

REVIEW

Racial and ethnic disparities in kidney transplantationSayeed K. Malek,¹ Brandon J. Keys,² Sanjaya Kumar,³ Edgar Milford⁴ and Stefan G. Tullius⁵

1 Division of Transplant Surgery, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

2 Drexel University College of Medicine, Philadelphia, PA, USA

3 Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

4 Division of Nephrology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

5 Division of Transplant Surgery, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

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Correspondence

Sayeed Khan Malek MD, FACS, Division of Transplant Surgery, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115, USA. Tel.: +1 617 7326446; fax: +1 617 5826167; e-mail: smalek@partners.org

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Summary

Success of renal transplantation, as a viable alternative to dialysis, has been tempered by long-standing racial disparities. Ethnic minorities have less access to transplantation, are less likely to be listed for transplantation, and experience a higher rate of graft failure. Reasons for the existing racial disparities at various stages of the transplantation process are complex and multi-factorial. They include a combination of behavioral, social, environmental, and occupational factors, as well as potential intended or unintended discrimination within the healthcare system. Immunologic factors such as human leukocyte antigen matching, composition of the organ donor pool, and patient immune response, all of which affect post-transplantation graft rejection rates and patient survival, also contribute to health disparities between ethnic groups.

Access to kidney transplantation

In the United States, waiting times for kidney transplantation continue to increase, with a nationwide median time to transplant projected to be nearly 4 years for candidates added to the list in 2008, and 6 years for sensitized patients added the same year. Nearly 70% of White patients added to the waiting list in 2001 had received a transplant in 5 years, while only 54% of African Americans and 57.0% of Asians had received a transplant during this time period. The number of patients who die prior to transplant, ranges from 13.7% among Asians to 18.7% among African Americans. Mortality of patients on the waiting list, however, is nearly twice as high in non-White patients as in White patients [1]. In the United States, frequencies of end-stage renal disease (ESRD) are 3.6, 1.8, and 1.4 times higher in African Americans, Native Americans, and Asians

compared to White people. More than 50% of patients on the kidney transplant waiting list in the United States are members of ethnic minorities, and African Americans account for more than 33% of those listed [2,3]. Conditions predisposing patients to renal insufficiency, including diabetes mellitus and hypertension are more prevalent among African Americans suggesting a disproportionately increased need for organs in addition to a potentially inadequate care in the pretransplant stage.

Several reasons are brought forward to explain the lower likelihood of African Americans being placed on the renal transplant waiting list. Previous studies [4,5] have suggested that African Americans are less likely to believe that their quality of life or survival will improve after transplantation. Prior experience with discrimination in the healthcare setting seems also associated with a reluctance to seek a higher level of care. Lower socioeco-

conomic status (SES) and education level have been shown to correlate with delays in renal transplantation, conceivably associated with a lack of awareness of the benefits of transplantation, poor compliance with medications, and inadequate access to medical insurance.

Approximately 700 000 Americans are projected to progress from chronic kidney disease (CKD) to ESRD by 2010, with a risk of ESRD in Black people being almost four times that of White people [6]. Black people have a higher prevalence of diabetes and hypertension, which account for 75% of the new cases of ESRD. Of the 20 million Americans who have CKD, prevalence among Black people, is seven times that of White people, and Black people are diagnosed with CKD on average 7 years earlier, at 57 vs. 64 years of age in White people [7,8]. Low SES, illiteracy, obesity, and insurance status are some of the risk factors linked to disparities in CKD prevalence, and severity [9]. Black people experience higher rates of urban poverty (67% vs. 12% for White people), and 31% of Black people are below the poverty line compared to 11% for White people. In addition, 45% of Black people are uninsured or have minimal public insurance, compared to 22% for White people. They also experience a higher incidence of exposure to environmental toxins associated with elevated risks of hypertension and impaired renal function [6,7,9].

Physician perceptions also contribute to disparities. Ayanian *et al.* surveyed 278 nephrologists of various national backgrounds in four US regions about quality of life and survival for African American and Caucasian patients undergoing renal transplantation. Their results showed that physicians were less likely to believe that transplantation will improve survival in African Americans compared to Caucasians (69% compared to 81%), however, at the same time, they believed that renal transplantation will improve quality of life in a race-independent fashion (84% vs. 86%) [10].

