Dissecting the Delicate Dynamics of Donation in Dysglycemia

In July 2022, the US Organ Procurement and Transplantation Network (OPTN) published its updated guidelines, which excluded all type 1 and type 2 diabetics with any end-organ damage or with an "unacceptable lifetime risk of complications from donating organs." But did the guidelines really include diabetics, or did they exclude a specific subset of diabetic patients? If so, which ones? The question remains about how one assesses the risk of donation in a dysglycemic patient.

The Conundrum

The challenge of organ shortage and long waitlists forces us to consider expanding the donor pool. People with dysglycemia form an important segment of our population. In 2017, up to 29.1 million people in India were diagnosed with prediabetes, and by the year 2045, this number is expected to increase to about 50 million.[S1] One of the most common reasons for the rejection of a donor is impaired glucose tolerance.[S2]

The diabetic kidney donor falls under the term "medically complex donor." Most kidney donations and studies on donors are from healthy individuals who have no comorbidities. It may be inaccurate to extrapolate data from nonmedically complex donors to medically complex ones. An unaddressed issue concerning donation in these settings is the wish of the kidney donor to donate despite the potential risks involved.

Prediabetes and Kidney Donation

A recent study published by Chandran *et al*. suggested that prediabetic living kidney donors maintain normal kidney function for as long as ten years after donation.[S3] However, prediabetic patients have a seven fold higher risk of developing diabetes over a period of 10 years than patients with normal fasting glucose at the time donation.

We pose the question as to whether we are "medicalizing" large portions of the population whose dysglycemia would spontaneously revert or whether we can use this opportunity to ensure appropriate prevention. To answer this question, we need to consider the natural history of prediabetes. In general, about 50% of prediabetic patients remain dysglycemic while 25% revert to having normal glucose levels.[1] Another subset (25%) progresses to overt diabetes. Risk assessment for the development of prediabetes to diabetes and then diabetes-related chronic kidney disease (CKD) takes 19 years. Prediabetes itself is associated with altered glomerular hemodynamics, proteinuria, and CKD, even without the development of overt diabetes. A systematic review and meta-analysis of the risk of prediabetes and CKD showed that the relative risk of CKD was 1.12 (95% CI 1.02–1.21).[S4] One must remember that these risk estimates do not include the added risks of kidney donation. Donation carries its own risk of mild proteinuria and a decrease in glomerular filtration rate (GFR), usually attenuated by compensatory hyperfiltration by the remaining normal kidney.

The dangers associated with prediabetes extend well beyond the kidney. This fact was highlighted by Khalil *et al*., linking the association of prediabetes with other illnesses such as cerebrovascular accidents, retinopathy, neuropathy, cardiovascular events, dementia, depression, cancer, metabolism-associated liver disease, and all-cause mortality.[2] Prediabetes is often accompanied by obesity and metabolic syndrome, each bringing an additive risk of developing CKD.

Diabetes and Kidney Donation

For over 88 months, Okamoto *et al*. followed up with 27 voluntary kidney donors with well-controlled diabetes.[S5] None of these individuals developed end-stage kidney disease (ESKD). Shinzato *et al*. studied the effects of voluntary kidney donation on 14 diabetic patients who were followed up for 4.3 years.[S6] None of them developed any significant albuminuria or proteinuria.

Ibrahim *et al*. published their seminal work on voluntary kidney donors in 2017, showing that among 4014 kidney donors, about 7.7% developed diabetes at a median of 18 years after donation.[3] Prior to the development of diabetes, both diabetic and nondiabetic donors did not have any significant difference in GFR decline. After diabetes developed, those individuals who had proteinuria and hypertension had a steeper decline in estimated (e) GFR. Diabetes itself is associated with the development of hypertension and proteinuria over time. All this leads us to understand that the risk of decline in GFR is steep among donors who have diabetes with hypertension and proteinuria, and it takes several years to manifest. An essential consideration in kidney donation is the motivation for follow-up. A survey among donors from Canada found that a majority of donors endorsed lifelong follow-up.[S7] Will this be the same in a resource-limited setting?

Outcomes of Kidney Transplants from Diabetic Donors

In a reassuring study, Truong *et al*. showed that diabetic kidney disease is present in only a small proportion of diabetic donor kidneys, and the changes are often mild and in early stages.[S8] After the transplant, these changes may stabilize or only slowly and mildly increase

in severity. Gilbert *et al*. analysed the survival of diabetic vs nondiabetic allografts. They reported an increased risk of diabetic kidney disease-related allograft loss in donors who had diabetes for more than six years and in whom the frozen section biopsy had histological evidence of diabetes.[S9] Longer studies in clinical research published by Singh *et al*. showed that diabetic kidneys given to diabetic recipients have lower one-, three-, and five-year survival when compared to those from a nondiabetic donor and nondiabetic recipient pairs.[4] In short, the diabetic kidney may have a reduced allograft survival if the donor is older and diabetic for long and the recipient has diabetes.

What is the Solution?

