Cardiovascular Evaluation of Renal Transplant Recipients

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Abstract

Cardiovascular disease (CVD) is one of the major causes of death among renal transplant recipients. Moreover, several prospective studies among renal transplant recipients showed that increased incidence of CVD is still present after transplantation. Therefore, evaluation for the presence of CVD before transplantation is strongly advised. Although several screening tests are used for the detection of CVD, the relative performance of these tests for coronary artery disease (CAD) is uncertain. This review discusses the definition, risk factors, epidemiology, and the most used screening tests that might help cardiologists in providing information about the diagnosis and risk stratification before renal transplantation.

Introduction

Cardiovascular disease (CVD) is one of the major causes of death among patients with chronic kidney disease (CKD). Moreover, CKD is a major and serious risk factor for CVD and recurrent cardiovascular events [1,2]. The mortality from CVD in patients with end-stage renal disease (ESRD) is 10-30 times higher when compared with general population [1]. Therefore, renal transplantation is the treatment of choice for many patients in this group [1]. However, several prospective studies among renal transplant recipients demonstrated that increased incidence of CVD are still present after transplantation [3-6]. Traditional risk factors such as hypertension (HT), diabetes mellitus (DM), hyperlipidemia (HL), and non-traditional risk factors such as anemia, hyperhomocysteinemia, inflammatory state, impaired coagulation and increased oxidative stress are well-recognized risk factors for the development of cardiovascular complications after renal transplantation [7]. Given the significant morbidity and mortality of CVD in renal transplant recipients, aggressive risk management before and after transplantation and screening for coronary artery disease (CAD) are strongly advocated. However, the relative performance of different screening tests for CAD is uncertain [7,8]. In this review, definition, risk factors, epidemiology and screening for CVD before kidney transplantation is discussed.

Definition and Risk Factors

An appropriate renal transplant recipient is defined as "a patient whose survival and quality of life are expected to improve with transplantation as compared to remaining on dialysis" [9]. However, there is no accurately and reliably clinical criteria to predict this. Therefore, it is logical to choose the appropriate candidate with reasonable long term prognosis [9]. CAD is one of the major disease entity with high prevalence in patients with CKD. However, CAD is not synonymous with CVD. Heart failure (HF), CAD, cerebrovascular disease (CVD), and peripheral artery disease (PAD) are the spectrum of CVD. Moreover, left ventricular (LV) hypertrophy, cardiac valvular disease especially calcific aortic and mitral valve disease may be present in a renal transplant recipient. Additionally, same patient may have multiple coexistent CVD conditions [10].

Despite traditional risk factors as identified by the Framingham study such as DM, HT, HL, age, gender and smoking non-traditional risk factors such as abnormal calcium-phosphate metabolism, hyperparathyroidism, hyperhomosysteinemia, anemia, and increased pro-inflammatory cytokines have been associated with CVD in patients with ESRD [11]. Immunosuppression, cyclosporine vascular toxicity, graft rejection, viral infections such as cytomegalovirus and risk factors related to chronic loss of graft function such as anemia and volume overload are also associated with increased burden of CVD [12].

Although the mechanism in which hyperparathyroidism causes atherosclerosis is unclear, growth factor effects of secondary hyperparathyroidism and sclerosis of major vessels causing increased afterload and subsequent LV dysfunction are the possible mechanisms [13,14]. Despite the association of abnormal calcium-phosphate metabolism and coronary calcification, data linking coronary calcification and CVD is associative and has not been to be causative [11,15].

There was no clear information about the exact prevalence of risk factors for CVD in patients with ESRD as they were not systematically evaluated due to short duration of follow-up, incomplete characterization of the type of CVD, inconsistent reporting, and different definitions [11]. The prevalence of HT and LV hypertrophy was reported to be 87-90% depending on the definitions used in different series. Moreover, the prevalence of HT and LV hypertrophy increase parallel to stages of CKD, reaching 75% at the time of dialysis initiation [11].

