of the two groups, the univariate analysis showed that the differences between the following factors of group A and group B had statistical significance: recipients age >50; Male recipients; Cadaveric donor; Pre-transplant DM and Pre-transplant CVD; Primary diabetic nephropathy; Preoperative duration of dialysis >12 months; Preoperative BMI >30 kg/m^2; Postoperative dyslipidemia; Postoperative Scr >200 μmol/L; PTDM; DGF; AR; Graft failure ($P<0.05$) (table 1).

The variables that referred to those differences between the two groups showed in table 1that had statistical significance were listed into the Cox proportional hazard model to be proceeded multiple-factor analysis. It turned out that recipients age>50, pre-transplant DM, pre-transplant CVD, primary diabetic nephropathy, preoperative duration of dialysis >12 months, postoperative Scr >200 μmol/L, DGF, AR and graft failure were the risk factors of developing CVD after the kidney transplantation (table 2).

DISCUSSION

With the lengthening of the recipients lifetime, the morbidity of CVD increased by years and about 40% recipients developed at least 1 time cardiovascular event 10 years after the kidney transplantation (Aalten *et al*., 2008). This survey showed that 10.21% ESRD patients had pre-transplant CVD and pre-transplant CVD was the main risk factor to develop CVD after the operation. 19.5% patients developed CVD after the kidney transplantation, most of them developed CVD within 1 year after the operation and the morbidity within three months after the operation was highest (4.2%). 37.3% recipients died of postoperative CVD, which approached the overseas research results (Humar *et al*., 2001).

This research found that the traditional high-risk factors such as advanced age, diabetic nephropathy, diabetes and long-time preoperative dialysis were independent risk factors of post-transplant CVD (Kasiske *et al*., 2006). Some researches pointed out that smoking, male patients, female in menopause, fat, hypertension, hyperlipidemia and anemia were also the risk factors of post-transplant CVD (Kavanagh *et al.*, 1999). Notwithstanding this research ever mentioned that gender and fat were connected to the occurring of post-transplant CVD, they could not be deeded as the risk factors to forecast CVD yet. On the other hand, the above-mentioned circumstance may be caused because of that the proportion of female and fat recipients was less, so there were no enough samples to support the comparison between the two groups. Otherwise, 94.85% cases in this research had hypertension before the kidney transplantation, and the patients with hypertension were almost same in two groups. After listing those patients into the analytical model, no signs showed that the pre-transplant hypertension correlated to the postoperative morbidity of CVD. In spite of this, compared with the common people, male recipients and recipients with fat and pre-transplant hypertension still were regarded as high risk groups of developing CVD after the kidney transplantation.

Although hyperlipemia was the risk factor of developing CVD for the common people, it was still debatable whether it had predictive value for the post-transplant CVD. And the reason may be attributed to the different delamination criteria for determining the dyslipidemia. One research even found that recipients with post-transplant CVD had lower LDL and TC level (Goel *et al*., 2003). The pre-transplant inspection data of blood lipid were lacking and the blood lipid level fluctuated greatly, therefore, the relationship between hyperlipemia symptom and the morbidity of developing CVD after the transplantation could not be analyzed yet. It remained further study in the future (Feng *et al*., 2014).

Table 1: Univariate analysis on the risk factors of CVD after the kidney transplantation

Variables	Group A (n=216)	Group B (n=890)
Recipient age (year)	49.0 ± 14.7	40.2 ± 12.4
> 50 years	86 (39.8%) (1)	154 (17.3%)
Male recipient	173 (80.4%) (1)	606 (68.1%)
Cadaveric donor	204 (94.4%) (1)	771 (86.6%)
Pre-transplant DM	60 (27.8%) (1)	163 (18.3%)
Primary diabetic nephropathy	30 (13. 9%) (1)	75 (8.4%)
Pre-transplant CVD	60 (27.7%) (1)	53 (6.0%)
Systolic hypertension > 140 mmHg	208 (96.1%)	841 (94.9%)
BMI > 30 kg/m^2	33 (15.3%) (1)	90 (10.1%)
Duration of dialysis > 12 months	193 (89.4%) (1)	634 (71.2%)
Anti-hypertension medication	170 (78.5%)	645 (72.5%)
Post-transplant dyslipidemia	96 (44.5%) (1)	313 (35.2%)
Scr > 200 μmol/L after 1 year	95 (43.8%) (1)	278 (31.2%)
DGF	70 (32.4%) (1)	201 (22.6%)
AR	63 (29.2%) (1)	177 (19.9%)
Graft failure	26 (12.0%) (1)	65 (7.3%)
PTDM	29 (13.3%) (1)	70 (7.8%)
Ciclosporin A vs Tacrolimus	43.5 vs 56.5	42.2 vs 57.8

DM. Diabetes mellitus; CVD. Cardiovascular disease; BMI. Body mass index; Scr. Serum creatinine; DGF. Delayed graft failure; AR. Acute reaction; PTDM. New-onset post-transplant diabetes mellitus. (1) P<0.05 compared with group B

Table 2: Cox proportional hazard model analysis on the risk factors of CVD after the kidney transplantation

