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CORONARY ARTERY DISEASE IN KIDNEY TRANSPLANT RECIPIENTS

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ABSTRACT

Coronary artery disease is a common condition among patients with chronic kidney disease, whether they are on dialysis or have received a transplant. It is the leading cause of death and the second leading cause of kidney graft loss in this population. This situation results from the interaction between kidney failure and non-traditional cardiovascular risk factors, such as inflammation, oxidative stress, and abnormalities in calcium-phosphate metabolism, as well as complications related to the graft and immunosuppressive treatments. Currently, there is a lack of specific studies on the diagnosis and treatment of coronary artery disease in kidney transplant recipients, which leads healthcare professionals to use methods suited to the general population, without considering the particularities of transplanted patients. This highlights the importance of conducting further research to better understand the epidemiological, diagnostic, therapeutic, and preventive issues of this disease in these patients.

INTRODUCTION

Kidney transplantation is considered the treatment of choice for end-stage chronic kidney disease, a condition that has been recognized and treated for over 50 years. This surgical procedure involves replacing a failing kidney with a kidney from a donor, whether living or deceased. Chronic kidney disease manifests as a progressive and irreversible decline in kidney function, often due to factors such as hypertension and diabetes.

When kidney function falls below 15 ml/min, it is referred to as end-stage renal failure, requiring either dialysis or transplantation. Transplantation is generally the best option for

improving the quality of life for patients. However, those who receive a transplant must follow immunosuppressive therapy to prevent graft rejection, which can lead to complications, including infections and cardiovascular diseases.

Chronic kidney disease increases the risk of coronary artery disease, and this risk escalates with the progression of the disease and the use of dialysis. This highlights the need for regular screening for heart diseases in these patients. The study focuses on analyzing various aspects of coronary artery disease in patients who have undergone kidney transplantation, relying on clinical cases and literature reviews.

Reminders

Cardiovascular diseases are the leading cause of morbidity and mortality in patients with chronic kidney disease. Even with good control of risk factors such as diabetes and hypertension, the risk of mortality increases as chronic kidney disease (CKD) worsens. When the glomerular filtration rate (GFR) is between 60 and 75 ml/min/1.73 m², the risk of coronary artery disease increases linearly. For patients in stages G3a to G4 (GFR of 15 to 60 ml/min/1.73 m²), the risk of cardiovascular mortality is two to three times higher than in those without chronic kidney disease.

Chronic kidney disease also influences the clinical manifestation of coronary disease. Additionally, patients with chronic kidney disease are more likely to experience a myocardial infarction as the first manifestation of coronary artery disease, often in the form of a non-ST elevation myocardial infarction (NSTEMI). This may indicate an imbalance between blood supply and cardiac needs, as well as a predisposition to left ventricular hypertrophy. As GFR decreases, the prevalence of clinical manifestations of coronary artery disease and associated diseases increases.

Plaque rupture and superficial erosion lead to acute coronary syndrome, but it is unclear how the presence of chronic kidney disease influences each of these anomalies, and the causes and treatments are likely different. In symptomatic patients or asymptomatic potential kidney transplant recipients, functional exercise tests and computed tomography angiography measuring coronary calcium score are used to quantify the extent of atherosclerosis, assess prognosis, and stratify risks for coronary revascularization or optimization of medical treatment.

The choice between medical treatment alone or revascularization (percutaneous coronary intervention or aortocoronary bypass) in symptomatic patients with CKD and/or end-stage renal disease is controversial. In the absence of dedicated clinical trials, patients with chronic kidney disease presenting with STEMI undergo the same invasive approach as those with normal kidney function.

