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Preoperative Cardiac Evaluation in Kidney Transplant Patients: Is Coronary Angiography Superior? A Focused Review

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Cardiovascular disease is the major cause of morbidity and mortality in chronic kidney disease patients. Because of a higher occurrence of asymptomatic coronary artery disease and increased perioperative cardiovascular mortality in kidney transplant patients, screening for coronary artery disease before transplant surgery is essential. Various studies have shown that cardiac stress testing is an unreliable screening method in these patients because of significant variability in sensitivity and negative predictive value. We suggest that high-risk candidates such as those with diabetes or a prior history of myocardial infarction, stroke, peripheral vascular disease, or coronary artery disease should perhaps be considered for coronary angiography rather than stress testing as cardiac screening before kidney transplantation.

Key words
Preoperative cardiac evaluation, kidney transplantation, coronary angiography, cardiac stress testing

Introduction

Cardiovascular disease (CVD) is the major cause of morbidity and mortality in chronic kidney disease (CKD) patients. The incidence of CVD is higher by a factor of about 3 – 5 in CKD patients than in the general population (1). Almost half the patients with a creatinine clearance less than 25 mL/min were found to have CVD (2). Cardiovascular mortality remains higher by a factor of 5 in dialysis patients compared with patients having normal kidney function (1). In dialysis patients, cardiovascular mortality 1 and 2 years after an acute myocardial infarction (MI) is 59% and 73% respectively, higher than in individuals with normal kidney function (3).

Apart from coronary artery disease (CAD), other cardiovascular comorbidities such as left ventricular hypertrophy and heart failure are similarly higher among CKD patients. Cardiovascular disease is the most common cause of mortality in kidney transplant patients, accounting for 35% – 50% of all-cause postoperative mortality (4). A prior history of CAD is an independent risk factor for postoperative MI in kidney transplant patients (5). In CKD patients, CAD is often asymptomatic, and such individuals commonly have proximal coronary stenosis, resulting in higher cardiovascular mortality (6).

Because of the higher occurrence of asymptomatic CAD and the increased cardiovascular mortality in kidney transplant patients, screening for CAD before transplant surgery is a common practice. Screening for CAD also helps in the risk stratification of patients before surgery. Screening usually consists of noninvasive testing modalities—such as myocardial perfusion scan (MPS), dobutamine stress echocardiography (DSE), dobutamine stress cardiac magnetic resonance (DSCMR), coronary artery calcium score (CACS), computed tomography coronary angiography (CTA), and exercise electrocardiography (ECG) stress test—or invasive diagnostic methods such as coronary angiography. Almost all of the published guidelines thus far recommend noninvasive cardiac stress testing in kidney transplant patients before surgery if they have multiple cardiac risk factors. The present article compares the diagnostic accuracies of the noninvasive stress tests and coronary angiography in kidney transplant patients; it also discusses the potential benefits of coronary angiography.

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Discussion

Current guidelines for preoperative cardiac screening
For high-risk kidney transplant patients, such as those with prior CAD or diabetes or those with 2 or more traditional cardiovascular risk factors, existing guidelines recommend preoperative noninvasive stress testing (7–12).

A 2012 Scientific Statement from the American Heart Association and the American College of Cardiology (11) recommends consideration of preoperative noninvasive stress testing in kidney transplant patients without any active cardiac conditions, if, regardless of their functional capacity, they have 3 or more CAD risk factors. The pertinent risk factors in transplant patients are prior CVD, diabetes mellitus, left ventricular hypertrophy, more than 1 year on dialysis, age greater than 60 years, hypertension, dyslipidemia, and smoking (class IIb, level of evidence C). That recommendation is modified from the 2007 version for non-cardiac surgery (8), which did not recommend any cardiac testing in patients with good functional capacity (>4 metabolic equivalents).

The 2007 Lisbon Conference report on the care of kidney transplant patients (7) recommends that noninvasive or invasive testing (or both) should be considered in high-risk kidney transplant patients with prior CAD, diabetes mellitus, or any of the cardiac risk factors (for example, more than 1 year on dialysis, age greater than 60 years, left ventricular hypertrophy, hypertension, smoking, and dyslipidemia).

The 2005 guidelines from the National Kidney Foundation and the Kidney Disease Outcomes Quality Initiative (9) recommend noninvasive stress testing in kidney transplant patients every 12 months if they have diabetes or a prior history of CAD with or without prior percutaneous revascularization. In surgically revascularized patients, the first noninvasive cardiac testing can be considered 3 years after the revascularization and every 12 months thereafter. In nondiabetic patients, noninvasive cardiac testing is recommended every 24 months if they have 2 of the more traditional cardiovascular risk factors, a left ventricular ejection fraction below 40%, peripheral vascular disease, or known CAD.

