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Contents

Quarterly Volume 14 Number 1 March 18, 2024

EDITORIAL

REVIEW

MINIREVIEWS

ORIGINAL ARTICLE

Retrospective Cohort Study

World Journal of Transplantation

Quarterly Volume 14 Number 1 March 18, 2024

Contents

World Journal of Transplantation

Quarterly Volume 14 Number 1 March 18, 2024

Contents

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REVIEW

Pros and cons of live kidney donation in prediabetics: A critical review and way forward

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Abstract

There is shortage of organs, including kidneys, worldwide. Along with deceased kidney transplantation, there is a significant rise in live kidney donation. The prevalence of prediabetes (PD), including impaired fasting glucose and impaired glucose tolerance, is on the rise across the globe. Transplant teams frequently come across prediabetic kidney donors for evaluation. Prediabetics are at risk of diabetes, chronic kidney disease, cardiovascular events, stroke, neuropathy, retinopathy, dementia, depression and nonalcoholic liver disease along with increased risk of all-cause mortality. Unfortunately, most of the studies done in prediabetic kidney donors are retrospective in nature and have a short follow up period. There is lack of prospective long-term studies to know about the real risk of complications after donation. Furthermore, there are variations in recommendations from various guidelines across the globe for donations in prediabetics, leading to more confusion among clinicians. This increases the responsibility of transplant teams to take appropriate decisions in the best interest of both donors and recipients. This review focuses on pathophysiological changes of PD in kidneys, potential complications of PD, other risk factors for development of type 2 diabetes, a review of guidelines for kidney donation, the potential role of diabetes risk score and calculator in kidney donors and the way forward for the evaluation and selection of prediabetic kidney donors.

Key Words: Live kidney donation; Prediabetes; Impaired fasting glucose; Impaired glucose tolerance; Review

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Core Tip: An increasing number of prediabetic kidney donors are encountered by transplant physicians. The decision to allow or to not allow these donors is always challenging. Prediabetics are prone to multiple complications in the future, including diabetes mellitus and chronic kidney disease. Variability in recommendations by various organizations and societies about kidney donation in prediabetics leads to even further confusion in decision making. This extensive review focuses on evidence from both the general population and kidney donors regarding kidney donation in prediabetics. This review will help clinicians to take well informed decisions and to identify a direction for further research and the need for a uniform position by international transplant societies like The Transplantation Society or International Society of Nephrology.

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INTRODUCTION

Prediabetes (PD) is described as high blood glucose levels which do not satisfy the criteria for the diagnosis of diabetes mellitus (DM). A fasting plasma glucose level of 126 mg/dL (6.99 mmol/L) or greater, and glycated hemoglobin (HbA1c) level of 6.5% or greater, or a 2-h post prandial level of 200 mg/dL (11.1 mmol/L) or greater are consistent with the diagnosis of type 2 diabetes. On the other side, a fasting plasma glucose level of 100 to 125 mg/dL (5.55-6.94 mmol/L), an HbA1c level of 5.7% to 6.4%, or a 2-h post prandial glucose level of 140 to 199 mg/dL (7.77-11.04 mmol/L) are consistent with PD[1]. The World Health Organization (WHO) and numerous other diabetes organizations define the impaired fasting glucose (IFG) cutoff to be 110 mg/dL (6.1 mmol/L)[1]. The global prevalence of PD reported in literature has been variable due to a variety of reasons. Firstly, the definition of PD by WHO and the American Diabetes Association (ADA) has been different and as a result prevalence has varied among different studies depending on the definition being used. Secondly, studies used different parameters such as fasting glucose, glucose tolerance test or glycosylated hemoglobin to define PD, which could also have led to variable prevalence. Rooney *et al*[2] used the WHO definition of PD and reported the global prevalence of impaired glucose tolerance (IGT) in 2021 as 9.1% (464 million) and projected it to go up by 10% (638 million) in 2045. Similarly, the global prevalence of IFG in 2021 was 5.8% (298 million) and it was projected to increase by 6.5% (414 million) in 2045[2]. Bullard *et al*[3] used the ADA definition and reported the prevalence of PD in adults aged ≥ 18 years as 29.2% in 1999-2002, increasing to 36.2% in 2007-2010 in United States population[3]. A study from China used the ADA 2010 definition and reported prevalence at 50.1%[4]. Around 5%-10% of people with PD develop DM annually[5,6] although the conversion rate varies by population characteristics and the exact criteria used for the definition of PD. IFG is a predictor of cardiovascular mortality and it increases cardiovascular mortality by 20%[7,8].