The association between chronic kidney disease and coronary artery disease is primarily due to the high prevalence of traditional and uremia-related risk factors. Management of coronary artery disease in these patients must consider the changes in its clinical presentation, as well as comorbidities and risks of treatment side effects. Although there are opportunities for treatment improvement, the effectiveness of interventions remains uncertain, and KDIGO guidelines provide specific recommendations for kidney transplant recipients and lipid management in chronic kidney disease. However, the treatment of cardiac risk factors is often inadequate, due to limited evidence of effectiveness or extrapolation of data from non-CKD contexts. Further research is needed to better understand the epidemiology, pathophysiology, diagnosis, and treatment of coronary artery disease in chronic kidney disease.

In less than fifty years, kidney transplantation has become the treatment of choice for patients with end-stage chronic kidney disease. Although the quality of life of transplanted patients is recognized as superior to that of patients on dialysis, it took longer to establish that transplantation also improves life expectancy. Kidney transplantation is considered for patients with a life expectancy of less than five years, provided they have no cardiac contraindications, are fit for immunosuppressive treatment, and are committed to transplant preparation, including measures such as smoking cessation and weight control.

Clinical case

Male patient, 43 years old, with cardiovascular risk factors including well-controlled hypertension under ACE inhibitors and thiazide diuretics, and a history of end-stage chronic kidney disease on peritoneal dialysis since 2016 (the initial nephropathy being hereditary segmental and focal hyalinosis followed since 1989) who underwent kidney transplantation in 2023, with post-operative complications marked by hepatic cytolysis likely of drug origin (patient on prednisone, mycophenolate mofetil, and tacrolimus), declared cured pulmonary tuberculosis, and a parathyroidectomy.

The history of his illness dates back to the day of his admission to cardiology in 2023 at 11 AM due to the sudden onset of severe left axillary pain described as tingling without radiation, and without associated dyspnea or palpitations, which prompted an electrocardiogram and biological assessment. Furthermore, the infectious history was negative.

The clinical examination upon admission at 5 PM (6 hours after the presumed onset of pain) found a conscious patient, eupneic, able to tolerate the supine position, with persistent pain in the left axilla rated at 7/10, icteric conjunctivae, blood pressure at 160/100 mmHg, heart rate at 89 beats/min, and SaO₂ at 99% in ambient air.

The cardiovascular examination revealed well-perceived heart sounds without murmurs or added sounds, no signs of right heart failure, and symmetrical peripheral pulses without murmurs. The pleuro-pulmonary examination did not reveal any rales upon auscultation. The rest of the examination was unremarkable.

The ECG performed at 6 hours showed a regular sinus rhythm, ST segment elevation in the septo-apico-lateral and inferior leads with a mirror image in the high lateral lead. The chest X-ray showed a normal-sized cardiac silhouette with free pleural effusions.

The biological assessment showed an initial normal troponin at 30 minutes, a second troponin three times the normal level at 3 hours post-pain onset, hemoglobin at 11.6 g/dl, urea at 0.44 g/l, creatinine at 14.2 mg/l (resulting in an eGFR of 60 ml/min), and hepatic cytolysis with ASAT at 243 (7N) and ALAT at 670 (> 10N).

Echocardiography showed signs of ischemic heart disease with moderate left ventricular dysfunction and an ejection fraction of 45%, with global and segmental kinetic disorders characterized by hypokinesia of the apex and adjacent segments, akinesia of the inferoseptal and inferior walls, and the mid-segment of the anterior wall. The right ventricle was not dilated and had good systolic function.

The patient received a loading dose of PLAVIX 300 mg and KARDEGIC 300 mg, as well as LOVENOX 0.3 cc IV before undergoing coronary angiography and primary angioplasty.

Coronary angiography revealed single-vessel disease with a long, tight thrombotic lesion in the proximal LAD, an occlusion of the distal LAD, and a tight thrombotic lesion in the proximal-mid segment of a large diagonal artery (figure 1).

Primary coronary angioplasty of the tight thrombotic lesion in the proximal LAD was performed after angiography, with direct stenting of the lesion using a BIO Matrix stent 3x29 mm deployed at a pressure of 14 atm, complemented by a post-dilation with a non-compliant balloon of 3.5 x 12 mm inflated to a pressure of 12 atm, resulting in a good immediate angiographic outcome (figure 2).

