

Renal transplant outcomes and diabetes

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Designing and performing new trials requires extraordinary expenditures of effort, time and money. Less costly and often surprisingly helpful are efforts to revisit existing databases with current advanced epidemiologic analyses. The subject of kidney transplantation is particularly relevant due to the high cost of chronic dialysis with its accompanying lifestyle impediments indicating the need to identify reasons for slow progress in treating end-stage renal disease (ESRD).

Harding *et al* in this issue of the journal sift through a massive amount of data collected in the United States Renal Data System (USRDS), using statistical equations to analyze relationships between diabetes and both patient and graft survival outcomes after an initial kidney transplant. More than 250 000 new kidney transplant recipients were identified with more than 72 000 subsequent deaths. Outcome data were evaluated for diabetes mellitus as physician-assigned primary cause of ESRD for adults listed in the USRDS between 2000 and 2018, elucidating a contemporary database fraught with limitations, biases and confounders. Admirably, they stay on target, demonstrating that adjusting for the available variables, the presence of diabetes increases the likelihood of adverse outcome. Regardless of the origin of the donor organ, adjusted mortality rates are 75% higher with rates of adjusted graft losses 25% higher in cohorts identified by diagnosis of diabetes in the allograft recipient. For those familiar with kidney transplantation, these findings are not surprising.

How then does this manuscript derive importance enough to merit publication? We would submit that it is the journey through these data that will lead to important observations. Analysis of these data by Harding *et al* elucidates a need to expand data accumulation in persons with diabetes to improve outcome following kidney transplantation. Among these we must note that:

1. There are flaws in the database that require correction in order to explain why the diabetic cohort still does not attain some of

the benefits achieved in the non-diabetic cohort.

- a. Does either duration or severity of glucose intolerance play a role?
 - b. How long were the cohorts exposed to prior forms of renal replacement?
 - c. What is the impact of invasive cardiovascular therapies?
 - d. How much misclassification is prevalent in the USRDS database?
2. The USRDS is a powerful resource that should be mined for additional information that may focus our attention on where we can improve care.
- a. We note an imbalance of care that has led to greater than 60% of initial kidney recipients being male with less than 40% female.
 - b. Mortality being significantly higher in the non-Hispanic white cohort and graft failure being higher within the non-Hispanic black cohort.
 - c. A decrease in age standardized mortality is noted during the last decade. It is unclear whether this is associated with increases body mass index and rising rates of obesity or represents increased susceptibility to infections from current immunomodulation protocols.
 - d. Data are generally unavailable regarding diabetes diagnosed after the transplantation procedure.¹
3. Information regarding underlying disease leading to kidney transplantation is not sufficiently granular. Non-diabetic cohorts are populated by glomerular lesions associated with hypertension with or without unique genetic or immunologic processes. Cohorts with diabetes exhibit higher cardiovascular and immune-deficiency risk than non-diabetic transplant recipient cohorts. Statistical methods that assess associated relationships do not substitute for documentation of pathology indicating cause. Type 1 diabetes is insulinopenic because the immune system destroys beta cells. Is there another process immunologically involved that raises the risk to a



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donated kidney? Type 2 diabetes is associated with insulin resistance followed by insulinopenia. Finding a root cause that can be treated in allograft recipients could increase survival. Future analyses should focus on SGLT-2 inhibition for non-glycemia-related effects on preservation of renal function in the type 2 diabetes population.² Should we be focusing on SGLT-2 inhibition or GLP-1 receptor antagonism for their non-glycemia related and non-diuretic effects in the type 2 diabetic population?³⁻⁷

We hope that the data presented by Harding *et al* will stimulate efforts to improve outcome for persons with ESRD and diabetes mellitus who become candidates for transplantation.

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