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COMMENTARY

Identifying Drivers of Poor Kidney Transplant Outcomes in Indigenous Populations

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The importance of social determinants in conjunction with the intractable effects of implicit bias and structural racism can scarcely be overstated regarding health outcomes, including kidney-related health.[1,2] In the setting of kidney transplantation in particular, the indefensible fact that Indigenous populations experience worse access and outcomes compared with non-Indigenous groups has been well documented.[3–6] With the ultimate goal of addressing structural drivers of disproportionate kidney transplant outcomes, it is important to identify potentially modifiable mechanisms or clinical mediators on which transplant providers and patients can focus their collective attention and efforts. In this issue of *KI Reports*, Zheng *et al*.[7] report findings from a well-designed Australia and New Zealand Dialysis and Transplant registry analysis. The investigators specifically assessed acute rejection as one of the potential proximal clinical mediators of the known associations between Indigenous Australian (Aboriginal and Torres Strait Islander peoples) status and worse kidney transplant outcomes.

Of the nearly 10,000 first-time kidney recipients who underwent transplantation between 2005 and 2018 and were included in the analysis, 4% were Indigenous Australians by self-report. The investigators confirmed that Indigenous status was significantly and independently associated with higher risk of overall graft loss, all-cause death, and infection-related death with adjusted hazard ratios of 2.27, 2.36, and 3.01, respectively. Acute rejection was also independently associated with these subsequent outcomes with adjusted hazard ratios of 1.72, 1.21, and 1.36, respectively. Using mediation analyses, they then determined that approximately 10% of the effect of Indigenous status on overall graft loss was mediated or explained by acute rejection. The investigators had hypothesized that acute rejection also mediates some proportion of the effect of Indigenous status on all-cause mortality, and especially infection-related recipient mortality; however, their results did not support those hypotheses.

This work competently demonstrates how mediation analysis can be used to assess potential underlying drivers of disparate clinical outcomes between groups. To illustrate this, consider what it could mean if acute rejection were shown to explain 100% of the effect of Indigenous status on overall graft loss (i.e., complete mediation by acute rejection). If true, then the transplant community could theoretically eradicate disproportionate graft losses for Indigenous compared with non-Indigenous people by focusing solely on better treatments or complete avoidance of acute rejection. The key issue is the disproportionate aspect, however.

Continued singular focus on developing broad new therapies or preventative strategies for improving graft survival for all kidney transplant recipients may have the unintended effect of perpetuating or even exacerbating race-based inequities in transplantation. With no concerted attention paid by the wider transplant community to deeper structural drivers of biological and societal disparities, subsequent improvements in transplant care and outcomes will undoubtedly be disproportionately applied and realized according to those deeper structural drivers. One can see similarities between this issue and the recent racial backlash

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sparked by protests against disproportionate policing and use of lethal force by law enforcement in the United States. Many could miss the point by arguing that "all graft survival matters." More individual providers and those in positions of power regarding policy decisions within transplantation need to take dedicated steps to address historic drivers of inequities and show that Indigenous graft lives matter. Until then, we are likely to witness ongoing, unjust imbalances in transplant survival and other outcomes between these marginalized communities and more privileged groups.

One of the possible structural reasons for the increased risk of graft rejection for Indigenous compared with non-Indigenous people involves kidney allocation policies. As noted by these and other investigators, Indigenous groups tend to have human leukocyte antigen profiles that differ substantially from non-Indigenous groups. The vast majority of kidneys available for transplant come from the much larger group of non-Indigenous donors, on average resulting in higher degrees of human leukocyte antigen mismatching for Indigenous kidney recipients and increasing their risk of immunological injury. Beyond the critically important posttransplant outcome of rejection, kidney allocation policies that heavily favor human leukocyte antigen matching in an effort to increase deceased-donor kidney transplant utility unfortunately also contribute to disproportionate transplant access.

This work shines additional light on inequitable access to transplant by revealing that <10% of the Indigenous Australian group received living-donor kidney transplants compared with 35% of the non-Indigenous group. The authors skillfully discuss some of the deeper social determinants of health care access and outcomes in disadvantaged people groups (e.g., increased comorbidities, and thereby higher risk and lower center approvals for living donation for candidates from disadvantaged populations). They also refer the reader to other very important work about promoting cultural safety in health care for Indigenous people with kidney disease.[8]

A central idea of cultural safety is that those in the position of power (health care providers in this context) ensure that Indigenous patients and their support groups feel safe and respected within the health care system as a whole. The unacceptable but all-too-common practice of victim blaming by providers and others within the health care system is one example of why Indigenous peoples may feel disrespected if not unsafe when interacting with the medical establishment. It can be almost second nature for a transplant team to blame the patient for their rejection risk based solely upon assumed degrees of nonadherence to medical therapy or follow-up. Individual providers and teams could make fundamental strides in this regard by considering different approaches to culturally sensitive pretransplantation and posttransplantation care as well as culturally sensitive ways of engaging with Indigenous families and their communities.

Another form of victim blaming in the context of kidney transplantation, which may seem medically justifiable on first impression to some providers and health care teams, is a distorted focus on recipient comorbidities and their associations with posttransplant outcomes. Arguably, few medical comorbidities disproportionally affecting Indigenous peoples compared with non-Indigenous people groups have led to more victim blaming than diabetes. With this unfair historical reality in mind, Zheng *et al*.[7] noted that 47% of the Indigenous Australian group had diabetes compared with only 18% in the non-Indigenous group. The investigators then performed the same type of mediation analysis for diabetes that they did for acute rejection. They found that diabetes mediated (explained) 31% of the effect of Indigenous status on all-cause graft loss. However, unlike rejection, diabetes was also shown to be a significant mediator for all-cause death and infection-related death, explaining 34% and 29% of the effects of Indigenous status on those outcomes, respectively.

Similar to how broadly applying novel therapies to treat rejection would likely fail to address racially or ethnically apparent structural inequities regarding immunological risk, additional noncritically thought-out discussions about known associations between diabetes and poor kidney transplant outcomes will likely not help mitigate these deep-seated disparities. Even worse, unnuanced acknowledgment of diabetes as a mediator of the effects of Indigenous status on poor kidney transplant outcomes could amplify implicit bias by health care teams toward individuals from these populations. Zheng *et al*.[7] are to be commended not only for performing a well-done study but also for their thoughtful discussion and well-referenced and thorough call-to-action for investigating the deeper structural drivers of these inequities and culturally appropriate interventions. Moving forward in this direction, the recently released Caring for Australian and New Zealanders with Renal Impairment recommendations for culturally safe kidney care in First

Nations Australians provide a vitally useful roadmap.[9] Kidney health care providers in other countries should take careful note of these recommendations and specifically partner with their own Indigenous providers, patients, and leaders for individualized implementation in disparate communities throughout the world.

DISCLOSURE

All the authors declared no competing interests.

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