About 20% of CKD patients had worsening of HF or anginal symptoms due to the changes in cardiac functions which were most likely caused by preexisting CVD [11]. On the other hand, at least 35% of patients with CKD were reported to have an ischemic event and 30-40% of all patients seen by nephrologists had a history of ischemic heart disease [11]. Although ischemic heart disease and HF share several risk factors in common, older age, lower diastolic blood

pressure, higher triglycerides were reported to be predictors of NYHA class HF change, whereas baseline kidney function, DM, lower diastolic blood pressure, and baseline CVD were reported to be predictors of CCS class angina [16].

Epidemiology

The incidence of CVD among renal transplant recipients was reported to be increased three to fourfold compared with control population [12]. In a retrospective cohort of 1021 renal transplant recipients, documented history of ischemic heart disease and HF were reported to be 10% and 11%, respectively, whereas history of both disorders was detected as 2%. After the first post-transplant year, the incidence of *de novo* major ischemic event was 1.2 events/100 patient-years, similar to the incidence observed in general population. On the other hand, the incidence of *de novo* HF was again 1.2 events/100 patient-years, the same as *de novo* ischemic heart disease in post-transplant patients but two-to threefold higher incidence observed in general population [17]. In multivariate analysis age, DM, anemia, elevated systolic blood pressure, low serum albumin, and cadaveric donation were found to be independent risk factors for *de novo* HF, whereas age, gender, DM, allograft rejection were significant predictors of *de novo* ischemic heart disease. Acute rejection episodes were associated with increased risk of ischemic heart disease. Additionally, only 30% of *de novo* HF events were associated with a *de novo* ischemic heart event suggesting that these clinical syndromes are etiologically distinct and HF is more often due to an overload cardiomyopathy from HT and anemia [12,17].

It was reported by Gowdak et al. that in high-risk renal transplant recipients, the incidence of cardiovascular events was 30.1% in the overall population [18]. In patients with significant CAD (defined as coronary stenosis ≥ 70% at least one coronary artery), the incidence of cardiovascular events was 45.2%, whereas it was only 18.1% in those without significant CAD. This finding suggested that significant CAD was a predictor of future cardiovascular events [18]. In another study, post-transplantation cardiac events and survival were reported to be 31.3% and 82.8% in high-risk patients, whereas it was 6.5% and 93.1% in low risk patients [19]. However, the study by Gowdak et al. showed that in the overall population for each 100 CAG performed, there would be 55 patients with no significant CAD and 10 cardiovascular events associated with it [18]. Another important finding of this study was DM, and clinical evidence of cardiac or extra cardiac atherosclerosis (PAD, previous myocardial infarction) were independently associated with angiographically proven CAD reaching a 33% increase in the probability of detection of CAD [18].

Evaluation

The optimal method of pre-transplant screening for CVD, particularly CAD, is not known. Imaging modalities of transplant centers vary from non-invasive, easy predictable cardiac stress testings to more invasive testing such as coronary angiography (CAG). Screening for CVD before transplantation is needed to guide pre-transplant management in order to maximize the post-transplant success (survival and allograft success) and to inform the transplant candidate and the surgeon about the risk for a cardiac event before and after the transplantation as cardiovascular events tend to occur during the first few months of a transplant [10,20,21].

Patients at high risk for post-transplant cardiovascular events are defined as: DM, male>45 years, female>55 years, previous ischemic heart disease, abnormal baseline electrocardiography (ECG), echocardiographic evidence of LV dysfunction, smokers, duration of dialysis>2 years [22]. 2001 American Society of Transplantation guidelines defines high-risk for CAD and referred for detailed cardiac evaluation of renal transplant candidates as: patients with DM, prior history of ischemic heart disease, an abnormal ECG, or age>50 years [23]. Recently, 2012 American Heart Association Scientific Statement recommends noninvasive stress testing in renal transplant candidates with no active cardiac conditions on the basis of the presence of at least 3 CAD risk factors regardless of functional status:

- Patients with DM,
- Prior cardiovascular disease,
- >1 yr on dialysis,
- Presence of LV hypertrophy,
- Age>60 years,
- Smoking,
- Hypertension,
- Dyslipidemia with a Class IIb indication and a level evidence of C [24]. For symptomatic patients screening should include CAG, whereas for asymptomatic patients screening should start with non-invasive tests. Screening asymptomatic patients for CAD is valuable if screening is cost-effective and the benefits of screening out weights the harms and the results of the tests lead to management changes [24]. The frequency of using methods for screening CAD with pharmacological-nuclear, exercise nuclear, DSE, CAG were 40%, 33%, 31% and 15%, respectively [24].

