Ionizing Radiation During Pretransplant Evaluation: Time to Reconsider the Evaluation Process

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Patients with CKD presenting for evaluation for renal transplant often undergo an extensive pretransplant assessment. The purpose of the evaluation is to detect underlying medical conditions that pose potential perioperative risk to the patient. Although kidney transplant prolongs life expectancy compared with remaining on dialysis, it is an elective surgery. As such, centers often leave no stone unturned when it comes to assessment of risk. Cardiovascular evaluation of potential renal transplant candidates is one of the most controversial topics dominating selection committees. The leading cause of death after transplant is cardiovascular. Diabetes and hypertension are the leading causes of kidney disease, both of which are significant risk factors for cardiovascular disease. In addition, CKD is felt to be an independent risk factor for cardiovascular disease.

In this issue of *CJASN*, Nguyen *et al.* (1) report on their retrospective analysis of radiation exposure to potential renal transplant recipients undergoing evaluation at a single transplant center. Their study included only imaging examinations performed for evaluation for transplant and therefore may underreport the full radiation exposure to patients. Imaging studies ordered by primary care physicians, nephrologists, or other medical subspecialists were not captured. Nuclear medicine studies were the predominant source of radiation exposure, 89.2% of which were nuclear medicine cardiac stress tests. Nearly 30% of patients were exposed to radiation doses considered high (>50–100 mSv) or very high (>100 mSv). An average nuclear medicine perfusion study results in exposure to 41 mSv, whereas coronary arteriography is associated with exposure of 2–30 mSv (2), depending on such factors as procedural complexity, imaging equipment, and operator experience. Routine posteroanterior chest radiography provides an estimated 0.02 mSv of radiation exposure compared with 2–16 mSv for computed tomography, 7 mSv for cardiac catheterization, and 15 mSv for percutaneous intervention (3,4). One must take pause when the average background exposure is 3 mSv per year and the recommended maximum occupational exposure is 20 mSv per year, or 100 mSv over 5 years.

In Nguyen and colleagues' study, factors associated with more exposure to radiation included black race, with an odds ratio (OR) of 3.39; age >40 years, with an OR of 6.97; and diabetes, with an OR of 3.35. In a study by De Mauri and associates, this same pretransplant population was at increased risk for excessive exposure to ionizing radiation during pretransplant evaluation, although in the form of computed tomography (5). The risk factors associated with increased exposure to radiation reflect the population at greater risk for cardiovascular disease.

The real question to address is whether the studies being performed during pretransplant evaluation are providing the information needed to make a decision about the need for intervention. Imaging to ascertain the presence of underlying malignancy is reasonable and not under question. An occult malignancy could become aggressive and more difficult to treat with exposure to immunosuppression. However, the evaluation for asymptomatic coronary artery disease must be reconsidered. Nuclear medicine myocardial perfusion studies are routinely performed to assess ischemic heart disease. The reported sensitivity and specificity of nuclear medicine stress testing for detecting ischemia are 85% and 91%, respectively (6). The ironic point is that the clinical scenario in which nuclear medical myocardial perfusion studies are weakest involves balanced ischemia, where there is no differential perfusion of the myocardium due to diffuse disease.

The transplant community needs to take a step back and seriously consider what the right study is for the given situation. What is the goal when imaging studies are ordered? The DIAD study (7) randomly assigned 1123 patients with type 2 diabetes and no symptoms of ischemia to nuclear medicine myocardial perfusion screening versus no screening and found no difference in outcomes. The Coronary Artery Prophylaxis (CARP) study found no benefit to cardiac revascularization in the absence of three-vessel disease or left main disease (8). The CARP investigators randomly assigned 510 patients to revascularization versus no revascularization before elective major vascular surgery. Three-vessel coronary artery disease, left main disease, or unstable angina warrants revascularization. A study by Friedman *et al.* compared the disparate guidelines put forth by the Kidney Disease Outcomes Quality Initiative and by the American Society of Transplantation, the Lisbon guidelines, and the guidelines of the American College of Cardiology as they apply to renal transplant cardiac risk assessment (9). The

American College of Cardiology guidelines may underestimate cardiovascular risk in this population, whereas the American Society of Transplantation guidelines may subject patients to unnecessary testing.

