Kidney Transplantation

Chapter 1

Care and Follow-up after Kidney Transplantation

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Primary Care Follow-up: Is there a role for yet another doctor's visit?

Death and survival after transplant

Kidney transplant recipients' survival after transplantation has seen marked improvements in recent years, despite there being increasing numbers of older, frailer recipients with complex comorbidities. Recent 10-year survival rates are approximately 67% for patients transplanted during the 2008-2011 period [1], and in the US as of 2022 there are approximately 250,000 kidney transplant recipients alive with a functioning graft [2]. While previously, attention was focused on standardizing care in the one year after transplant and metrics surrounding 1-year patient and graft survival, interest is now increasingly shifting to care of kidney transplant recipients (KTRs) in the longer term. Who provides this longer-term care is variable, oftentimes a combination of primary care and nephrology. While the Kidney Disease Improving Global Outcomes (KDIGO) guidelines make recommendations for frequency of checking creatinine, blood counts, and other labs after transplant [3], there remains no standardization or recommended practice for frequency of follow-up by primary care providers.

While the most common cause of death with a functioning graft in the 1 year after transplant is by far cardiovascular disease, beyond the first year, cancer becomes the most common cause of death, followed closely by cardiovascular disease [1,4]. In contrast, after graft failure, cardiovascular disease remains the most common cause of death [4]. Infection is the third most common cause of death in KTRs. Therefore, promoting survival in the post-transplant period

must involve attention to these non-renal diseases. It remains unknown whether more consistent care from providers outside of the kidney transplant specialist can improve outcomes, and currently no data exists on the extent to which KTRs utilize primary care in the post-transplant period.

The transplant clinic versus the primary care clinic: contrasts and overlaps

When considering the role of primary care in the post-transplant period, the intense regimen of transplant clinic visits must be considered. KDIGO recommends intervals for monitoring several labs, the most frequent of which is serum creatinine: daily in the week after transplant, then 2-3 times per week for until the end of month 1, then weekly until month 3, then every two weeks until month 6, then monthly until the end of the first year, then every 2-3 months thereafter [3]. In many centers, this becomes the frequency of transplant clinic visits after transplant, consuming much of the patient's time and attention in the post-transplant period.

In our center's experience, the typical transplant clinic visit is usually structured and focused. Although there is some overlap in the typical transplant nephrologist's areas of concern and those of the typical primary care provider (such as graft function, hypertension, diabetes, and dyslipidemias), there remain many aspects of health (such as cancer screening, immunizations, tobacco and alcohol cessation, reproductive health, and mental health) that often cannot be covered in transplant clinic visits. In general, primary care availability is associated with higher rates of adherence to preventive health recommendation such as COVID vaccination [5], and increased life expectancy.[6] Given the high frequency of transplant clinic visits, fitting additional appointments into a patient's busy post-transplant schedule may be challenging early on, but may become more feasible – as well as more important – as months and years pass by post-transplant.

Protocol Biopsies: A necessary intervention or a needless needle stick?

Kidney transplant recipients may experience graft injury from a multitude of different causes, at various time points after transplant, likely contributing, in some cases, to graft failure, and subsequent morbidity and mortality. While few would dispute the necessity of indication biopsies, done when clinical signs of kidney injury occur, protocol biopsies, done at pre-determined intervals regardless of clinical graft function at the time, remain controversial. No strong evidence supports or rejects the use of protocol biopsies for managing graft injuries such as subclinical rejection, calcineurin inhibitor toxicity, chronic allograft injury, or pre-transplant disease recurrence. However, protocol biopsies remain an indispensable component of research studies. The risk and cost of protocol biopsies must also be considered, as well as emerging alternative non-invasive diagnostics.

Subclinical rejection

Subclinical rejection refers to having histologic signs of acute rejection as defined by the Banff classification, without any change in serum creatinine. Subclinical rejection usually occurs within the first year. As no traditional indication for biopsy is present in a patient with subclinical rejection, this entity is therefore by definition found on protocol biopsy. An early trial showed benefit of treating subclinical rejection with steroids in patients on cyclosporine and azathioprine.[7] However, nearly 20 years later, with significant improvement in immunosuppression regimens, a study in the same institution found no benefit of protocol biopsies among patients on tacrolimus and mycophenolate mofetil [8], at 6 months post-transplant. This change is likely due to much lower rates of subclinical rejection on more modern, usually tacrolimus-based, immunosuppression regimens – 4.6% in the 2007 study. Thus, using protocol biopsy to detect and treat subclinical rejection likely remains relevant only for patients who need to be treated with higher-risk regimens.