History and physical examination

The optimal modality to predict cardiovascular risk in renal transplant recipients is unclear. In patients with ESRD, traditional Framingham risk factors are predictive of CAD although there is a tendency for the Framingham risk score to underestimate the risk in a transplant candidate, especially in patients with DM. On the other side, Framingham risk score may be informative to clinically establish both pre-and post-transplant management [10,22].

It is difficult to determine the functional status of renal transplant recipients as they have limited exercise capacity. Their musculoskeletal system impair mobility and they avoid exercise long enough to provake chest pain or shortness of breath and give clinician a negative history. Still, patients who have ability to walk four blocks and climb two flights of stairs are considered to have good exercise tolerance for pre-operative cardiac fitness [10]. Shortness of breath is more common then chest pain in patient's history at the time of presentation with ischemic heart disease [24]. However, the differential diagnosis for patients with CKD who presented with dyspnea is complicated as this symptom may also be due to volume overload, anemia, valvular heart disease, arrthymia or combinations of these factors [24]. Prior history of endocarditis, unexplained recurrent hypotension on hemodialysis, palpitation, jugular venous congestion, hepatomegaly, peripheral edema, displacement of cardiac apex, wide pulse pressure, claudication raises suspicion of underlying CVD [10,22].

Electrocardiography (ECG)

Resting ECG is a non-invasive, simple, widely used test to screen preexisting CAD in all patient populations. Although it is insufficient for the definite diagnosis of CAD, it may guide the cardiologist to perform other screening tests. LV by voltage criteria, pathological Q

waves, ST segment depression or elevation>1 mm, T wave inversion, bundle branch block may be signs of underlying CVD [25]. Supraventricular arrhythmias, particularly atrial flutter and atrial fibrillation are common rhythm disorders in patients with ESRD. It is recommended to obtain a resting ECG annually and especially within 30 days of transplantation in a transplant recipient in order to detect evolving new abnormalities [10].

Dimensional transthoracic echocardiography (2D TTE)

2D TTE is the first step non-invasive method to detect the type of cardiac disease. Although it is insufficient to use as a screening test for CAD, increased LV size, decreased LV ejection fraction, resting wall motion abnormalities, reduced coronary sinus flow may indicate underlying CAD [10]. Moreover, it is a useful diagnostic tool for the differential diagnosis of dyspnea as this may be caused by volume overload, HF, or ischemia in patients with CKD [26]. Therefore, it is recommended to obtain resting 2D TTE in all renal transplant recipients only after a dry weight has been achieved (1-3 months of dialysis initiation) [10]. Additionally, valve abnormalities especially aortic and mitral valve calcification and stenosis, pulmonary artery hypertension can be detected by TTE [10].

Reduced LV ejection fraction is one of the strong independent predictor for cardiovascular mortality. Median survival in patients with LV ejection fraction<40% and higher LV ejection fraction was reported to be 49 months, and 72 months, respectively [27]. In another study, 7 years event free rates from cardiovascular death were 84.2%, 83.7%, 73.6%, 59.4%, and 30.9%, in order of groups with each 10% decrease in LV ejection fraction,respectively [28]. However, LV ejection fraction it is not sensitive to measure contractility by load dependency, operator-dependency (operator's experience) and image quality (acoustic windows). Moreover, LV ejection fraction is not an accurately and reliably measurement to identify mild degrees of systolic dysfunction especially in patients with EF>45% which is common in early CKD stages [26]. Therefore, new echocardiographic techniques such as 2D speckle tracking (angle independent, highly reproducible, minimally affected by intra- and inter-observer variability) and 3D TTE (better reproducibility and accuracy in LV volume estimation compared with 2-dimentional TTE) are evolving [26].