Kidney transplantation (KT) is the treatment of choice for end stage renal disease (ESRD)[9]. KT improves quality of life and survival rates of patients with ESRD[10,11]. Living kidney donation leaves the kidney donor with a single kidney for the rest of their life, hence increasing their vulnerability to acquire kidney impairment in the future. Recent studies comparing donors to healthy non-donors found that kidney donation is related to a small but statistically significant increased risk of ESRD[12,13]. Prediabetic kidney donors have a seven-fold increased risk of DM (15.6%) compared to donors with normal glucose levels (2.2%)[14]. In view of this significant risk, it is important for KT physicians to carefully assess donors with PD for eligibility of donation.

PATHOLOGICAL EFFECTS OF PREDIABETES ON KIDNEYS AND POTENTIAL IMPLICATIONS FOR KIDNEY DONORS

Abnormal glomerular hemodynamic homeostasis has been proposed as an important factor in the pathogenesis of renal diseases. This is usually manifested as increased hyperfiltration leading to an increase glomerular filtration rate (GFR)[15]. PD has been shown to cause hyperfiltration and increased GFR in both animal and human studies. Experimental glucose infusion in dogs has been shown to cause a reactive increase in GFR[16]. Similarly, in human clinical studies, hyperfiltration was implicated in the development of diabetic nephropathy[17,18]. The association of impaired fasting with hyperfiltration has been shown to be independent of age, sex, body mass index (BMI), blood pressure and insulin status[19]; with subsequent development of microalbuminuria. A Korean study reported an odd ratio (OR) of 2.57 in an individual having both IFG and IGT[20]. Two studies from Italy and Australia showed high prevalence of microalbuminuria in IFG and IGT as compared to a normoglycemic individual. The study from Italy reported the prevalence of microalbuminuria as 6.9%, 5.6%, and 4.3% in IFG, IGT and normoglycemic groups, respectively[21]. The study from Australia reported the prevalence of microalbuminuria as 8.3% in IFG, 9.9% in IGT, and 4.3% in those with normal glucose[22]. Presence of microalbuminuria is of clinical importance because it is an established risk factor for cardi-

ovascular events and chronic kidney disease (CKD)[23]. Furthermore, the presence of microalbuminuria in donors with PD could result in a suboptimal kidney being donated to the recipient. Histological evaluation of PD through kidney biopsy is not done routinely in this group of patients, hence it is often not easy to determine the extent of pre-existing kidney damage. Mac-Moune Lai *et al*[24] were the first to describe the histological manifestation of PD through an analysis of 23 patients who had diffuse thickening of the glomerular basement membrane on electron microscopy. They found that the basement membrane thickness was associated with incidental abnormalities of glucose levels with no correlation with age, smoking, body weight, hyaline arteriosclerosis, and hypertension. The authors followed their cohort for development of glucose metabolism. They found diabetes in 20% of patients at the time of biopsy. On further follow up, 44% developed diabetes at 6 months and another 70% develop diabetes latter at 24 months. Seven patients showed no evidence of diabetes at the follow-up[24]. The authors speculated that isolated diffuse thickening of glomerular capillary basement membrane may be a renal lesion in PD. Thickening of the glomerular basement membrane has also been identified as an early diabetic lesion in young diabetics[25,26]. From a pathophysiological standpoint, it can be deduced that PD induces high GFR with subsequent microalbuminuria and compensatory histological thickening of glomerular basement membrane.