In fact, protocol biopsies for patients at a higher risk of subclinical rejection may improve outcomes as these patients have a higher likelihood of lower eGFR at 1 year [9], and higher rates of bona fide acute rejection and graft failure in 3 years [10]. Additionally, belatacept is an immunosuppressant with increasing recent popularity due to its superior metabolic side effect profile (see Cardiovascular Health section below) but is associated with higher rates of acute rejection [11]. Patients on belatacept may be a group that could benefit from screening biopsies.

Chronic allograft injury

In the modern era of immunosuppression, acute and subclinical rejection are rarer, and chronic allograft injury (CAI, previously called chronic rejection) and glomerular disease recurrence are now the most common causes of graft failure[12]. CAI appears histologically as interstitial fibrosis with tubular atrophy. Causes are thought to be multifactorial, including from both immunologic and non-immunologic causes [3]. Acute rejection, including subclinical rejection, even if successfully treated, is associated with a high risk of developing CAI [13]. It is unknown whether treating subclinical rejection found on protocol biopsy reduces CAI. No specific treatment exists for CAI currently, representing a need for further research. Newer research methods applied to tissue samples from either indication or protocol biopsies, such as transcriptomics and elucidation of novel biomarkers [14], may eventually identify targetable risk factors for CAI.

Pre-transplant disease recurrence

Recurrence of glomerular diseases after transplant accounts for some 37% of graft failure (Nakivell et al.). At 10 years post-transplant, recurrence occurs among 10% of patients with

IgA nephropathy, 16% of those with membranoproliferative nephropathy, 16% with membranous nephropathy, and 9% with focal segmental glomerulosclerosis [15]. Among these, IgA nephropathy has been found to recur early in allografts without clinical changes [16]. It is unknown whether pre-emptive treatment of this "sub-clinical" early recurrence provides benefit.

Safety, cost, and alternative diagnostics

In general, kidney biopsies are very safe, and transplant biopsies are even more so given the superficial anatomical location of the new graft. One study of 2514 transplant biopsies found a low complication rate of 1.9%, and among protocol biopsies even lower at 0.33%; no transplant loss or death occurred [17. However, biopsies are expensive – as of 2002, the Mayo clinic reported costs of $3000 per biopsy including radiology and pathology evaluations [18]. Given the unclear clinical benefit at this time, institutions may understandably opt not to take on the expense of protocol biopsies. Furthermore, emerging non-invasive diagnostics are now being investigated as an alternative to protocol biopsies for routine monitoring. Examples include novel risk prediction scores [19], biomarkers in blood or urine, blood gene expression profiling, and donor-derived cell-free DNA, among others [20] – however none are yet in routine clinical use.

Varying current practice of surveillance biopsies

The 2009 international KDIGO guidelines made no recommendation for or against protocol biopsies, stating only that more research is needed in this area [3]. The United States-based Kidney Disease Outcomes Quality Initiative (KDOQI) group's commentary on the KDIGO guidelines make no comment on the topic of protocol biopsies [21], and neither does the European Renal Best Practice (ERBP)'s commentary [22]. Meanwhile, the Canadian Society of Transplantation & Canadian Society of Nephrology suggest that protocol biopsies may be worthwhile in specific groups including pediatric recipients or recipients at risk of rejection, such as those with pre-formed donor-specific antibodies, receiving ABO-incompatible transplants, or on immunosuppression minimization protocols [23]. Given the equivocal guidelines, actual practices are, unsurprisingly, inconsistent and variable.

In the US, surveys of transplant centers done from 2017-2021 (with different response rates and different centers included) found that between 39% and 46% of transplant centers use protocol biopsies in at least some patients [24-26]. Protocol biopsy results were used to diagnose subclinical T-cell mediated or antibody-mediated rejection, for which treatments also varied among different centers [24]. In centers that performed protocol biopsies on select patients only, the select patients were those who were at high risk of rejection or were enrolled in research protocols.

Currently, protocol biopsies are not being commonly used to specifically diagnose early

recurrence of pre-transplant kidney disease such as IgA nephropathy or other glomerular diseases, and protocols for immunosuppression withdrawal or immune tolerance remain for the most part in the research stage. Based on the available data, protocol biopsies are best reserved for those at high risk for subclinical acute rejection, and recurrence of native kidney disease. Future research needs to focus on accurately phenotyping recipients who would benefit from protocol biopsies.