Options for noninvasive cardiac evaluation without ionizing radiation should be considered. Echocardiographic assessment of ejection fraction correlated well with post-transplant outcomes. de Mattos and colleagues (10) demonstrated a correlation with outcomes. Patients with an ejection fraction of <40% had a worse prognosis after transplant, even in the absence of ischemia. There was a graded reverse-stepped correlation between ejection fraction and mortality. This finding supports the value of noninvasive studies without the use of ionizing radiation. Dobutamine stress echocardiography has been reported to have the best sensitivity and specificity among noninvasive studies in assessing underlying coronary artery disease (11). Positive results on dobutamine stress echocardiography demonstrated an 88% sensitivity and 94% specificity for predicting severe coronary artery disease in renal transplant recipients, values similar if not superior to those seen with nuclear medicine myocardial perfusion studies.

Perioperative cardiovascular risk may be adequately assessed from noninvasive evaluation of a patient's physical functioning status. A recent study by Rosas *et al.* (12) demonstrated that assessment of physical functioning correlates with post-transplant cardiovascular events. A Physical Activity Scale for the Elderly (PASE) questionnaire was used to assess physical activity within 2 weeks of transplantation. Although the PASE was designed for the elderly, this questionnaire has been validated in the chronically ill and nonelderly, the sedentary, and patients with CKD. Lower scores for physical activity were associated with all-cause mortality, as well as death with a functioning graft. These data are consistent with data from other studies that demonstrate a relationship between physical functioning and outcomes after transplant (13,14). However, there is no consensus on what constitutes adequate physical functioning. The 6-minute walk test, sit-stand studies, ability to climb stairs, and maximal oxygen consumption with ambulation have been used to assess physical functioning in patients with CKD. Those with low physical functioning may benefit from an intervention, such as referral to physical therapy or cardiac rehabilitation program.

The concern regarding exposure to ionizing radiation is the potential to increase the risk of malignancy. Patients presenting for evaluation for transplant typically need to wait a specified amount of time if they have had a malignancy before transplant, to assure there is no evidence of recurrence. The risk of malignancy is certainly increased in the renal transplant population; it is estimated to be 2.5–5 times higher than that in the general population. Immunosuppression impairs immune surveillance and increases malignancy risk. The amount of radiation exposure during the pretransplant evaluation may be contributing to post-transplant malignancy risk. In 2010, the U.S. Food and Drug Administration issued an initiative to reduce unnecessary radiation exposure from medical imaging (15). This was borne from the recognition that radiation exposure among the United States population has nearly doubled over two decades. The initiative recommends that the healthcare community develop criteria for use of procedures that expose patients to ionizing radiation in the form of computed tomography, nuclear medicine studies, or fluoroscopy.

In conclusion, the study by Nguyen *et al.* brings attention to one of the most controversial topics in transplantation: How should patients be evaluated for cardiovascular risk? The authors conclude that a less invasive approach to the evaluation of the transplant patient be considered. This echoes the "Call to Action" paper by Friedman and colleagues (9), which highlights the need to reconsider the pretransplant cardiac evaluation of transplant candidates. The transplant community might consider the use of a combination of assessments that involve evaluation of physical functioning and dobutamine stress echocardiography to predict patients at higher perioperative cardiovascular risk. Those patients deemed at high cardiovascular risk on the basis of risk factors, physical functioning, and dobutamine stress echocardiography could then be further evaluated with coronary angiography to assess underlying coronary artery disease. Such an approach may limit unnecessary exposure to ionizing radiation in a population already at an increased risk of malignancy after transplant.

Disclosures

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