The synergistic deleterious effects of PD and donor nephrectomy in the development of CKD in kidney donors is not well studied. Post-kidney donation often causes mild proteinuria and reduced GFR, with incidence of proteinuria ranging from less than 5% to more than 20%[27]. The proteinuria usually becomes more pronounced over a period of time[27]. Kidney donation is also associated with a 30%-35% dip of GFR in the earlier period[28], but compensatory hyperfiltration in the remaining kidney can lessen the expected GFR reduction.

RISK OF CHRONIC KIDNEY DISEASE

Early CKD in kidney donors is mostly due to glomerulonephritis[13,29-32]. However late CKD in kidney donors is due to Denovo DM[13,29-31] and hypertensive nephrosclerosis[32]. PD has been implicated in hyperfiltration[16-18] and the development of microalbuminuria[21,22] in the general population, which are usually early manifestations of renal injury. Though the risk of conversion from PD to diabetes is higher in kidney donors (15.6%) when compared to healthy control (2.2%)[14], the real risk of CKD reported in few studies is minimal. Chandran *et al*[14] found that prediabetic patients are not at risk of developing CKD in the short term[14]. Similarly, a study from Japan compared donors with PD and diabetes with those having normal glucose and found no difference in surgical complications, mortality or risk of ESRD[33]. Hebert *et al*[34] and his colleagues also did not find increased risk of CKD in donors with PD[34]. The annual incidence rate of development of DM is 6%-11%. Around 70% of individuals with PD will eventually develop DM in their life time[35]. About 40% of diabetics will develop CKD in their life span[36]. Microalbuminuria and hyperfiltration develop 5-10 years after the initial diagnosis of DM (or PD). Macroalbuminuria develops in another 15 years and ESRD will ensue in 19 years from the diagnosis of diabetes[37]. Therefore, to know the real impact of PD we need long term studies of at least greater than 19 years to see the real sequalae of PD. Most of the studies done in prediabetic donors have a short period of follow up ranging from 88 months[33] to 10.4 years[14], which may miss out patients with late onset DM and diabetic kidney disease.

Many studies have been conducted on PD and the risk of CKD in the general population, with mixed findings. In the Framingham Heart Study, odds of developing CKD were 0.98 (95%CI: 0.67-1.45), 1.71 (95%CI: 0.83-3.55), and 1.93 (95%CI: 1.06-3.49) among those with IFG or IGT, newly diagnosed DM, or known DM when compared to those with a normal glucose level. The authors of this study proposed that cardiovascular disease risk factors explained much of the relationship between PD and the development of CKD[38]. With a mean follow-up of 14 years, study participants without baseline diabetes had glycosylated hemoglobin of 5.7%-6.4% and ≥ 6.5%, and < 5.7% were found to have a hazard ratio (HR) of 1.12 (0.94-1.34) and 1.39 (1.04-1.85) for development of CKD. Selvin *et al*[39] in their study with a mean follow-up of 14 years of study participants without baseline diabetes compared glycosylated hemoglobin of 5.7-6.4% and ≥ 6.5%, with < 5.7%, and found a HR of 1.12 (0.94-1.34) and 1.39 (1.04-1.85) for development of CKD. The corresponding HR for ESRD were 1.51 (0.82-2.76) and 1.98 (0.83-4.73), respectively[39]. In a study from Korea[20], the OR for microalbuminuria and CKD in an individual with PD having impaired fasting were 1.54 (95%CI: 1.02-2.33) and 1.58 (1.10-2.25). The OR significantly went up to 2.57 (1.31-5.06) in individuals having both IFG and IGT. The National Health and Nutrition Examination Survey study (1999-2006) showed that 17.7% of participants with PD had CKD as compared to 10.6% with no diabetes[40]. Redon *et al*[41] found that there was a close relationship between abnormal urinary albumin excretion and renal insufficiency in patients with essential hypertension, which was more pronounced in patients with the highest IFG (110-125.9 mg/dL).