Physicians viewed patient's preferences and the limited availability of living donors as the most important reasons to explain why African American patients are less likely to be evaluated for transplantation. Inadequate communication on treatment options or limited information provided to African Americans may be of importance in this context. Half of the nephrologists surveyed felt that co-morbid illnesses and inability to complete the transplant evaluation process were critical reasons for racial differences in referral rates. Interestingly, this assessment seemed twice as common in Black physicians compared to White physicians. Of note, 12% of patients considered a racial bias as an important reason for a limited access to transplantation [10].

When full disclosure on the options for renal transplantation were provided to Black patients with ESRD, they were significantly less likely to continue with the

necessary steps to proceed with transplantation [11]. Physicians believe that survival rates are not improved for Black patients undergoing renal transplant, as co-morbidities, such as diabetes, hypertension, and obesity are more prevalent in African Americans. Epstein and co-workers found that Black people were less likely to be rated as appropriate candidates for transplantation and were more likely to have incomplete evaluations [9].

Black patients are viewed as being at a higher risk for substance abuse, noncompliance with medical advice, and an insufficient social support [12]. Previous studies had postulated that socioeconomic factors including health care coverage contributed to the unbalanced referral rates and extended wait times for Black Americans. Lack of private insurance is another significant factor in care of transplant patients. In general, patients on Medicare experienced greater impediments to referral and listing for deceased-donor transplantation compared to those with private insurance [13]. The access to transplantation was affected most in racial and ethnic minorities on Medicaid in addition to those with less education and those with fewer financial resources.

Of note, even after adjusting for socioeconomic factors, age, co-morbidities, and financial resources, Black Americans remained less likely to be listed for transplantation and continued to experience consistently longer waiting times [14]. It is well appreciated that there is an impact of race on both waiting list entry and receipt of a kidney transplant. Poverty, which can be geographically concentrated, is also strongly correlated with the access to transplantation. Yet disparities remain, even after accounting for income, health, and functional status and there still remains a large disparity which is unaccounted for by 'proximate causes' [15,19]. Recently, there has been an interest in the substantial variation in transplant center geography as it relates to kidney transplantation and outcome [4,10] both related to the variability in ease of patient access, and the vagaries of shipping donated organs [7,12]. Indeed patients from more rural areas are less likely to be wait-listed and transplanted than those hailing from urban areas [5,11]. It has also become evident that center characteristics intimately associated with geography, are important in the survival of candidates listed for deceased-donor kidney transplantation [2].

Deceased-donor kidney transplant percentages for Black people, Asians, and Hispanics lag behind their respective proportions of the waiting list. Among kidney transplant recipients, White people were transplanted at a rate greater than their representation on the waiting list. This was not the case for Black people, Hispanics, and Asians who were all transplanted at rates lower than expected based on their prevalence on the waiting list [16]. Factors accounting for disparities in transplantation rates after listing include

differences in human leukocyte antigen (HLA) matching. Patient insurance and the Organ Procurement Organization (OPO) where the patient is waitlisted, play an additional role. Even after accounting for these variables there is an 18% lower transplantation rate for Black patients compared to White patients. Black patients are also 70% less likely than White patients to receive a pre-emptive kidney transplant before dialysis or to receive a living donor kidney. The amount of time a potential recipient spends on dialysis adversely affects transplant outcomes. Meier-Kriesche and colleagues analyzed the USRDS data base and found that wait times on dialysis >6 months resulted in a progressive increase in the relative risk (RR) of patient death following transplantation [17]. In general White patients are more likely to receive a pre-emptive kidney transplant and less likely to be exposed to >3 years of dialysis before transplantation. Hepatitis C is associated with an increased RR of graft loss of 1.37 and African Americans are far more likely to be Hepatitis C positive compared to recipients of other ethnic groups [16].

Immunologic aspects: donor/recipient pool HLA – composition and mismatching

African American renal transplant recipients are at increased risk for both acute rejection and chronic allograft failure. Immunologic risk factors contributing to these racial differences include differences in HLA polymorphism, variability in the pharmacokinetics, and dosing of immunosuppressive medications, and differences in immune responsiveness. Eckhoff and colleagues [18] retrospectively analyzed all primary deceased-donor adult renal transplant recipients in a single center report over three eras (1987–1995, 1995–1998, 1998–2004). Analysis included the impact of recipient and donor characteristics, HLA typing, and immunosuppressive regimens on graft outcomes. This study demonstrated that Black recipients had inferior graft survival rates even after normalizing for 20 risk factors. A multivariate analysis showed that HLA matching and sensitization had an impact on the risk for early graft loss. During the later phase, immunologic risk persists (chronic graft failure) but recurrent disease, graft quality, and recipient's co-morbidities played an increasingly important role. The authors concluded that advances in immunosuppressive regimens have contributed to improvement in allograft survival, however, while all racial groups experienced improvement in graft survival, Black patients still lagged behind.