This imbalance between risks and resources was highlighted well by Blond *et al*.,[S10] who emphasized various strategies to use resources for prediabetes. They suggested stratifying all prediabetics to identify those likely to progress to diabetes, and interventions are targeted to these individuals. This "stratified approach" seems to be the most reasonable solution.

A similar solution could be applied to voluntary kidney donation. All people with prediabetes and diabetes are not alike. Soliman *et al*. suggest stratification where older (more than 55 years), well-controlled diabetic patients [hemoglobin A1C (HbA1C) <7% on at least three occasions in over two years] without any target organ damage are identified.[5] These patients are then evaluated for additive risk factors such as obesity, hypertension, smoking, and dyslipidemia. Individuals without these risk factors are considered for donation.

Mohan *et al*. have recently published data on the unique phenotypic clusters of diabetes among Indians when compared to a Scandinavian cohort. They analyzed 19,084 individuals with diabetes and found four phenotypes: mild age-related diabetes (MARD), insulin-resistant obese diabetes (IROD), combined insulin resistance and deficient diabetes (CIRDD), and severe insulin-deficient diabetes (SIDD). Of these, IROD and CIRDD were unique to the Indian population. CIRDD is associated with the development of diabetic kidney disease.[S11] Hence, further risk stratification within the Indian subcontinent is required before applying data from Western populations.

For the Indian population, the Indian Diabetes Risk Score (IDRS) is used to evaluate pretransplant risk in individuals at high risk of developing diabetes. The IDRS was first validated as a screening tool to identify diabetes in the population without blood tests so that public health resources could be utilized properly. Since then, validation studies have been done. The Chennai Urban Population Study (CUPS) showed that individuals with an IDRS > 60 have the highest conversion to diabetes over time.[S12] This score has hence found its place as a valid tool for assessing future risk of diabetes even in individuals with normal glucose tolerance. A higher IDRS has also been linked to several other diseases, such as metabolic syndrome, peripheral vascular disease, peripheral neuropathy and sleep disorders. A few recommendations for guidance in dysglycemia are summarized in Table 1.

Table 1: Eight things to remember about donation in dysglycemia

1. All prediabetics and diabetics are not alike. A "one-size-fits-all" approach will not work.
2. Risk stratification and individualization is required for both diabetic and prediabetic donors.
3. The Indian diabetics show a different phenotype than the Scandinavian population.
4. The Indian Diabetes Risk Score (IDRS) has been validated in our population and may be an effective strategy to risk-stratify prediabetics prior to kidney donation.
5. A similar tool needs to be developed for diabetes, using the duration and control of diabetes, age of the patient, complications of diabetes, and additive risk factors like hypertension, smoking, and obesity. A phenotypical classification of diabetes according to the newly described phenotypes should also be included in this risk stratification.
6. There is no information on long-term outcomes in different phenotypes of diabetic patients in India; this should be conveyed to the potential donor and the need for long-term follow-up should be emphasized.
7. The receipt of a kidney from a donor with dysglycemia may be associated with poorer outcomes; this risk should also be explained to the recipient.
8. Long-term data on donor outcomes needs to be collected, including those with various forms of dysglycemia not just someone classified as diabetic.

To conclude, the unique phenotypes of diabetes in the Indian subcontinent may need to be taken into consideration when accepting diabetic individuals for voluntary kidney donations. Other factors to be considered include the age of the individual, the likelihood of future complications, and additive risk factors. Although many risk-predictive tools to estimate the lifetime risk of complications are present, they have the disadvantage of not factoring in the effect of donor nephrectomy. The potential perils of receiving older and diabetic kidneys need to be discussed a priori with the recipients, and their consent must be obtained. We still have miles to go before reaching a meaningful consensus. While awaiting short- and long-term data, an expert working group of nephrologists, transplant physicians, surgeons, endocrinologists, and donor advocates could help individualize therapy and generate more specific guidelines.

Conflicts of interest: There are no conflicts of interest.

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References

1. Yang J, Singh AK, Magee CC, Pendergrass ML, Ahmed SB. A potential living kidney donor with prediabetes. Kidney Int 2009;76:673-7.
2. Khalil MAM, Sadagah NM, Tan J, Syed FO, Chong VH, Al-Qurashi SH. Pros and cons of live kidney donation in prediabetics: A critical review and way forward. World J Transplant 2024;14:89822.
3. Ibrahim HN, Berglund DM, Jackson S, Vock DM, Foley RN, Matas AJ. Renal consequences of diabetes after kidney donation. Am J Transplant 2017;17:3141-8.
4. Singh N, Washburn K, Schenk A, El-Hinnawi A, Bumgardner G, Logan A, *et al*. The impact of donor and recipient diabetes on renal transplant outcomes. Clin Transplant 2020;34:e14115.
5. Soliman KM, Daoud A, Posadas Salas MA, Rice T, Uehara G, Shayto R, *et al*. Accepting living kidney donors with preexisting diabetes mellitus: A perspective on the recent OPTN policy change – July 2022. Clin J Am Soc Nephrol 2023;18:127–9.

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