However, there are also studies which did not find associations between PD and development of CKD. In a study from Germany, the prevalence of risk for CKD and the incidence of CKD were higher in subjects with PD than in subjects with euglycemia. However, the authors found that the increased risk did not persist after adjusting for established cardiovascular risk factors. After careful adjustments for established cardiovascular risk factors, the relative risk (RR) for IFG was 0.97 (95%CI: 0.75-1.25) and for HbA1c -defined PD was 1.03 (95%CI: 0.86-1.23). This led the authors to conclude that the higher incidence reduced kidney function in subjects with PD is most likely caused by increased cardiovascular risk factors[42]. In secondary analysis of the Systolic Blood Pressure Intervention Trial, where participants were followed for a median of 3.3 years, 41.8% had IFG but IFG was not associated with worsening kidney function or albuminuria[43]. Similarly, a study from Japan found an association of PD with the development of proteinuria but it failed to show any association between PD and CKD[44].

A meta-analysis of 9 cohort studies, the participants of which were mainly Asian and white, found increased risk of CKD in PD. Eight studies used the definition of impaired fasting as 6.1-6.9 mmol/L and after adjustment for established risk factors, the RR of CKD was 1.11 (95%CI: 1.02-1.21). One study in this meta-analysis used definition of IFG as 5.6-6.9 mmol/dL. Combining all studies together, the overall RR of CKD was 1.12 (95%CI: 1.02-1.21; Table 1)[45].

IS CKD THE ONLY CONCERN OF PD?

PD causes various other complications other than CKD. These complications should be kept in mind and should be taken into consideration before allowing a potential donor to donate. PD can cause overt DM, cardiovascular events, stroke, microvascular complications such as neuropathy and retinopathy and has been associated with dementia, depression, cancer and an increase in all-cause mortality[46,47].

Development of diabetes

Risk of progression from PD to diabetes varies widely due to differences in the definition of PD, heterogeneity of PD, and social and physical environment[48]. The lower cut-off point for IFG, which is still used by WHO, is 6.1 mmol/L[49]. In 2003, this cut-off point was lowered to 5.6 mmol/L by the ADA[50]. As a result, there is variability in the prevalence of PD and its subsequent progression to diabetes. Around 10%-50% of individuals will develop diabetes in next 5-10 years [35,51,52]. On the other hand, 30%-60% will revert to normoglycemia within 1-5 years[51].

The risk of progression of PD to diabetes is less well studied in kidney donors. Various studies done in kidney donors reported the incidence of diabetes as 1.5%-7.4%. However, most of these studies were cross sectional in nature, having a sampling bias with a lack of baseline glucose levels before donation[53-62]. The risk of diabetes in kidney donors with PD is 6 times more compared to donor without PD[14]. In a retrospective review with 1826 kidney donors, patients with IFG (100-126) were compared to those with normal blood glucose (< 100 mg/dL) and donors with a fasting glucose ≥ 126 mg/dL[34]. IFG was associated with a higher risk of diabetes and hypertension, but these patients were not found to be at higher risk of proteinuria or ESRD. Only 3.5% of donors from this cohort with normal glucose developed diabetes, at 15.4 ± 10.9 years, compared to 5.5% donors with IFG who developed diabetes 10.6 ± 8.8 years after donation.

Risk of cardiovascular diseases

Post kidney donation living donors are prone to high blood pressure and proteinuria[27,63-65]. Proteinuria, hypertension and reduced GFR are known risk factors for cardiovascular events[66-68]. There are mixed findings regarding the post donation risk of cardiovascular events. A recent long-term follow-up (11.3 years) of kidney donors showed that donors were at an increased risk of ischemic heart disease when compared with healthy controls[69]. Conversely, there are also studies which did not find an increased risk of cardiovascular events[70,71]. PD is a well-known risk for cardiovascular events. Unfortunately, there is paucity of data linking PD to cardiovascular events in kidney donors. However, most of the evidence linking PD to cardiovascular illness has been gathered from the general population. PD has been implicated as a risk factor for cardiovascular diseases in a range of studies[7,72,73]. PD shows a 20% higher risk of developing cardiovascular disease compared to those with normal blood sugar[74]. Insulin resistance, inflammation and endothelial dysfunction in PD are linked to more cardiovascular events[75]. IGT is more often associated with cardiovascular events than IFG[76-78], with an overall similar cardiovascular risk to type 2 DM in many landmark trials such as Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe[76], Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Asia[79] and Funagata Diabetes study[73]. Similarly, increase in glycosylated hemoglobin even within a normal range has been shown to cause more cardiovascular mortality. In the European Prospective Investigation into Cancer (EPIC) Norfolk study, even a small 1% increase in HbA1c within the normal range caused an increase in 10-year cardiovascular mortality[80]. Since PD causes insulin resistance, inflammation and endothelial dysfunction[75], KT physicians have to be more mindful on potential future cardiovascular risks.