The evolution in the intensive care unit 10 minutes after transfer from the catheterization room was marked by the onset of chest discomfort followed by cardiac arrest due to reduced ventricular tachycardia after initiating cardiopulmonary resuscitation with a single external shock of 200 joules, resulting in the recovery of a regular rhythm. However, the patient went into asystole after 3 minutes, where cardiopulmonary resuscitation (intubation, adrenaline, external cardiac massage) was resumed for one hour. The patient presented with electromechanical dissociation (no cardiac activity on echocardiography) followed by asystole. He was declared deceased at 9:30 PM.



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Figure 1: Coronary angiography showing a long thrombotic tight lesion in the proximal LAD and a tight thrombotic lesion in the proximal-mid segment of a large diagonal artery.

Figure 2: Angioplasty with direct stenting of the tight thrombotic lesion in the proximal LAD with a good immediate angiographic result.

DISCUSSION

In kidney transplant recipients, coronary artery disease is the leading cause of death and the second leading cause of graft loss. The incidence of coronary artery disease in kidney transplant patients is higher than in the general population, ranging from 5% to 8%, with a cumulative incidence of 1.5% per year. The post-transplantation period carries a high risk of myocardial infarction, particularly during the first year. The immediate postoperative period is associated with significant hemodynamic stress in a pro-inflammatory environment, which can promote the destabilization of atherosclerotic plaques and endothelial dysfunction, leading to myocardial infarction. This period is associated with an exacerbation of factors that contribute to increased shear stress in the coronary arteries, leading not only to plaque rupture and thrombus formation but also to an increased myocardial oxygen demand. Finally, Kasiske showed that myocardial infarctions are more frequent when the kidneys come from deceased donors than from living donors.

Donor/Recipient Selection: Between Living > Deceased, Female > Male: Kidney transplantation from a deceased donor is the most common organ donation procedure. However, brain death is associated with severe hemodynamic disturbances, such as increased blood pressure, decreased cardiac output, and hormonal imbalances that impair tissue perfusion and activate the inflammatory process. The sex of the recipients may also be important: some animal studies have shown increased production of superoxide radicals and a risk of secondary kidney damage related to 17-beta-estradiol levels, which may suggest greater oxidative stress in male recipients.

Current management of kidney transplant recipients requires maintenance immunosuppressive therapy. Immunosuppressive drugs can be divided into several subgroups, and their influence on atherosclerosis includes the following:

- Cytokine production inhibitors involved in cell activation and clonal expansion: Calcineurin inhibitors (cyclosporine A and tacrolimus), the main immunosuppressive drugs, have long-term use that increases the risk of adverse effects such as cardiovascular risk factors, manifesting as hypertension secondary to endothelial damage and dysfunction, causing vasoconstriction and direct vascular toxicity by damaging vascular smooth muscle cells.
- Proliferation signal inhibitors: Mammalian target of rapamycin inhibitors (sirolimus and everolimus) are associated with an increased risk of hyperlipidemia, endothelial

dysfunction, and diabetes, which are known risk factors for atherosclerosis and heart disease.