Cancer Screening: Known Risk, Unknown Prevention

Malignancy post-transplant: epidemiology and causes

Kidney transplant recipients are at higher risk of developing cancer, and cancer is the most common cause of death with a functioning graft more than 1 year after transplant, narrowly surpassing cardiovascular disease [4]. The relative risk varies for different types of cancer and different geographic areas. In the US, among KTRs in the first 3 years after transplantation, compared to the general population, incidence of kidney cancer is increased approximately 15-fold; Kaposi's sarcoma, non-Hodgkin lymphoma, and nonmelanoma skin cancers, 20-fold; the most common cancers (colon, lung, prostate, and breast) approximately 3-fold [27]. Similar increased incidences were found among KTRs in Canada and the UK for renal cell carcinoma (RCC) and lymphoma, as well as increased risk for lip cancers in Canada [28,29]. In Japan and Korea, >10-fold increase in RCC was also observed among KTRs, as well as increased incidences of skin, breast, cervical, colon, and – not studied in the North American and European cohorts – gastric cancers [30,31].

The causes of such higher rates of malignancy among KTRs is thought to be due to immunocompromise interacting with oncoviruses and oncogenic effects of calcineurin inhibitors (CNIs) [32]. Immunocompromise results in decreased ability to detect and eliminate mutated, malignant cells, as well as decreased ability to respond to vaccinations against oncogenic viruses. CNIs are also thought to have direct oncogenic effects independent of their immunosuppressive effects, such as inhibiting apoptosis and modifying the actions of TGF-beta. Despite this, CNIs currently remain favored given their efficacy at preventing acute rejection. However, for patients with high cancer risk, non-CNI regimens have been considered as a strategy to reduce cancer incidence among KTRs. Mammalian target of rapamycin inhibitors (mTORs) such as sirolimus and everolimus are associated with lower cancer incidence [33,34]; however, they are also associated with increased infections and cardiovascular disease [35]. More recently, belatacept – a fusion protein that blocks CD-28-mediated T-cell co-stimulation – is gaining popularity due to its superior metabolic side effect profile compared to CNIs. However, belatacept is associated with higher rates of post-transplant lymphoproliferative disease (PTLD), especially among patients who are seronegative for Epstein-Barr virus (EBV) [11]. For this reason, in the US, belatacept is currently contraindicated for EBV-negative KTRs.

Malignancy post-transplant: screening and prevention

Despite the increased incidences of various cancers among KTRs and significant resulting morbidity, no clear guidelines for cancer screening specifically for KTRs exist. The 2009 KDIGO guidelines for care of the KTR recommend annual skin examinations; otherwise, only an ungraded recommendation for providing an "individualized screening plan for each KTR" is given. The reasonable default then becomes following evidence-based screening guidelines designed for the general population. Screening guidelines may differ slightly by region. For example, the United States Preventive Task Force presents clear recommendations for colorectal, breast, cervical, and lung cancer screening [36]; Japanese and Korean guidelines made additional recommendations for gastric cancer screening given the high incidence of gastric cancer in East Asia [37]. Such guidelines, of course, cannot address cancers less common in the general population but highly common among KTRs – such as RCC. Currently, no high-quality evidence exists to support RCC screening among KTRs. The 2009 KDIGO guidelines expressed that "a RCT should be performed to assess the benefits and harm of screening vs. no screening for renal cell carcinoma." As of 2023, such a trial has not yet been conducted. Nevertheless, several centers are currently routinely screening for RCC in KTRs without evidence of a mortality benefit [3].

One such center is Osaka University Hospital in Japan. In 1993, the hospital initiated a cancer screening program for KTRs. Screening procedures included annual abdominal CT and ultrasonography, chest CT, neck ultrasonography, gastroscopy, and tumor marker tests, as well as an annual mammography, breast ultrasonography, and Pap test for female patients. Patients also underwent annual skin and lip examinations and received fecal occult blood test (FOBT) and urine cytology every 3–6 months. 20 years after implementing this program, a retrospective chart review compared patients who underwent the screening and patients who did not. Interestingly, non-screened patients were found to have a *higher* risk of being found to have post-transplant malignancy (relative risk 2.3). Of note, however, in this retrospective study, non-screened patients did not undergo the protocolized screening for "various reasons" not specified by the authors, and thus may have significantly different characteristics compared to the screened group. The most common cancers to occur were post-transplant lymphoproliferative disorder, RCC, breast cancer, and gastric cancer. Cancers most detected by screening were RCC, breast cancer, and gastric cancer. Mortality was not reported, however the authors postulate that early detection of these malignancies were beneficial for patients [38].

It is worth noting, however, that earlier detection of a lesion does not necessarily translate to mortality benefit – as in the case of a very slow-growing prostate lesion, or a patient already faces a limited lifespan from other causes – and may result in unnecessary additional procedures and anxiety for the patient. The current evidence is mainly from observational studies and it has yet to prove a mortality benefit from cancer screening for KTRs outside

of existing general population guidelines. Randomized trials are needed in the field of post-transplant cancer screening to help guide recipient care and follow up. Until more evidence is available, given KTRs' undoubtedly higher risk of cancer and resultant mortality, at the very least, general screening guidelines should be vigilantly adhered to.