The 2001 guidelines from the American Society of Transplantation (10) recommend noninvasive stress testing for high-risk patients (defined as those having diabetic renal disease, a prior history of ischemic heart disease, or 2 or more traditional cardiac risk factors). The 2000 European best practice guidelines for renal transplantation (12) recommend MPS for high-risk clinical features such as prior MI.

Preoperative noninvasive cardiac testing
Noninvasive cardiac testing is well studied in renal transplant patients (Table I). Although most of the published literature has estimated the diagnostic accuracy of 2 stress testing modalities (DSE or MPS), few studies have assessed the accuracy of DSCMR, CTA, and exercise ECG stress test.

The most-studied preoperative cardiac testing modality in kidney transplant patients is the DSE. Multiple studies of DSE reported significant variability in the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of this test for detecting obstructive CAD in kidney transplant patients. "Obstructive CAD" was defined as stenosis of 70% or more in a major epicardial vessel or 50% or more in the left main coronary artery. In a prospective study by Reis *et al.* (15), DSE demonstrated 95% sensitivity, 86% specificity, 96% PPV, 86% NPV, and 80% diagnostic accuracy for the detection of obstructive CAD. A total of 97 end-stage renal disease patients underwent DSE as part of a preoperative evaluation, with 30 patients subsequently undergoing coronary angiography, and 25 undergoing renal transplantation. During the follow-up period, which ranged between 1 and 24 months, 6 patients died, 4 of whom had inducible ischemia on DSE. Interestingly, 70% of the patients had no cardiovascular symptoms. In two separate prospective studies in U.K. kidney transplant patients, Sharma and colleagues (18,20) reported higher sensitivity and specificity, and a higher NPV, for DSE in identifying obstructive CAD. They also concluded that positive DSE is an independent risk factor for obstructive CAD.

In contrast to the foregoing studies, De Lima *et al.* (17) reported lower sensitivity, specificity, PPV, and NPV for DSE in detecting obstructive CAD (44%, 87%, 72%, and 68% respectively). In that study, 89 renal transplant patients underwent DSE, and the test was positive in 22 (24.7%) and negative in 67 (75.3%). On coronary angiography, 34 of the 89 patients had obstructive CAD (38.2%). The authors concluded that the probability of event-free survival at 48 months postoperatively was 94% in patients with less than 70% coronary stenosis and 54% in patients with 70%

TABLE I Summary of the studies with preoperative noninvasive cardiac testing in patients undergoing kidney transplantation

Reference	*Study type*	*Patients (n)*	*Type of stress test*	*Sensitivity (%)*	*Specificity (%)*	*PPV (%)*	*NPV (%)*
Boudreau *et al.*, 1990 (13)	Prospective	80	MPS	86	79	82	84
Marwick *et al.*, 1990 (14)	Prospective	45	MPS	29	71	31	69
Reis *et al.*, 1995 (15)	Prospective	30	DSE	96	86	96	86
Herzog *et al.*, 1999 (16)	Prospective	50	DSE	75	71	45	90
De Lima *et al.*, 2003 (17)	Prospective	89	DSE	44	87	72	68
		65	MPS	35	76	45	68
Sharma *et al.,* 2005 (18)	Prospective	125	Treadmill exercise ECG stress	36	91	62	79
		125	DSE	88	94	86	95
Ferreira *et al.*, 2007 (19)	Prospective	126	DSE	71	85	63	89
Sharma *et al.*, 2009 (20)	Prospective	140	DSE	90	95	88	96
De Lima *et al.*, 2010 (21)	Prospective	228	MPS	70	74	69	71
Dundon *et al.*, 2015 (22)	Prospective	47	DSCMR imaging	100	89	75	100
Winther *et al.*, 2015 (23)	Prospective	138	CACS	67	77	44	89
		138	CTA	93	63	41	97

PPV = positive predictive value; NPV = negative predictive value; MPS = myocardial perfusion scan; DSE = dobutamine stress echocardiography; ECG = electrocardiography; DSCMR = dobutamine stress cardiac magnetic resonance; CACS = coronary artery calcium score; CTA = computed tomography coronary angiography.

or greater stenosis. De Lima *et al.* (21), Ferreira *et al.* (19), and Herzog *et al.* (16) also described lower sensitivities of 70%, 71%, and 75% respectively for DSE in detecting angiographically significant CAD.