The composition of donor availability and HLA compatibility plays an important role when analyzing racial disparities.

As a consequence of racial and ethnic differences in the frequency of alleles at each locus, White patients are more

likely than those in other racial or ethnic groups to find a beneficial match. Indeed, the effect of HLA matching on kidney allocation contributes to a higher transplant rate among White patients and HLA sensitization negatively impacts African Americans and female recipients of all races. The Organ Procurement and Transplantation Network (OPTN) affected a modification of the kidney allocation policy in 2003 which resulted in improved access to transplantation for African Americans without a significant disadvantage on organ allocation for the general population. The modification in allocation was based on a simulation study which showed that matching for HLA-DR only, while eliminating HLA-B matching in deceased-donor kidney allocation could increase the number of transplants in the disadvantaged non-White population, with only a modest increase in graft loss.

An analysis of various bone marrow registries demonstrated that African Americans are more polymorphic with respect to HLA and consequently less likely to find donors at any given registry size [19]. Clearly, links between race, HLA compatibility, enhanced alloreactivity, and transplant outcomes have not yet been completely elucidated.

Post-transplant outcomes: graft loss and rejection

In a recent review of the OPTN/SRTR database graft outcomes varied by racial/ethnic groups irrespective of donor type, and the differences tended to increase with time after transplantation. Graft survival analyzed at different time points (3 months, 1 year, 5 years, and 10 years), showed that African Americans had the lowest graft survival at each interval [16].

Previous studies have suggested that the immune response of Black Americans is more vigorous, reflected by increased rates for acute rejections and delayed graft function (DGF) [20]. While mechanisms of a more potent immune response in Black transplant recipients are only incompletely understood higher levels of co-stimulatory molecules have been suggested. Non-AB-O antigens on the surface of erythrocytes such as Duffy antigens are present in 65% of Black Americans compared to <1% in White Americans and may help to understand racial differences of the immune response. The Duffy antigen structure is a receptor on red blood cells and binds selected chemokines. It was therefore renamed the Duffy antigen receptor for chemokines (DARC) and has been associated with an anti-inflammatory capacity. A previous study on the relationship of Duffy blood group type to renal allograft outcome concluded that Duffy (a-,b-) patients have lower allograft survival in the presence of DGF [21]. A more recent prospective multi-center cohort study was not able to confirm the increased

susceptibility of African American recipients to acute rejection and to DGF with DARC alleles or genotypes [22].

To examine the influence of race on kidney transplant outcomes within and outside the Department of Veteran Affairs an observational study was carried out in patients who received their transplant care in a universal access-to-care system such as the United States Department of Veteran Affairs (VA). The authors hypothesized that as a result of differences in access to care, including coverage of immunosuppressive medications during the post-transplantation period, racial disparities in outcomes would be less pronounced in recipients with VA coverage. However, data from almost 80 000 renal transplant recipients showed that African American patients were at increased risk of graft failure (RR 1.31 compared to White recipients) suggesting that racial disparities persist even in a universal access-to-care system such as the VA [23].

Racial disparities in Europe, Canada, and Australia

While the majority of studies on racial disparities have been carried out in the United States, few reports from Canada, Europe and Australia are available. The association of race and ethnicity has been studied in almost 1000 Caucasians and 140 African Europeans (AE) renal transplant recipients in France and demonstrated comparable patient, graft survival and acute rejection frequencies. This study suggested that racial disparities observed in the United States may be related not only to race specific immunologic differences, but also to metabolic factors [24].