Stroke/cerebrovascular accident

Stroke is one of the macrovascular complications of PD. The prevalence of PD in patient with a recent ischemic stroke or transient ischemic attack (TIA) is around 37%[81]. Two-hour IGT is a stronger predictor of stroke and cardiovascular events compared to IFG[76,82,83]. IGT has also been implicated in recurrent ischemic stroke and TIA and it increases risk of recurrent TIA and minor stroke by 2 folds[82]. A meta-analysis of 15 prospective cohort studies found a positive association between PD and stroke. The authors, after excluding studies with undiagnosed diabetes, found that IGT or the combination of IFG and IGT were independent risk factors for stroke[84]. Unfortunately, the association of PD with stroke in kidney donors is not well studied and there is need to explore this group of individuals for risk of stroke.

Neuropathy

Neuropathy is one of the microvascular complications. Around 35% of newly diagnosed type 2 diabetics have peripheral neuropathy indicating an early subclinical phase before the development of diabetes[85]. PD has been linked to the development of peripheral neuropathy in the general population, though its prevalence is varied in different studies. The 1999-2004 cohort from Katon *et al*[86] reported the RR of peripheral neuropathy of 1.1 in PD and 1.7 in diabetes[86]. A study from Germany reported significant peripheral neuropathy of 24% in individuals who have both IFG and IGT. However, isolated IFG or IGT in this study failed to show significance for development of peripheral neuropathy[87]. The MONICA/KORA study found that neuropathy was more common in patients with IGT when compared to control[88]. Authors of this study used Michigan Neuropathy Screening Instrument and found that neuropathy, predominantly