Immunization: Are we doing a good job at prevention?

Infections are a major cause of mortality after transplant. The risk for different infections varies at different time points after transplant [39], and the incidences of specific infections vary slightly by age group. Some infections that cause significant mortality, such as urinary tract infections and cytomegaloviral infection, are not vaccine preventable. Nonetheless, many infections, such as pneumococcal pneumonia, influenza, and zoster [40], as well as COVID-19, cause significant hospitalization among KTRs and are vaccine-preventable, representing an area of opportunity for improving care.

In general, KTRs have diminished immunological response to vaccines, and live vaccines are considered unsafe [3,41]. Therefore, whenever possible, patients should receive vaccines before transplant and before starting immunosuppression. For vaccinations after transplant, KDIGO and the American Society of Transplantation administering vaccines at least 3 months post-transplant, when lower levels of immunosuppression have been achieved, for optimal immune response – except for the influenza vaccine [3,41].

KTRs' household members and close contacts should be fully vaccinated including with live vaccines. Other than the smallpox vaccine (which experienced a revival during the 2022 monkeypox outbreak) and the oral polio vaccine, all other live vaccines are safe for close contacts to receive and is not transmitted to KTRs [41].

In the context of the COVID-19 pandemic, the efficacy and importance of various COVID vaccines has been well-established and publicized, especially for immunocompromised individuals; as with other immunizations, KTRs have diminished response to the vaccines [42,43] and close contacts should be vaccinated as well.

The remainder of this review will focus on pneumococcal, influenza, and varicella zoster vaccinations for the adult KTR.

Pneumococcal pneumonia

Until recently, the available recommended vaccines against pneumococcal pneumonia included a 13-valent protein-conjugated vaccine (PCV13), and a 23-valent polysaccharide vaccine (PPSV23). In 2021, the FDA approved two new protein-conjugated pneumonia vaccines: PCV15 and PCV20. Currently there is no available data on the clinical efficacy of these new vaccines at preventing infection; their approval was granted after showing a robust sero-

logical immune response [44].

Previous recommendations from the American Society of Transplantation for solid organ recipients were to receive PCV13, followed by 2 separate doses of PPSV23 [41]. Adult KTRs had varying serological response to these pneumococcal vaccines, ranging between nearly no-response to similar levels to controls [45]. With the introduction of PCV15 and PCV20, the US Centers for Disease Control (CDC) recommends the following for adults with immunocompromising conditions: patients who have not received any prior pneumococcal vaccine, can get the PCV20 only, or PCV15 followed by PPSV23; patients who have received part or all of the previously recommended series (PCV13, with or without one of two recommended doses of PPSV23), one additional dose of PCV20 [46]. It remains to be seen whether PCV15 and PCV20 will provide sufficient, or superior, protection for KTRs.

Uptake of the pneumonia vaccine is sub-optimal. A quality improvement initiative at the Children's Hospital of Philadelphia found a baseline pneumonia vaccination rate of 6% among pediatric KTRs, with improvement to 52% after intervention [47]. Rates among adult KTRs are unknown, and if adult vaccination rates are similar to those among the pediatric population, this becomes an additional crucial area to implement change and optimize outcomes for KTRs.

Influenza

In the US, multiple formulations of the influenza vaccine are available, in three general categories: standard dosing, adjuvated (with adjuvant to stimulate enhanced immune response), and booster dosing (containing three or four times the amount of antigen than standard dosing, depending on formulation) [48]. A nasal spray live attenuated vaccine is also available – however as with other live vaccines, should be avoided in KTRs [41,48]. Adjuvated and higher dosing formulations are recommended for all patients ≥65 years old and immunocompromised patients, including KTRs.

Multiple trials have found that influenza vaccines, especially adjuvated and booster formulations, can induce seroprotection among KTRs, albeit at lower rates than among the general population [49,50]. Fewer studies have examined clinical effectiveness. Among patients at a hospital in Okinawa, Japan, during a single flu season, receiving the influenza vaccine did not appear to reduce rates of infection [51]; however, a 5-year prospective study at multiple centers in Canada, the United States, and Spain showed significantly decreased disease severity, as evidenced by decreased rates of pneumonia and ICU admissions [52].

Unlike for other vaccinations, given the seasonality of influenza, KDIGO and the American Society of Transplantation recommend administering the influenza vaccine as early as 1 month after transplantation, if flu season is impending [3,41].