Risk factor (yes/no)	OR (95%CI)
Recipient age > 50	2.39 (1.65-3.61) (1)
Male recipient	1.04 (0.78-3.12)
Pre-transplant DM	3.18 (1.56-6.42) (1)
BMI > 30 kg/m^2	1.24 (0.78-2.32)
Cadaveric donor	1.39 (0.96-4.14)
Primary diabetic nephropathy	2.12 (1.14-3.98) (1)
Pre-transplant CVD	3.85 (2.15-7.54) (1)
Duration of dialysis > 12 months	1.27 (0.98-1.38) (1)
Post-transplant dyslipidemia	1.14 (0.82-1.56)
Scr > 200 μmol/L after 1 year	2.78 (1.35-4.53) (1)
Delayed graft function	1.24 (1.08-1.42) (1)
AR	2.98 (1.56-5.72) (1)
Graft failure	4.86 (3.15-7.78) (1)
PTDM	1.22 (0.93-1.92)

DM. Diabetes mellitus; BMI. Body mass index; CVD. Cardiovascular disease; Scr. Serum creatinine; AR. Acute reaction; PTDM. New-onset post-transplant diabetes mellitus. OR. Odds Ratio; CI. Confidence interval. (1) P<0.05

The above-mentioned traditional risk factors of developing CVD which based on the study of the common people could not sufficiently forecast the morbidity of post-transplant CVD. Some risk factors related to the transplantation did have more predictive value especially for the early developing of post-transplant CVD. The research pointed out that early renal insufficiency after the transplantation was the risk factor of developing CVD (Kaul *et al*., 2011). Some retrospective analysis on large samples proved that the probabilities of occurring severe cardiovascular events and death events correlated or uncorrelated to cardiovascular increased when the serum creatinine value rose especially when it was more than 200 μmol/L 1 year after the kidney transplantation (Fellström *et al.*, 2005). On the one hand, the occurrence of AR may cause the graft failure. On the other hand, large dose usage of hormone during the treatment may damage the vascular endothelial cells. Therefore, the frequencies of AR were deemed to positively correlate to the occurring of post-transplant CVD and were independent of the following two risk factors: transplanted kidney functions and proteinuria (.Kasiske, 1988). This research had proved that Scr >200 μmol/L, DGF, AR and graft failure were predictive risk factors of post-transplant CVD. Especially within the first three 3 months after the transplantation,

the occurrence rates of relevant complications such as DGF, AR and graft failure were at the highest level, and the morbidity of CVD and death rate were at the highest level at the same time, which was conformed to the previous research results. Different with some research results, this research did not prove that kidney transplantation with cadaveric donor was the risk factor of post-transplant CVD. The reason was that data of kidney transplantation with living donor in this research were too less to proceed comparison among groups.

After the transplantation, because of the large dose usage of hormone in the early time and long-term taking calcineurin inhibitors (CNI) such as tacrolimus and ciclosporin, the morbidity of PTDM increased with the lengthening of the transplant ages, which caused the increasing of the morbidity of CVD and mortality hazard of recipients. Although this research proved that pre-transplant diabetes was the risk factor of post-transplant CVD, and recipients with post-transplant CVD plus recipients with PTDM were obviously more than recipients in control group, the analysis in multivariate regression model did not show that PTDM had predictive value for post-transplant CVD. The reason may be that the following-up periods of two groups were relatively short and the influence from the rising of the blood glucose on the microangiopathy was a chronic process. Consequently, whether PTDM was the risk factor of developing post-transplant CVD should be further verified by more long-term following-up data.

The usage of immunosuppressive agents after the transplantation was another important risk factor of CVD. Nevertheless it was found that notwithstanding the reducing of dosage of immunosuppressive agents could improve the morbidity of traditional risk factors of CVD such as hypertension, hypertipidemia and hyperglycemia, the morbidity of relative non-traditional risk factors of CVD such as rejection reaction and graft loss slightly increased. It was not determined yet which project was with lower morbidity of post-transplant CVD between ciclosporin and tacrolimus (Marcén, 2006). In this research, the quantities of recipients who took ciclosporin and tacrolimus in CVD group and control group were nearly same, and above 90% patients were taking mycophenolate mofetil. Therefore, it was not verified that which immunosuppressive agent was with higher risk of developing CVD for the recipients. But in the context of effective anti-rejection treatment, it was fully necessary that reasonable application of immunosuppressive agents should be arranged on the basis of specific situation of every patient for the sake of reducing the risk of post-transplant CVD (Zhao *et al*., 2013).

CONCLUSION

In conclusion, the above-mentioned factors in this research: Recipients age >50; Pre-transplant DM and Pre-transplant CVD; Primary diabetic nephropathy; Preoperative duration of dialysis >12 months; Postoperative Scr >200 μmol/L; AR; Graft failure are risk factors of post-transplant CVD. At the same time, although the following factors: Male recipients; Cadaveric donor; PTDM; Preoperative BMI >30 kg/m^2 have not achieved statistical significance for the risk of developing CVD, they have rising tendency. In addition, some risk factors such as hyperhomocysteinemia, post-transplant hyperlipidaemia, smoking, anemia, inflammation and oxidative stress reported from some researches should be paid more attention (Zhao *et al*., 2013; Yuan *et al*., 2014). Although the evidences based medicine that aim to the kidney transplantation recipients are less, on the basis of the research in common people, it is reasonable to hold the thoughts that revising or excluding the risk factors of CVD and improving graft functions and overall body status can help to reduce the morbidity of post-transplant CVD thus improve the long-term survival ratios of the transplanted kidney.

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