pISSN 2394-6032 | eISSN 2394-6040

Review Article

DOI: https://dx.doi.org/10.18203/2394-6040.ijcmph20212342

Common complications post-kidney transplantation: a literature review

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Received: 31 May 2021 Accepted: 07 June 2021

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ABSTRACT

The most efficacious management modality for patients with end-stage renal disease is kidney transplantation. Although dialysis of the conditions and obstacles might be a temporary solution, it has been previously correlated with increased risk of many complications, including mortality and reduced health-related quality of life. In this literature review, the aim to discuss the commonly reported complications of post-kidney transplant, including complications that are usually caused by immune-mediated pathologies and non-immunological. Nevertheless, allograft rejection post-kidney transplant is the most common reported immunological complication following transplantation because it can be acute, subacute, accelerated, or chronic. However, after induction of the immunosuppressive modalities, the rates of graft rejections were significantly reduced but many other drug-related complications and have emerged as posttransplantation DM, malignancies, cardiovascular diseases, and infections. Many risk factors for developing posttransplant DM have been reported in the literature, such as the type of the administered immunosuppressive modality, obesity, ethnicity, hypomagnesemia, cytomegalovirus (CMV), and hepatitis C viral (HCV) infections. Early identification and adjustment of the risk factors for these modalities might be associated with significant improvement in prognostic outcomes. The most commonly diagnosed post-transplant carcinomas, including renal cell carcinoma, squamous cell cancer of the lip and skin, salivary gland cancer, and cholangiocarcinoma. Besides, HCV, CMV, and BK virus were the most commonly reported infections following kidney transplantation.

Keywords: Kidney transplantation, Complications, Mortality, Morbidity, Immunity

INTRODUCTION

The most efficacious management modality for patients with end-stage renal disease is kidney transplantation. Although dialysis of the conditions and obstacles might be a temporary solution, it has been previously correlated with increased risk of many complications, including mortality, and reduced quality of life. 1 Allograft loss has been most commonly caused by graft rejection of the transplanted kidney, which is a common complication for these patients. Graft loss might also be caused by fibrosis, infections, administration of calcineurin inhibitors,

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glomerular diseases, and nephropathy.^{2,3} Other than graft rejections, which are mainly immune-mediated, many other non-immunological complications have also been previously reported following graft rejections and are attributable to many causes.

Within the past 20 years, reports showed that the practice of kidney transplantation has significantly increased and the complications regarding graft rejections have been significantly reduced as a result of the introduction of the recent immunosuppressive modalities, which were meant to reduce the intensity of the immune response towards the transplanted kidney. However, previous investigations have reported that many complications can develop secondary to the administration of some of these drugs which might also be life-threatening. Among the reported complications, cardiovascular diseases and posttransplantation diabetes mellitus (DM), have increased the risk of some malignancies. Also, infections have been reported to be the most common complications.^{4,5} Moreover, many burdens have been associated with the development of such complications, including acute graft rejection, increased costs for healthcare, graft loss, and even mortality.6

In the present study, the aim to review the previously reported common complications following kidney transplantation according to the evidence from the current literature.

METHODOLOGY

A cross-sectional study conducted in the rural field A systematic search was conducted to identify relevant studies in the following databases: PubMed, Medline, Web of Science, Embase, Google Scholar, and Scopus. The following search terms were used "kidney transplantation" or "renal transplantation" and "management" and "complication" or "outcome" and "immunology" or "immunological". The reference lists were manually searched to identify additional relevant studies meeting inclusion criteria. We included any study that reports post kidney transplantation complications. No restrictions were applied.

DISCUSSION

Graft rejections

Allograft rejection post-kidney transplant is the most common reported immunological complication following transplantation because It can be acute, subacute, accelerated, or chronic. The main cause of such events is the direct involvement of humoral immunity as a result of the insufficient intake of immunosuppressing medications. Moreover, previous studies reported that having a history of acute graft losses is a significant predictor for chronic or late graft rejection. Additionally, the prevalence of graft rejection has been previously reported to attribute to around one-fourth for late graft

rejections. 10 Studies have also stated that the pathology that can induce the rejection significantly worsens with time according to long-term follow-up investigations. 11 In addition, microvascular inflammation, arterial wall thickening, remodeling of the peritubular and glomerular capillaries are the main factors that are involved in the pathology of graft rejections. Cell-mediated injury contributes to all of these events as antigen-presenting cells identify and present the donor's kidney cells to the T-cells.8 Then, T-cells pass to the microcirculation of the transplanted kidney and initiate the pathology. Following this step, it has been shown that many inflammatory cytokines have been involved and released, inducing a state of generalized inflammation, and leading to tubulitis. which is the main feature in graft rejection events.¹² Internial fibrosis and significant arterial inflammation might also develop secondary to T-cell involvement, which might be determined by the severity of the case and intensity of the immune response.¹³