Like the studies investigating DSE, several studies investigating MPS demonstrated high variability in sensitivity, specificity, PPV, and NPV for that technique in diagnosing obstructive CAD in kidney transplant patients. An early study in end-stage renal disease patients by Marwick *et al.* (14) showed that MPS had a sensitivity of 29% and a specificity of 71%, a PPV of 31%, and a NPV of 69% in detecting CAD. Of 49 patients undergoing MPS, 19 (39%) had obstructive CAD, and 14 had a positive MPS, but with 7 of those 14 being false positives. In a more recent study, De Lima *et al.* (17) reached similar results for MPS, with a lower sensitivity of 35% and a lower NPV of 65% in kidney transplant patients. Interestingly, a study conducted by Boudreau *et al.* (13) reported a sensitivity of 86%, a specificity of 79%, and diagnostic accuracy of 83% for the detection of CAD by MPS.

The exercise ECG stress test has also been proved to have a lower sensitivity for diagnosing CAD in transplant patients. Sharma *et al.* (18) reported a sensitivity of 36%, a specificity of 91%, and diagnostic accuracy of 79% for detecting obstructive CAD.

The CACS, which is measured using non-contrast computed tomography, provides an accurate measure of coronary calcification that correlates with obstructive CAD (24). Although a study done by Matsuoka *et al.* (25) suggested that CACS is an independent predictor of mortality in dialysis patients, its accuracy in diagnosing obstructive CAD in dialysis patients is uncertain.

The CTA is an established noninvasive diagnostic test for identifying obstructive CAD. In a meta-analysis of 54 studies, Vanhoenacker *et al.* (26) showed that 64-slice CTA had a sensitivity of 93% and a specificity of 96% in detecting more than 50% coronary stenosis in a non-CKD population. In a recent prospective observational study, Winther *et al.* (23) assessed the diagnostic accuracy of CACS and cardiac CTA as a preoperative cardiac risk evaluation tool in transplant patients. Their 138 kidney-transplant-listed patients underwent a CACS calculation, CTA, coronary angiography, and single-photon-emission computed tomography. The sensitivity and specificity of CACS and CTA were 67% and 77%, and 93% and 63% respectively. Interestingly, when the authors included

MPS with either CACS or cardiac CTA in a hybrid model, the sensitivity decreased, but the specificity increased for both modalities.

More recently, DSCMR has been widely used for detecting obstructive CAD. A prospective study by Dundon *et al.* (22), assessing the diagnostic accuracy of DSCMR in kidney transplant patients, demonstrated a sensitivity of 100%, a specificity of 89%, a PPV of 75%, and a NPV of 100%. Despite the small sample size, the study's results should not be discounted. Further large-scale randomized controlled trials (RCTs) to evaluate the diagnostic role of DSCMR in kidney transplant patients are warranted and could be valuable.

The studies described so far have a wide range of sensitivities and specificities in diagnosing CAD. That range contrasts with the pooled sensitivity of 80% – 90% and specificity of 70% – 80% in the non-CKD population (27). The evidence for stress testing before renal transplantation is therefore equivocal, in part because of the limited accuracy of those tests in CKD patients.

Preoperative coronary angiography and revascularization

Coronary angiography not only detects, but also allows for intervention in obstructive CAD. Data on outcomes of revascularization with respect to postoperative cardiovascular mortality and major cardiac events in kidney transplant patients are limited. In 2004, the Coronary Artery Revascularization Prophylaxis trial was the first large-scale RCT to address preoperative revascularization before a vascular surgery (28). The study's investigators randomized 510 patients (from 18 Veterans Affairs medical centers) who had obstructive CAD in 1 or more major coronary arteries on coronary angiography to either medical management or revascularization. No mortality difference was observed at a median follow-up of 2.7 years, nor MI during the 30-day postoperative period. Based on those results, the investigators concluded that revascularization before elective vascular surgery might not be beneficial in patients without active cardiac symptoms. The DECREASE-V trial, conducted 3 years later, also determined that preoperative coronary revascularization in high-risk patients undergoing major vascular surgery did not result in improved outcomes (29). In contrast, Monaco *et al.* (30) demonstrated in a randomized prospective trial that preoperative coronary revascularization improved long-term outcomes in patients undergoing major vascular surgery. With respect to kidney transplant patients, one RCT and two observational studies showed that preoperative coronary revascularization was associated with less postoperative cardiovascular mortality and fewer major cardiovascular events (31–33).