Zoster

The incidence of herpes zoster among KTRs is approximately 8-10x that of the general population [53]. KTRs are additionally at higher risk for developing severe disease manifestations such as disseminated zoster [54]. Seropositivity to varicella zoster, conferred by pre-transplant infection or immunization, can decrease the risk of post-transplant zoster by 3-fold [55].

The live attenuated varicella vaccine (Zostavax) is contraindicated in KTRs due to the concern for the vaccine strain of the virus causing active zoster disease in these immunocompromised patients, though it is safe for non-immunocompromised close contacts [41]. Another vaccine, Shingrix, is a recombinant subunit vaccine, and several trials have demonstrated its safety and immunogenicity among KTRs. One large phase 3 randomized controlled trial included 264 KTRs, among whom those who received the recombinant vaccine had higher cellular and humoral response to viral glycoprotein E, and had no difference in safety adverse events including rejection [56]. In the United States, Shingrix is currently recommended for all adults age >=50 [57], and is easily accessible in most clinics or pharmacies. The clinical efficacy of Shingrix in reducing the incidence or severity of post-transplant zoster infection remains to be evaluated.

Cardiovascular Health: diabetes and more

Epidemiology and risk factors

Cardiovascular disease (CVD) is highly prevalent among KTRs. As of 2018, more than half of all KTRs in the US (53.7%) had CVD, and the most common were coronary artery disease (CAD, 26.1%), peripheral arterial disease (PAD, 21.9%), and heart failure (HF, 18.1%). Valvular heart disease and TIA/stroke were also common (11.6% and 8.8% prevalence, respectively) [58]. Among KTRs, cardiovascular disease accounts for approximately one-third of deaths with functioning graft [1,4]. Clearly, CVD risk mitigation is a crucial area of long-term post-transplant care.

Pre-transplant, many waitlisted candidates already have pre-existing risk factors such as diabetes, hypertension, hyperlipidemia. Additionally, independent of diabetes, hypertension, and dyslipidemia, chronic kidney disease itself promotes the development of CVD, via pathways involving mineral and bone disease abnormalities, anemia, inflammation, and oxidative stress [59]. Post-transplant CVD outcomes are far superior compared to outcomes while on dialysis, but still fall behind those of the general population [58]. Optimal care for KTRs requires aggressive management of diabetes, hypertension, and dyslipidemia, as well as attention to immunosuppression regimens that can exacerbate these conditions.

Immunosuppression and Cardiovascular Disease

The 2009 KDIGO guidelines for long-term maintenance immunosuppression regimens for KTRs recommend a combination that includes, as first-line medications, tacrolimus (a calcineurin inhibitor, CNI) and mycophenolate mofetil (MMF, an antimetabolite), with or without steroids. The guidelines also provide recommendations for switching to a mammalian target of rapamycin inhibitor (mTORi, such as sirolimus) after graft function has stabilized and surgical wounds are healed [3]. While such regimens have proven highly effective at reducing acute rejection, in the longer term, these medications promote the development of CVD.

CNIs are diabetogenic, with tacrolimus being more diabetogenic than cyclosporine [60]. The mechanism of CNI-induced diabetes is thought to be via reversible toxicity to pancreatic beta cells [61]. Sirolimus, an mTORi, also causes a similar toxicity in pancreatic beta cells, and is also diabetogenic, though less so than tacrolimus – however it is associated with higher rejection rates. Additionally, mTORi cause dyslipidemia, via inhibiting lipid storage and promoting lipolysis, resulting in increased low-density lipoproteins and subsequent atherosclerosis [62]. Finally, steroids dose-dependently exacerbate diabetes, dyslipidemia, and hypertension. Hypertension is also associated with CNIs (cyclosporine more than tacrolimus) [3]. Thus, switching among these immunosuppression agents may result in exacerbating one risk factor while mitigating another, and may not change a patient's overall risk for CVD.

Given this, much interest has been paid to the newer agent belatacept – FDA-approved in 2012 – that confers significant CVD benefit. Belatacept blocks T-cell co-stimulation by blocking CD28. Compared to tacrolimus alone, belatacept with or without tacrolimus resulted in lower risk of post-transplant diabetes [63]. Compared to cyclosporine, belatacept was associated with fewer cardiac disorders (2% vs 12%) over 5 years [64]. However, belatacept is also associated with increased acute rejection, and is not recommended for patients who are seronegative for Epstein-Barr virus, for whom belatacept is associated with post-transplant lymphoproliferative disorder [65]. Thus, the choice of immunosuppression regimen is a complex decision that must account for individual risk factors for rejection as well as cardiovascular and other diseases.