Diabetes mellitus

Early investigations described that the risk of developing diabetes mellitus following kidney transplantation could be observed in 50% of the patients that received corticosteroids for immunosuppression.¹⁴ Accordingly, high doses of corticosteroids were no longer administered for immunosuppression following kidney transplantation instead calcineurin inhibitors (CNIs) were indicated. However, the incidence of diabetes did not decrease following the administration of these modalities as they have been expected and previous investigations reported that CNIs, especially tacrolimus are associated with a significant diabetogenic effect.¹⁵ However, with the start of the 20th century, studies have reported that posttransplant DM rates have decreased, which is probably due to the increased rates of successful transplantation with reduced frequencies of corticosteroids and CNIs administration. 15,16 Moreover, the scientific registry of transplant recipients has estimated that the prevalence of post-transplant DM was 12% only in 2016. 16 It is important to be aware of the potential impact of DM and the prognosis on the affected patients, as various investigations have previously reported that pre-and posttransplantation DM can significantly increase the risk of graft rejections, cardiovascular risk, and even mortalit, which indicates the need to adequate conduct early diagnostic approaches.⁶

Many risk factors for developing post-transplant DM have been reported in the literature, including the type of the administered immunosuppressive modality, obesity, ethnicity, hypomagnesemia, cytomegalovirus (CMV), and hepatitis C viral (HCV) infections. Lifestyle modification and adjustment of these risk factors can significantly lower the risk of developing post-transplant DM as previous investigations showed that management of HCV in patients undergoing kidney transplantation has led to a significant reduction in the risk and incidence of post-transplant DM. Nevertheless, basal metabolic index

(BMI) is a significant problem for patients that are indicated with receiving a transplanted kidney, as many transplant centers usually exclude patients that have a BMI above 35-45 kg/m².¹⁹ Therefore, it is essential to modify and manage the modifiable risk factors before the inauguration of kidney transplantation and administration of the immunosuppressive modality.

Although induction of immunosuppression is essential for post-kidney transplant to intervene against acute immune-mediated complications as graft rejections, stopping and inauguration of this strategy should depend on the benefits and harms regarding the transplant procedure and not the risk of developing DM.²⁰ This has been indicated by a previous investigation by Ekberg et al which showed that tacrolimus administration is better than cyclosporine A in the population because the first poses a great potentiality in preventing rejections, although the latter possess a more significant immunosuppressive efficacy.^{21,22}

Risk of cancer

In general, Engels et al previously estimated that a twofold increase in the risk of developing cancer is significantly associated with patients that received any solid organ transplant as compared to other individuals from the general population.²³ Regarding kidney transplantation, previous investigations have demonstrated that post-transplantation infection-related malignancies have been frequently noticed among these patients. 23,24 Moreover, non-infection-related malignancies have also been previously reported in the literature. The most commonly diagnosed post-transplant carcinomas, including renal cell carcinoma, squamous cell cancer of the skin, salivary gland and cancer, cholangiocarcinoma.²³ Studies have also reported that kidney-transplant patients also have a higher risk of developing colorectal and lung cancers than the general population. 23,24 Accordingly, the appropriate early screening for these patients should be adequately conducted to reduce the risk and draft proper management and interventional modalities.

As with the diabetes case, it has also been previously reported that immunosuppression is a significant risk factor for post-transplant malignancies. Squamous cell carcinoma has been previously stated to have a significant correlation with azathioprine administration, while mycophenolate might have a protective effect. 25,26 Controversial findings have been found among the different studies in the literature about the risk of tacrolimus over cyclosporine.^{27,28} Lymphoproliferative disorders have been previously correlated with the administration of belatacept, especially in patients with Epstein bar virus (EBV) seronegativity. 29,30 Non-Hodgkin lymphoma, thyroid, and colorectal cancers have been previously reported to have a significant correlation with alemtuzumab.²⁷ Moreover, melanoma but not lymphoma was also previously reported in correlation with anti-lymphocyte globulin.^{27,31} On the other hand, the study by Hall et al reported that no significant association was found between basiliximab and the risk of developing any type of malignancy.²⁷