Stress tests

Exercise stress testing: Although exercise ECG testing has greater sensitivity and specificity for CAD in general population, many renal transplant recipients have baseline ST-segment abnormalities making exercise stress testing less accurate for the detection of CAD in this group. Sharma et al. reported that exercise ECG had a 35% sensitivity for CAD in patients with ESRD [25]. The limited functional capacity of renal transplant candidate, failure to achieve target heart rate due to autonomic dysfunction are the other main limitations for exercise stress testing in patients with ESRD.

Dobutamin stress echocardiography (DSE) and Myocardial perfusion studies (MPS): As exercise stress test is not sensitive to detect ischemic heart disease, DSE and MPS have become more commonly used techniques in patients with ESRD in clinical practice. Thallium imaging and non-exercise based stress tests involving dobutamine or dipyridamole are preferable.

The sensitivity of DSE and MPS varies from 0.44 to 0.89 and 0.29 to 0.92 whereas the specificity of DSE and MPS varies from 0.71 to 0.94 and 0.67 to 0.89, respectively, depending on the type of stress and the number of coronary stenosis>70% [29-32]. In a meta-analysis of 12 studies involving either thallium-201 MPS or DSE, published in 2003, it was shown that risk of myocardial infarction increased 6 times, and risk of cardiac death increased 4 times in patients with inducible ischemia when compared those without inducible ischemia. Moreover, patients with fixed defects had almost 5 times increased risk of cardiac death [33]. In the same meta-analysis, it was reported that a positive MPS had a significantly greater RR of myocardial infarction [2.73 (95% CI: 1.25-5.97), p=0.01] and cardiac death [2.92 (95% CI: 1.66-5.12), p<0.001] than patients with a negative study. The same study also showed that the sensitivities of a positive MPS for a future myocardial infarction and death were 70% and 80%, respectively [33]. Antihypertensive and anti-anginal agents as well as higher resting blood flow due to higher baseline adenosine levels (especially if dipryradimole is used for MPS as it increases endogenous adenosine levels causing vasodilation and stress to myocardium as a result of challenging the flow reserve) decrease the sensitivity of MPS [10]. Recently, a systematic review showed that based on 19 studies, MPS had predictive value for major adverse cardiac events, on the other hand, based on 11 studies MPS did not have predictive value for all-cause mortality. Moreover, in the same review fixed perfusion defects (which intervention is not usually recommended) also had prognostic value [34]. Another important finding of this review was global ischemia might be due to balancing large vessels or as a result of diffuse microvascular disease especially in patients with DM [34].

Dobutamin stress echocardiography also provides diagnostic and prognostic information in patients with ESRD. It is more specific than MPS as it depends on the provocation of reversible systolic dysfunction due to underlying perfusion abnormality rather than depending on heterogeneity of myocardial blood flow [10,26,35]. Based on the results of Smart et al., that aimed to compare DSE and MPS (dipyridamole sestamibi scintigrapyh) for detecting CAD, both tests were found to be sensitive for the detection of CAD (87% and 80%, respectively) and moderately sensitive for the extent of the disease; however, DSE was found to be more specific (91% *vs.* 73%, p<0.01) [35]. Providing information on resting cardiac functions, and valvular heart disease, avoiding radiation exposure, and being less costly are the other advantages of DSE compared with MPS. Unlike these, dobutamin induced arrhymias especially atrial fibrillation, unable to reach target heart rate, LV hypertrophy and small intracavitary volume limits the utility of DSE.