Diabetes, old and new

Both pre-existing and new-onset diabetes are prevalent among KTRs, and confer increased risk for developing CVD. Pre-transplant, diabetes mellitus is the most common cause of chronic kidney disease and end stage kidney disease. Meanwhile, new onset diabetes mellitus after transplant (NODAT) occurs in approximately 30% of non-diabetic KTRs [60]. KTRs with NODAT are at a two- to three-fold increased risk of developing CVD and dying from CVD compared with non-diabetic patients [60]. Screening and treatment of NODAT is a crucial part of KTRs' care.

Diabetes is diagnosed by a fasting glucose measurement of ≥126 mg/dL (7.0 mmol/L), random glucose or 2-hour oral glucose tolerance test measurement of ≥200 mg/dL (11.1 mmol/L), or hemoglobin A1c of ≥6.5%. KDIGO guidelines recommend frequent screening for NODAT: weekly for the first 4 weeks, then every 3 months for 1 year, and annually thereafter [3].

Once NODAT is diagnosed, treatment goals are the same as for diabetes in general, targeting a hemoglobin A1c of 7.0% or less. In the general population, intensive glycemic control unequivocally improves microvascular outcomes such as nephropathy and retinopathy, but effect on macrovascular outcomes – including CVD – is controversial. For *newly diagnosed* diabetes in the general population, there is some evidence that intensive glycemic control results in fewer myocardial infarctions and lower all-cause mortality [66]. Among KTRs with NODAT, it is unclear whether glycemic control can improve CVD outcomes. However, the importance of treating NODAT is not disputed to help ameliorate the other comorbidities that can result from uncontrolled hyperglycemia.

Diabetes: diet, exercise, medications

The first line of treatment for diabetes, as well as NODAT, is intensive lifestyle modification, which includes dietary changes and physical exercise. It is often challenging to promote healthful eating patterns and address individual nutrition needs, while still maintaining the joy of eating. Additional challenges may be present depending on local food availability and cultural food preferences. The American Diabetes Association (ADA) recommends that all individuals with diabetes should be offered a referral for individualized nutritional therapy by a registered dietitian who is knowledgeable and skilled in providing diabetes-specific nutritional therapy [67].

The ADA also recommends that patients with diabetes engage in 150 min or more of moderate-to-vigorous intensity aerobic activity per week spread over at least 3 days/week, with no more than 2 consecutive days without activity, as well as 2–3 sessions/week of resistance exercise on non-consecutive days [67]. For many patients, reaching this level of exercise is difficult. Barriers may include work hours, local availability of exercise spaces, and personal habits. Consistent support from providers using intentional techniques such as motivational interviewing may be more effective than simple advice-giving [68]. Physical limitations, such as retinopathy, neuropathy, and peripheral arterial disease may require additional help from experienced physical therapists, and we recommend referral whenever available. Overall, we believe that lifestyle interventions are well-acknowledged to be essential, but challenging for patients to implement, and merit as much time and effort from providers as do pharmacological interventions.

Medications for diabetes require special considerations in the post-transplant context. Among older medications: metformin is contraindicated if serum creatinine ≥ 1.5mg/dL (133

umol/L); sulfonylureas and meglitinides may interact with cyclosporine; dipeptidyl peptidase 4 (DPP4) inhibitors must be dose-adjusted by eGFR. Thiazolidinediones do not require adjustment for eGFR or immunosuppressant medications.[3] Newer medications include sodium glucose transporter 2 (SGLT2) inhibitors (e.g. empagliflozin, dapagliflozin, and canagliflozin) and glucagon-like peptide 1 (GLP1) agonists (e.g. semaglutide and liraglutide). Multiple randomized trials have proven the CVD as well as renal benefits provided by SGLT2 inhibitors among non-KTR patients with diabetes [69-71]. In KTRs, small trials have shown safety [72,73]; larger studies are needed to confirm safety and prove benefit. GLP1 inhibitors have also been shown, for non-KTR patients with diabetes, to provide CVD and renal benefit [74,75]. No studies have yet been conducted among KTRs.

Hypertension

Hypertension is highly prevalent among KTRs, affecting approximately 50-90% of this population [3]. Rising blood pressure also results in rising CVD burden: for each 20mmHg higher systolic pressure, risk of CVD rises by 32% [76]. Given the multiple large studies among the general population showing efficacy of treating hypertension to lower CVD risk, the need to screen for and treat hypertension among KTRs is not disputed. Treatment goals are also extrapolated from large studies in the general population, usually targeting blood pressures of 130/80 or lower.

Causes of hypertension among KTRs include pre-existing hypertension before transplant, as well as post-transplant effect of CNIs, graft dysfunction, or graft vascular compromise. Screening for hypertension should be done via blood pressure measurements taken at every in-person clinic visit, with additional ambulatory blood pressure monitoring to differentiate white coat hypertension from bona fide hypertension [3].

