Minding the Missing Link
The Effect of Donor-Recipient Pairing on Kidney Transplant Outcomes

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**Introduction**
Outcomes in kidney transplantation are governed in part by individual donor and recipient characteristics at the time of transplantation. In separate analyses, kidney graft failure has been independently associated with increasing HLA mismatch (MM) (1) and suboptimal pairing of size (2), sex (2,3), race (4,5), and age (6,7) between donors and recipients (Figure 1). The collective effect of suboptimal donor-recipient pairing has only recently garnered attention. Given that optimal pairing of kidney donors and recipients may reduce the risk of kidney allograft failure and need for retransplantation, nonimmunologic donor-recipient pairing (in addition to immunologic pairing) should potentially be considered in future kidney transplant allocation practices.

**Immunologic Donor-Recipient Pairing**
The benefit of zero HLA MM kidneys is widely accepted in terms of better patient and graft survival, with fewer rejection episodes compared with higher degrees of HLA MM (1). Additionally, better HLA-matched kidneys affect the probability of retransplantation. It has been shown that patients might be negatively impacted by suboptimal HLA matching if their first kidney transplant fails, because this may cause increased sensitization and difficulty with finding a suitable subsequent kidney donor. However, not all HLA MM has an equal effect on transplant outcomes, and with the advent and uptake of safer and more potent immunosuppression, the benefit of HLA matching has been questioned. Despite this, many centers continue to prioritize zero HLA MM for kidney transplantation (8).

**Nonimmunologic Donor-Recipient Pairing**
Size MM between kidney donors and recipients has been associated with worse graft outcomes in the setting of a larger recipient than donor. This has been hypothesized to represent nephron underdosing with subsequent hyperfiltration injury and graft compromise when a recipient receives a kidney from a smaller donor (2). The effect of size MM is exaggerated in the setting of concurrent sex MM. When a recipient is >30 kg larger than their donor, the hazard ratios for death-censored graft loss are 1.35 (95% confidence interval, 1.25 to 1.45) for female donors/male recipients (FDMR) and 1.50 (95% confidence interval, 1.32 to 1.70) for male donors/female recipients (MDFR) (2). This is potentially due to compounded nephron underdosing in FDMR given that female kidneys are generally smaller than male kidneys with an average of 12%–17% fewer nephrons. Conversely, the graft loss observed in MDFR is believed to be on the basis of an H-Y minor histocompatibility antigen on the Y chromosome, which leads to increased sensitization and subsequent graft rejection in female recipients of male kidneys (2). However, other sex-based factors are also felt to affect graft survival. These include increased immunogenicity (higher rejection rates) (9) and altered kidney hemodynamics (more nonimmunologic postoperative complications) (10) with female kidneys. Testosterone and androgens have been associated with an increased risk of ischemia-reperfusion injury (10) but a decreased immune response (lower rejection risk) in male recipients (9). Conversely, estrogens in female recipients may reduce ischemic injury at the time of transplant (10), but they are immune enhancing with higher rejection risk (9). Lastly, adherence to immunosuppression (a factor well accepted to preserve graft survival) is believed to be better in female than male transplant recipients.

Graft outcomes related to race pairing are less well established. Although it has been shown that black transplant recipients have the lowest overall graft survival, the physiologic explanation for this is likely multifactorial and is not well defined. White donor/black recipient is associated with an increased risk of graft failure that is believed to represent increased presensitization in the black recipient (5). Additionally, black recipients have been shown to have immunologic hyper-responsiveness compared with white recipients when their cells are exposed to a litany of nonspecific immunologic tests (4). This has been proposed to account in part for the higher rates of acute rejection and reduced graft survival in this population. Additionally, genetic polymorphisms in cytokine production may also play a role in the immune response to mismatched kidneys, with significant differences in cytokine expression noted between black, white, Hispanic, and Asian recipients (4). Another important issue is the increased prevalence of hypertension and
cardiovascular disease in black transplant recipients, which has been shown to have a greater effect on graft survival post-transplant for black recipients than for white recipients (4,5). Other modifiable and important challenges associated with recipient race contributing to poor outcomes include disparities in socioeconomic status, immunosuppression adherence and access to health care/insurance (4). This is controversial, however, because some studies suggest that racial differences in graft survival still persist among cohorts with universal access to health care.

In terms of age matching, it has been proposed that, although transplanting younger donor kidneys into younger recipients may prolong life years of graft survival (better utility), age matching could lead to decreased survival among older recipients who are transplanted with older donor kidneys (less equitability) (6). It has also been suggested, however, that there may not be a disadvantage to transplanting older donors with relatively older kidneys if the donors are not expected to outlive their grafts. Conversely, giving older kidneys to younger recipients, in whom the graft is unlikely to survive the duration of the recipients life, may lead to increased sensitization and need for retransplantation with more strain on the donor pool (6). Additionally, it has been shown that long-term graft survival is reduced for younger recipients of older donor kidneys compared with all other age groups (7). This is believed to represent a heightened immune response in younger recipients and a decreased ability of older, more marginal kidneys to respond to physiologic and pathologic stressors (7).

**Future Directions**

Unlike donor and recipient factors in isolation, the strategic pairing of specific donors with appropriate recipients is a modifiable exposure that affects long-term graft survival and should potentially be considered in kidney transplant allocation programs. Nonimmunologic donor-recipient pairing could be incorporated into an overall kidney allocation strategy, whereby patients deemed to have the best nonimmunologic match are prioritized for transplant (similar to current practices for zero HLA MM). The relative efficacy of immunologic versus nonimmunologic matching should be explored. Certainly, at a minimum, the effects of nonimmunologic matching should be considered when allocating organs, with potential inclusion of liberal absolute thresholds beyond which transplant should be deferred (for example, in a recipient who weighs 50 kg or more than his/her donor). Although nonimmunologic matching has been less rigorously studied in live donation and the results may be attenuated in these relatively better organs, if nonimmunologic matching remains a significant factor, perhaps the same standard should be applied to selecting the most appropriate live donor for a given recipient through the kidney paired donation program.

However, the implications of incorporating nonimmunologic donor-recipient pairing into kidney allocation policies are not straightforward. For example, given the over-representation of older white men in the donor pool, strict donor-recipient pairing might disadvantage certain minority groups (for example, younger nonwhite women). It is important to note, however, that the equitability of prioritizing zero HLA MM kidneys has also been questioned, with white recipients more likely to find a perfect immunologic match in the available donor pool.

**Conclusions**

In light of the mounting evidence that nonimmunologic pairing of kidney donors and recipients plays an important role in graft outcomes, the incorporation of donor-recipient pairing in kidney allocation protocols deserves serious consideration. Regardless of the strategy proposed however, it is imperative that the risks, benefits, utility, and equitability of any changes to current allocation practices be prospectively considered, with a detailed review from both individual and societal perspectives.
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References


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