An analysis of the Canadian Organ Replacement Registry (CORR) on access to transplantation for minority patients with ESRD in Canada demonstrated increasing rates of disparity over time. In this study, a Cox regression model has been used to study transplantation rates among different ethnic groups which included White patients, Black patients, aboriginals, South Asian, and East Indians, over an 8-year period. This study showed that overall transplantation rates were lower for all other ethnic groups in comparison to White patients. Patient race was a significant predictor of access to transplantation and independent of other factors, including age, primary renal diagnosis, and co-morbid conditions [25]. Of note, a more recent analysis of the same data base showed, that even though Black transplant recipients were less likely to receive a kidney transplant, graft, and patient survival were not impacted by race differences [26]. The authors offered three possible reasons to explain their findings:

First, that Black Americans and Black Canadians are biologically different, as a result of historic patterns of migration. Second, relative levels of co-morbidity may differ between the two populations, accounting for differences in outcomes. As an example, a large number of

Black Americans had hypertension listed as their primary renal diagnosis, whereas this was not the case in the Black Canadian dialysis population. However, no direct comparison of American and Canadian data was made in this study. The third, and in the author's opinion, the most likely explanation for their findings was differential access to health care services after transplantation. In the US, costs for immunosuppressive medication are only reimbursed during 3–5 years after transplantation and much of the graft loss occurs when the reimbursement ends. As Black Americans have a higher probability to be socioeconomically disadvantaged, insufficient insurance coverage may contribute to a higher rate of graft loss.

While those conclusions may hold some truth, one has to analyze the limitations of this study acknowledged by the authors themselves. There was a limited availability of clinical variables collected by the CORR such as cold/warm ischemia time and donor characteristics. Ten percent of patients had missing data for race and findings could have been confounded by unmeasured co-morbidity or socioeconomic factors. In addition the number of Black patients in their study has been relatively small (3%).

Studies investigating differences in access to transplant and post-transplant outcomes for ethnic minority patients were also carried out in the United Kingdom and they showed that median waiting times for transplantation were significantly shorter for White patients than that for minority patients. In addition, 3-year transplant survival had been inferior in Black recipients compared to White and Asian recipients [27].

The indigenous Australians make up 2% of the total Australian ESRD population but comprise 6–10% of patients developing ESRD. Data from the Australian and New Zealand Transplant Registry (ANZDATA) demonstrate that ESRD rates among indigenous groups in Australia and New Zealand exceed nonindigenous groups by eightfold and mortality rates across all modalities of renal replacement therapies were reported as 70% higher [28].

Conclusions: potential solutions

Racial disparities in renal transplantation are not a new phenomenon and have been documented in several studies over the past 20 years. Barriers exist at different stages of the transplant process and are responsible for inferior outcomes. Both immunologic and nonimmunologic factors have been identified and include SES and education, geographic location, patient, and physician bias, cultural beliefs, lifestyle choices, and biologic factors. Some of the studies have been performed in the 1990s and may not reflect current findings as many immunologic barriers to successful transplantation in African Americans have been addressed, leading to similar short-term graft survival rates.

However, it is evident that racial disparities still persist, particularly in long-term outcomes after transplantation, as evidenced by recent reports [16,18,29]. Research is required to provide up-to-date and quantitative information which can inform patients, physicians, and policy-makers on modifiable and nonmodifiable factors influencing access to kidney transplantation and survival of grafts and patients. The impact of race, ethnicity, and socioeconomic variables, including income and insurance coverage needs to be analyzed further in prospective cohort studies.

In recent studies it has been suggested that studying disparities in the context of a framework facilitating interventional research may be useful in identifying causal pathways [29,30]. According to this study, most research on transplant disparities have so far been descriptive focusing on identifying risk factors along the pathway from ESRD to transplantation. Future research on understanding the entire transplant process seems crucial as many factors predicting disparities occur early in the causal pathway and may thus have a downstream impact. Social networks have the potential to influence health outcomes and health behaviors and may help, in the context of disparities in transplantation, to analyze why Black patients and White patients seek donation from social contacts at different rates and have different rates of living donation. Indeed, targeting a transplant patient's social support network can increase the number of living donor inquiries, evaluations, and living donor kidney transplants among Black patients [31]. Diversity and cultural awareness of health care providers have a significant impact on the effectiveness of care delivered to minority patients by reducing distrust and improving communication [32,33]. Furthermore, minorities tend to have greater participation in their care when the patient and provider are of the same ethnicity [34]. Educational programs provided to train minority transplant professionals and primary care providers may, thus help to alleviate the problem [35]. In spite of tremendous progress in transplant outcomes over the last decade, racial disparities still persist. The etiology is multi-factorial and complex and a concerted effort is required by physicians, patients, administrators, and policy-makers to improve outcomes and reduce racial disparities.

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