Treatment of hypertension among KTRs begins with the same intensive lifestyle interventions as for diabetes management. Pharmacological treatment may include any class of antihypertensives; first-line treatment usually consists of angiotensin converting enzyme inhibitors or angiotensin receptor blockers, beta blockers, or calcium channel blocker. Notably, dihydropyridine calcium channel blockers increase CNI levels, and thus using these agents requires close monitoring for CNI dose adjustment, ultimately resulting in a dose reduction and subsequent cost saving [3].

Hyperlipidemia

At least 50% of KTRs have hyperlipidemia. Individual risk is heavily influenced by immunosuppressive medications, with corticosteroids, cyclosporin, and mTORi most prone to causing elevated low-density lipoprotein (LDL) cholesterol [3]. Treatment lowers long-term CVD incidence and mortality: in a 5-year trial of fluvastatin for KTRs, initially no effect on

CVD was seen despite lowering of LDL by 32% in the treatment group, but after 2 additional years of follow-up, a 35% relative risk reduction was seen for cardiac death and non-fatal myocardial infarction [77].

KDIGO recommends screening for hyperlipidemia at 2-3 months after transplantation, then at least annually thereafter. Lipid panels should also be checked 2-3 months after any change in treatment that may affect lipid levels, such as initiating a statin or change of immunosuppression.

Treatment goals are extrapolated from general recommendations for those at high risk of CVD, targeting LDL cholesterol of <100 mg/dL, and non-HDL cholesterol of <130 mg/dL. Lifestyle interventions should be emphasized. Statins are safe in KTRs, though they require dose reduction; KDIGO recommends starting at 50% the doses used for the general population, then titrating accordingly. Ezetimibe and PCSK9 inhibitors do not need dose adjustments and are not contraindicated for KTRs, though currently no trials have directly examined these medications' effect on LDL cholesterol levels and CVD incidence or mortality among KTRs.

Obesity

Obesity is prevalent among KTRs, although prevalence and severity may vary based on geographic area. In Australia and New Zealand from 1991-2004, 15% of KTRs were obese at the time of transplant [78]; meanwhile in the United States Renal Data System, among KTRs registered between 1988 and 1997, approximately 40% obese at the time of transplant [79]. Additionally, KTRs tend to gain weight after transplantation, gaining approximately 5-10% of their pre-transplant weight in the first year [80]. Obesity after transplant adversely affects CVD mortality: at one center, with each 5-unit increase in body mass index, the composite incidences of congestive heart failure, atrial fibrillation, and myocardial infarction increased by 25% [81].

While lifestyle modifications are indispensable for the treatment of obesity, pharmacological and surgical treatments provide additional CVD and mortality benefit, and should be offered to KTRs. Treatment of obesity includes lifestyle modification, medications, and bariatric surgery. Orlistat is commonly used to treat obesity in the general population, however there are case reports of orlistat reducing cyclosporine levels [82,83]. GLP-1 agonists are newly being used for treating obesity. The US FDA approved liraglutide in 2014 for treating obesity, followed by semaglutide in 2021 [84], and tirzepatide is on track for approval in 2023 [85]. As with using GLP-1 agonists for diabetes, these medications are not contraindicated in KTRs, though efficacy on weight loss and CVD reduction has yet to be proven for this population. Other GLP-1 agonists are Bariatric surgery can provide mortality benefit for KTRs [86]. The global trend of increasing obesity rates is likely to affect the KTRs population, both as pre-transplant obesity and post-transplant weight gain. Experience with, and data on, treating

obesity in this population will likely become increasingly relevant.

Tobacco

Among kidney transplant candidates, 20-30% smoke, and despite guideline recommendations for smoking cessation prior to transplant, up to 90% of KTRs who smoked prior to transplant continue smoking after transplant [87]. Additionally, 5% of KTRs become new smokers [88]. Smoking among KTRs is linked to not only CVD development, but also malignancies, graft loss, and death [87,88].

KDIGO recommends screening for tobacco use at transplant, then annually. Smoking cessation is difficult and requires longitudinal, multi-modal treatment. Physiological addiction to nicotine, together with psychosocial factors contribute to continued tobacco use. Among the general population, combination of behavioral counselling and pharmacological treatment is more effective than either alone [89]. Among KTRs, nicotine replacement is safe and recommended. Bupropion is an effective pharmacotherapy but may interact with cyclosporine. Varenicline is effective; previously concerns had been raised regarding neuropsychiatric side effects, however a 2016 randomized trial that included 8144 found no increased incidence of such side effects [90]. Although these medications have not been specifically studied in KTRs, their benefits are underscored given the clear harms of continued tobacco use.