Previous studies showed that DSE might be useful in predicting prognosis in patients with CKD and renal transplantation recipients [36-40]. The largest study evaluating the prognostic value of DSE was among 485 patients with CKD in a study of Bergeron et al. According to the data of this study, both ECG and echocardiographic evidence of stress-induced ischemia and the percentage of ischemic segments during DSE were strong independent predictors of mortality, even in patients who subsequently underwent renal transplantation [41]. On the other hand, although negative DSE results were associated with low incidence of major adverse cardiac events, mortality rate was still high which might be due to high-risk characteristics of the study population or failure to achieve target heart rate (33% of the patients) resulting false-negative test result [41]. The positive and negative predictive values of DSE to detect significant CAD in renal transplantation recipients were reported to be 86% and 95%, respectively [40]. Moreover, in the systematic review by Wang et al. published in 2011, based on 11 DSE studies with 690 renal transplantation recipients, it was reported that DSE had moderate sensitivity of 80% (CI: 64%-90%) in detecting inducible myocardial ischemia [8].

It is a matter of debate which test (DSE or MPS) should be preferred for the detection of CAD in renal transplantation recipients. It generally depends on the experience and preference of the cardiologist and the center. However, DSE is more preferable than MPS especially in patients on waiting list that require repeat assessments.

Coronary angiography (CAG)

Although non-invasive testings are the most common first approach for the evaluation of CAD, CAG is the gold standard test for detecting CAD compared with non-invasive testings. However, it cannot applied to every patient, since it is an invasive, costly, contrast-, radiation-based and somewhat risky examination. Significant stenosis requiring revascularization is defined as a stenosis ≥ 70% based on the practice in general population. The prevalence of CAD documented with CAG in different series was reported to be ranging from 42% to 90%, with a higher prevalence in patients defined as high-risk [24].

It is known that DM, PAD, and previous MI were significantly associated with significant CAD in patients with ESRD [18,42]. Moreover, age>50 years, symptoms related to ischemia, abnormal stress test results, and LV systolic dysfunction raises the probability of CAD [10]. 2001 American Society of Transplantation guidelines recommends CAG for patients with ESRD as:

- Any patient with symptoms of angina, HF, or prior cardiac event (myocardial infarction or revascularization), prior stroke or documented extracardiac atherosclerosis
- DM and any of the following: age>50 years, >20 years duration of diabetes, history of smoking or dyslipidemia or an abnormal electrocardiogram suggesting prior, silent infarction [23].

Although coronary stenosis were the strongest predictor of cardiac events at 48 months (event-free survival 94% in patients without significant CAD *vs.* 54% in patients with critical CAD), it was shown that renal transplantation was associated with better survival regardless of the degree of coronary disease [42,43]. On the other hand, non-significant stenosis may progress while the patient is on the waiting list.

Waiting List

The question arises about the need and optimal frequency for repeat non-invasive testing of patients on the waiting list. Although the ''warranty'' on a normal MPS is at least 2 years in general population, it is recommended to repeat stress testing in patients on waiting list with imaging once a year regardless of symptoms including patients with DM [24]. A screening frequency of every two or three years in non-diabetic patients is suggested by some groups, especially when a scan is normal [10,24]. Periodic screening becomes important especially in patients with known CAD, presentation with acute coronary syndrome, HF, valvular heart disease. In case of acute coronary syndrome leading to loss of myocardial contractility, severe aortic stenosis, HF with a LV ejection fraction of<40% that cannot be improved by revascularization and accumulation of cardiac morbidity over time it may be advisable to suspend the patient from the waiting list [10]. If the patient has a high quality of life on dialysis despite his/her cardiac comorbidities, and the transplantation benefits does not outweigh the harm, this patient may also be removed from the transplant waitlist [10].

Conclusion

The incidence of CVD in patients with ESRD is three-to four times higher than control population. Renal transplantation is a treatment of choice for many patients in this group. Screening for CVD before transplantation is important as it provides important information about the morbidity and mortality of CVD in renal transplant recipients, as well as aggressive risk management before and after transplantation. However, each screening test has its own limitations. Guidelines and studies can serve as useful tools for informing clinician to choose the optimal screening strategy before transplantation. Still, screening strategy in renal transplant recipients generally depends on the experience and preference of the cardiologist and the center.

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