Thus far, only one small RCT has addressed the management of CAD in kidney transplant patients. Manske *et al.* (33) performed coronary angiography in 151 consecutive asymptomatic diabetic renal transplant patients and identified obstructive CAD in 31. Of those 31 patients, 13 were randomized to medical therapy with aspirin plus a calcium channel blocker, and 13 to bypass surgery or percutaneous angioplasty. Of the 26 randomized patients, 24 (92%) had diabetes. At a median time of 8 months, 10 of the 13 medically treated patients and 2 of the 13 revascularized patients had experienced a cardiovascular event ($p < 0.01$), and 4 medically treated patients had died of MI. The researchers concluded that postoperative major cardiovascular events and cardiovascular mortality was significantly lower in revascularized than in medically treated patients.

In a large, more recent single-center observational study conducted in the United Kingdom over a 3-year period, Kumar *et al.* (31) reported that revascularization was associated with improved postoperative cardiovascular mortality. Their 657 high-risk kidney transplant patients (47.2% with diabetes, 93.2% with hypertension, and 79.1% with hyperlipidemia) underwent pre-transplant screening by coronary angiography. Of those 657 patients, 184 (28.0%) who were found to have significant coronary stenosis [103 (54%) being asymptomatic and 123 (66.8%) being diabetic] were offered revascularization. Of those 184 patients, 16 (8.7%) declined revascularization, and 168 underwent revascularization by either the percutaneous (63.6%) or the surgical (27.7%) method. Survival in the patients who declined revascularization was poor (1- and 3-year survival rates: 75% and 37.1% respectively). Patients who underwent revascularization followed by transplantation had 1- and 3-year cardiac event-free survival rates of 98.0% and 88.4% respectively. Similarly, the 1- and 3-year cardiac event-free survival rates in patients who were revascularized but were waiting on deceased donor transplantation were 94.0% and 90.0% respectively.

Another recent retrospective study by Lindley *et al.* (32) confirmed that stress testing was a poor pre-

dictor of obstructive CAD in high-risk kidney graft recipients and that revascularization could be beneficial. The researchers reviewed the management of obstructive CAD in 685 kidney transplant patients over a period of 7 years. During the study period, 366 patients underwent transplantation. In the transplant cohort, 77 underwent preoperative angiography, 22 were found to have obstructive CAD, and 19 of the latter were revascularized. No cardiovascular events were reported in revascularized patients during the 30-day postoperative period, nor up to 1 year later. Of the 3 patients with obstructive CAD who were not revascularized, 1 died and 1 experienced a MI within the 6-month post-transplantation period. Interestingly, 16 of the 22 patients with obstructive CAD underwent some form of stress test before angiography, and only 2 of them had a positive stress test (sensitivity of 13%). Of the 289 patients who did not undergo angiography before transplantation, MIs were reported in 6 during the 30-day postoperative period. All 6 postoperative patients who experienced MI had a negative stress test before transplantation. In multivariate analysis, a history of vascular disease (prior MI, CAD, cerebrovascular accident, transient ischemic attack, peripheral vascular disease, or revascularization) was the only clinical risk factor associated with obstructive CAD.

Based on the foregoing observational studies, there appears to be a benefit for revascularization in patients with obstructive CAD before renal transplantation (improved cardiac event-free survival and postoperative MI). However, the only randomized trial that was conducted involved the use of calcium channel blockers and aspirin. Medical therapy for the management of stable CAD has undergone significant change, with the use of aspirin, statins, and antianginal therapy (beta-blockers and calcium channel blockers) being the current standard of care. A large RCT implementing the current standard of care, as in the COURAGE trial, should be performed to assess the benefit (or the lack thereof) in this patient population about to undergo kidney transplantation. Percutaneous coronary intervention guided by fractional flow reserve has been shown to be associated with better outcomes in the non-CKD population (34). Ideally, a RCT, if ever conducted, should make use of fractional flow reserve–guided percutaneous coronary intervention to guide revascularization.

Summary

Kidney transplantation improves survival and quality of life in patients with end-stage renal disease. In those patients, cardiovascular-related morbidity and mortality have a significant impact in the postoperative period. Risk factors such as prior MI, stroke, peripheral vascular disease, and diabetes are predictors of obstructive CAD in this group of patients. Revascularization before surgery has been shown to improve major postoperative cardiac events and cardiac mortality. Hence, to reduce postoperative cardiac events, it is important to screen kidney transplant candidates for obstructive CAD. Stress testing seems to be an unreliable method of assessing significant CAD in patients who are undergoing kidney transplantation, because the sensitivity and NPV show significant variability. Coronary angiography and fractional flow reserve–guided percutaneous coronary intervention are valuable in diagnosing and treating obstructive CAD. High-risk candidates—those with diabetes or a prior history of MI, stroke, peripheral vascular disease, or CAD—should perhaps be considered for coronary angiography rather than stress testing as cardiac screening before kidney transplantation.

Disclosures

All the authors declare no financial conflict of interest.

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