The management of post-transplantation malignancies is based on modifying the risk factors. Moreover, previous studies have demonstrated that mammalian targets of rapamycin (mTOR) inhibitors administration, especially everolimus and sirolimus, reduce the proliferation and growth of the underlying malignancies. 32,33 In 2014, a meta-analysis showed that the risk of developing posttransplantation malignancies was significantly reduced after mTOR administration.³⁴ On the other hand, recent investigations reported that the risk was not reduced and further management modalities might be needed. 35,36 Moreover, previous studies reported that administration of mTOR inhibitors immunosuppression post kidney transplant has been previously reported with increased risk of mortality and development of lymphoproliferative disorders.34,37 However, none of these studies have recommended against the administration of these modalities, except in one case where Kaposi sarcoma was suspected.³⁸

Other complications

Earlier studies have previously demonstrated that coronary artery disease (CAD) and atherosclerosis are significantly associated with chronic kidney diseases, and the risk is inversely proportional to the glomerular filtration rate.³⁹ Additionally, It has been previously estimated that the risk can increase up to 58% when end-stage renal disease (ESRD) develops. 40 Although it has been reported that the risk of developing CAD decreases following kidney transplantation, it has been stated that the risk of mortality from CAD events does not, with an estimated 30% rate following kidney transplantation.41 Three years posttransplantation, the incidence of developing myocardial infarction has been estimated to be 11.1%. 42 Accordingly, it has been previously reported that management by screening and justification of the modifiable risk factors should be essentially conducted before proceeding with the process of transplantation.

Some of the reported risk factors in patients with ESRD to develop CAD include having DM, prolonged dialysis for more than one year, hypertension, diabetes, old age, ventricular hypertrophy, and dyslipidemia.⁴¹ Besides, it has been reported that many of these factors can persist following transplantation, and some factors as posttransplantation DM and drug-induced hypertension and dyslipidemia can develop following transplantation.⁴³ Although many approaches and guidelines have been published to direct clinicians about the proper pretransplant screening and post-transplant management of CAD, there are still many controversies about the proper management and every published guideline has been found to have some deficiencies.44 Therefore, future studies might be needed to establish proper guidelines for care management and disease prevention strategies and to

elevate the quality of care for patients that received kidney transplantation.

Infections also constitute a major problem in patients that underwent the kidney transplants and contribute to a total of 13% of deaths from the overall complications following kidney transplantation.⁴⁵ It has been previously reported that infections might occur at three different time intervals.46 At first, it can occur in the first few weeks following transplantation as a surgery-related complication or from the donor. The second and third intervals constitute the first year when immunosuppression therapy has been inaugurated. During this period, mainly opportunistic infections have been observed among these patients. Many infections have been previously reported in the literature; however, the most common ones include HCV, CMV and the BK virus. Although HCV infections are associated with many morbidities as all types of allografts, CV risk, post-transplantation DM, hepatic complications and glomerulonephritis, reports showed that reduced morbidities and risk of mortality have been linked with performing kidney transplantation procedures. 47,48 The management of HCV should be adequately performed to reduce the morbidity and mortality rates and to increase the number of donors, which has significantly decreased as a result of the HCV burden. CMV infection has also been frequently observed following kidney transplantation it might cause active colitis, hepatitis, pneumonitis, retinitis, encephalitis, and indirect effects, leading to graft rejection.46,49 Tubulointerstitial nephritis has been previously reported in 1-10% secondary to BK viral infection in patients that underwent $transplantation. ^{50}\\$

CONCLUSION

In the present review, it has been discussed the common complications that can potentially occur following kidney transplant, including immunological and immunological events. Among the reported immunemediated complications, graft rejections are the most common, which have been a huge burden for the healthcare systems due to the reported increased morbidities and mortality rates. However, after induction of the immunosuppressive modalities, the rates of graft rejections were significantly reduced but many other drugrelated complications also emerged as post-transplantation malignancies, cardiovascular diseases, infections. Early identification and adjustment of the risk factors for these modalities might be associated with significant improvement in prognostic outcomes.

Funding: No funding sources Conflict of interest: None declared Ethical approval: Not required

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Cite this article as: Al-Amri TM, Alharthi YH, Alkhamis AS, Muhaif AIA, Almutairi MA, Mousa NMA, et al. Common complications post-kidney transplantation: a literature review. Int J Community Med Public Health 2021;8:3688-93.