- Cell division inhibitors: Non-selective (azathioprine) / Selective (mycophenolate mofetil).
- Other medications: Costimulation inhibitor (belatacept), some analyses demonstrate a lower intensity of vascular side effects, marked by a lower incidence of hypertension and other complications. Lymphodepleting therapy (antithymocyte globulin) should be considered in the mechanism of atheromatous lesion formation. Human and chimeric murine anti-CD20 monoclonal antibody (rituximab).
- Screening and Control of Cardiovascular Risk Factors Post-Transplantation: Kidney transplantation is considered the treatment of choice for kidney failure, offering significant benefits in terms of survival and quality of life compared to long-term dialysis. This reduction in mortality is particularly observed in high-risk populations for cardiovascular diseases, such as diabetic, elderly, or obese individuals. However, although transplantation reduces the risk of cardiovascular diseases compared to dialysis, transplant recipients continue to have an increased risk of cardiovascular diseases and death compared to the general population. This risk of cardiovascular death is particularly high, being 50 times greater in patients in their fifth decade of life.
- Blood Pressure Control: The ideal blood pressure target remains unknown, although experts often recommend a BP <130/80 mm Hg. The prevalence of hypertension post-transplantation is 80% to 90%, as observed in a retrospective cohort of 1,666 kidney transplant recipients followed for 5 years. At 1 year, only 4% of recipients had normal BP without any use of antihypertensive medications. In this cohort, hypertension was independently associated with graft failure.
- Diabetes, including Post-Transplant Diabetes: Glucose metabolism abnormalities are common after transplantation in patients without pre-existing diabetes and represent a range of disorders from impaired fasting glucose to impaired glucose tolerance and post-transplant diabetes. Impaired fasting glucose is observed as early as the first week post-transplant in up to 45% of patients, while post-transplant diabetes develops in 16% by 1 year and 24% by 3 years. Treatment strategies for post-transplant diabetes include modifying immunosuppression, lifestyle changes, and antidiabetic medications such as sulfonylureas and meglitinides, with metformin often avoided due to safety concerns, although some encourage its use.

- Smoking: Several studies support an association between tobacco use and worsened graft and patient survival, with higher risks of death related to graft loss and mortality observed. Clearly, smoking cessation should be encouraged before and after transplantation.
- Dyslipidemia: Dyslipidemia is common post-transplantation based on common comorbidities such as obesity, diabetes, and metabolic syndrome. Treatment of dyslipidemia after kidney transplantation is recommended.
- Other so-called non-traditional cardiovascular risk factors to control include obesity, left ventricular hypertrophy, mineral bone disease, oxidative stress, and immunosuppression.
- Coronary Artery Disease in Kidney Transplant Recipients: Kidney transplant recipients represent a high-risk population for coronary artery disease. Coronary artery disease is the most frequent cause of morbidity and mortality in this population. However, little data is available on favorable revascularization strategies for these patients, as they were often excluded from studies and not mentioned in guidelines.

CONCLUSION

Coronary artery disease, primarily an atheromatous and inflammatory cardiovascular disease, is the leading cause of death worldwide. It is associated with several traditional cardiovascular risk factors, such as hypertension, diabetes, smoking, and dyslipidemia. Chronic kidney disease is also considered a risk factor due to its link with these traditional factors and other non-traditional ones related to uremia, such as inflammation and oxidative stress.

Kidney transplantation is the preferred treatment for patients with end-stage chronic kidney disease, improving their quality of life and reducing morbidity and mortality compared to dialysis. However, cardiovascular diseases remain the leading cause of morbidity and mortality among kidney transplant recipients, who have a higher incidence of coronary artery disease than the general population. This is due to the combination of pre-existing risk factors and those related to post-transplantation, such as inflammation, oxidative stress, and the side effects of immunosuppressive treatments.

Currently, there are few studies on coronary artery disease in kidney transplant recipients, and further research is needed to better understand its epidemiology, pathophysiology, diagnosis, treatment, and prevention after transplantation.

Compliance with ethical standards***Disclosure of conflict of interest***

No conflict of interest to be disclosed.

Author contribution

- MB: Study concept, Data collection, Data analysis, writing the paper.
- RL: Study concept, Data collection, Data analysis.
- RF: Study concept, Data analysis, writing the paper.
- NM: Supervision and data validation
- IA: Supervision and data validation
- AB: Supervision and data validation
- All authors reviewed the final manuscript.

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Statement of informed consent

The authors confirm that written consent for the submission and publication of this case, including images, has been obtained from the patients in line with the Committee on Publication Ethics (COPE) guidance.

Availability of Data and Materials

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Consent for publication

Written informed consent was obtained from the patients for publication of this cases report.

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