In conclusion, management of CVD risk factors is complicated and multifaceted. At the very least, patients should receive consistent longitudinal counseling and monitoring, and many would likely additionally benefit from interdisciplinary treatment to focus on specific disease-modifying risk factors.

Virtual Care: Tech over trek?

During the COVID pandemic, telemedicine expanded rapidly in all areas of healthcare. Within the kidney transplant area, telemedicine was used in both live donor evaluation (a remarkable range of efforts that are unfortunately out of the scope of this review) and recipient follow-up care. For many KTRs, telemedicine was convenient, safer than in-person visits, and did not result in any worse outcomes. However, technical challenges, inequity of access, and impaired rapport-building remain potential barriers.

Feasibility and advantages of telemedicine

In the spring of 2020, as the first wave of the COVID-19 pandemic overtook New York City, many transplant centers implemented telemedicine programs in an effort to minimize in-person contact. At the New York Presbyterian Hospital, in a 1-month period during this time, the kidney transplant center recorded 116 telehealth visits for 108 KTRs.[91] Most of the visits were for routine follow-up (95%), and half were for patients within 1 year of transplant (56%).

As many as 74% of visits included blood pressure measurements, and 59% included blood sugar testing, showing remarkable feasibility for remotely conducting these evaluations.

Elsewhere in the world, telemedicine had been on the map before the COVID-19 pandemic created a particular necessity. At the Royal Melbourne Hospital in Australia, a telemedicine program was implemented in 2017. The program included not only consultation with transplant specialists but also joint visits with local physicians. In the 2 years since its inception, 263 clinical evaluations were conducted remotely, resulting in reductions of over 200,000km in travel distance, 2771 hours of travel time, 51 tonnes CO2 equivalents of greenhouse gas emissions, and approximately AUD $31,000 in fuel savings [92], making an argument for the convenience, environmental advantage, and financial sense of telemedicine.

Clinical outcomes do not seem to differ between patients using telemedicine and patients remaining with in-person visits only [93,94]. In an Australian 2-year prospective case-control study, among KTRs offered telemedicine versus non-telemedicine only, there were no differences in blood pressure or creatinine. Among those offered telemedicine in this study, uptake was as high as 71% of all visits in the first year, dropping to 50% in the second year, and patient satisfaction remained high in both the telemedicine and non-telemedicine groups, again supporting feasibility and high patient acceptance. Furthermore, expanding the use of telemedicine beyond the physician-patient interaction may have additional benefits. In Germany, a randomized controlled trial of a post-transplant telemedical case management program versus standard care resulted in improved adherence (82.6% vs 43.5%), as well as superior quality of life and ability to return to employment [94].

For patients, the improved quality of life was appreciated. In an Australian qualitative study, interviewed KTRs reported feeling that telemedicine was convenient, easy, and efficient, reduced their exposure to risk, minimized work disruptions, and alleviated financial burden. Some patients also felt empowered by the perceived increased responsibility for self-management [95]. Clearly, for some patients, telemedicine can significantly improve the complicated, often burdensome post-transplant healthcare experience.

Disadvantages and limitations of telemedicine

While some patients enjoyed the convenience and independence brought by telemedicine, others had concerns relating to relationship-building and technical challenges. In the Australian qualitative study, patients also reported feeling that telemedicine requires a pre-established rapport with clinicians, and sometimes hampered conversations, especially in a distracting environment. Patients acknowledged that telemedicine may not be the best option for some of their peers, especially those with language barriers or without stable access to technological infrastructure. Some patients reported that the technical difficulties were happening on the clinicians' end [95]. At the New York Presbyterian Hospital as well, 9% of virtual visits

failed due to technical issues, though it was not known whether the problems occurred on the patient or provider end [91].

Telemedicine may not be equally accessible to all patients. In the US, government-insured patients are less likely to use telemedicine [96]. These patients, as compared to those with private insurance, tend to be of lower socioeconomic status. Additionally, approximately one out of five US households are not connected to the internet at home [97]; 15% of US adults do not own a smartphone, and 20% do not own a computer [98]. This population is likely to be more remote, and of lower socioeconomic status – an important population that may stand to benefit significantly from the convenience and savings of telemedicine.

Given the density of follow-up visits after transplant, telemedicine will likely, for suitable KTRs, provide much-needed convenience and autonomy. Telemedicine may be best suited to patients who have already established a trusted rapport with their providers and are sufficiently technologically proficient or have proficient caretakers. Additionally, accessing telemedicine requires reliable basic infrastructure such as internet and a computer or smartphone, which, ironically, may not be available for the most remote of patients, who face the most difficulty travelling to an in-person visit.

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