Table 1 Showing association of prediabetes with chronic kidney disease

Ref.	Journal/Year	Study type	Objective	Findings
Fox *et al*[38]	*Diabetes Care*/2005	Follow up of Framingham Heart Study (1991-1995) after 75-gram oral glucose tolerance test	To study the impact of IFG and IGT on development of CKD	The odd of developing CKD was 0.98 (95%CI: 0.67-1.45), 1.71 (95%CI: 0.83-3.55) and 1.93 (95%CI: 1.06-3.49) among patients with IFG or IGT, newly diagnosed diabetes or known diabetes
Redon *et al*[41]	*J Am Soc Nephrol*/2006	Prospective multicenter, cross-sectional study	To assess the relationship between UAE and glomerular filtration rate in patients with glucose metabolism abnormalities having hypertension	The prevalence of abnormal UAE, > or = 3.4 mg/mmol across the spectrum of glucose abnormalities were 39.7%, 46.2%, 48.6%, and 65.6% for normoglycemic, low-range, and high-range impaired fasting glucose and diabetes. Predictors of low GFR < 60 mL/min were UAE ≥ 3.4 mg/mmol (OR 1.87; 95%CI: 1.61 to 2.17), IFG and diabetes (OR 1.30; 95%CI: 1.05 to 1.62), and BP ≥ 140/90 mmHg, or ≥ 130/80 mmHg if diabetes (OR 1.23; 95%CI: 1.04 to 1.45)
Plantinga *et al*[40]	*Clin J Am Soc Nephrol*/2010	Retrospective analysis of 1999-2006 national health and nutrition examination survey	To measure and compare the prevalence of CKD among people with diagnosed diabetes, undiagnosed diabetes, PD, or no diabetes	39.6% of people with diagnosed and 41.7% with undiagnosed diabetes had CKD; 17.7% with PD and 10.6% without diabetes had CKD. Among those with CKD, 39.1% had undiagnosed or PD
Okamoto *et al*[33]	*Transplantation*/2010	Retrospective study	To assess the indications for live kidney donation in glucose intolerance and to analyze perioperative complications associated with donor nephrectomies and its long-term consequences	Perioperative complications, survival rates and mortality were not significant between glucose intolerance and those with normal glucose tolerance
Selvin *et al*[39]	*Diabetes*/2011	Prospective cohort and cross-sectional analyses of ARIC study	To examine association between 2010 American Diabetes Association diagnostic cut points for glycated hemoglobin and microvascular outcomes (CKD, ESRD and retinopathy)	Risk of CKD, with adjusted HRs of 1.12 (0.94-1.34) and 1.39 (1.04-1.85) was found for glycated hemoglobin 5.7%-6.4% and ≥ 6.5%, respectively, as compared with < 5.7% (P = 0.002). HR for ESRD were 1.51 (0.82-2.76) and 1.98 (0.83-4.73)
Schöttker *et al*[42]	*Prev Med*/2013	Prospective study	(1) To determine the risk for incident reduced kidney function in participants with pre-diabetes; and (2) To determine dose-response relationships of fasting glucose and HbA1c with reduced kidney functions in subjects with manifest diabetes mellitus	Reduced kidney function risk factor prevalences and incidences were higher in participants with pre-diabetes than without PD. Increased risk did not persist after adjusting for established cardiovascular risk factors [RR (IFG): 0.97 (95%CI: 0.75-1.25) and RR (HbA1c-defined pre-diabetes): 1.03 (95%CI: 0.86-1.23)]
Chandran *et al*[14]	*Transplantation*/2014	Retrospective study	To compare development of diabetes, the estimated glomerular filtration rate, and the level of albumin excretion in donors with IFG to matched controls with normal pre-donation fasting glucose	(1) Higher proportion of IFG donors had developed DM (15.56% *vs* 2.2%, P = 0.06); (2) eGFR at 10.4 years was 70.7 ± 16.1 *vs* 67.3 ± 16.6 mL/min/1.73 m^2, P = 0.21) was similar between 2 groups; and (3) Urine albumin/creatinine 9.76 ± 23.6 *vs* 5.91 ± 11 mg/g, P = 0.29) was similar between 2 groups
Echouffo-Tcheugui *et al*[45]	*Diabet Med*/2016	Metanalysis	To assess the effect of PD on the incidence of CKD	Relative risk of CKD after adjustment for established risk factors was 1.11 (95%CI: 1.02-1.21) when IFG was defined as 6.1-6.9 mmol/L
Bigotte Vieira *et al*[43]	*J Clin Endocrinol Metab*/2019	Post hoc analysis of participants of the SPRINT trial	To find association of PD with adverse kidney outcomes	Impaired fasting glucose was not associated with higher rates of the composite outcome (HR: 0.97; 95%CI: 0.8 to 1.16), worsening kidney function (HR: 1.02; 95%CI: 0.75 to 1.37), or albuminuria (HR: 0.98; 95%CI: 0.78 to 1.23)
Furukawa *et al*[44]	*Diabet Med*/2021	Retrospective analysis of health check-up in 2014 in Japan	To investigate the associations of PD with the proteinuria and eGFR decline	PD was independently associated with the proteinuria development (OR 1.233; 95%CI: 1.170-1.301). No association was found with eGFR decline (OR 0.981; 95%CI: 0.947-1.017)
Hebert *et al*[34]	*Transplantation*/2022	Retrospective data analysis of The RELIVE study	To study mortality, proteinuria, and ESKD according to donation FPG: < 100 mg/dL, 100-125 mg/dL, and ≥ 126 mg/dL	IFG was associated with a higher diabetes risk (adjusted HR, 1.65; 95%CI: 1.18-2.30) and hypertension (adjusted HR 1.35; 95%CI: 1.10-1.65; P = 0.003 for both), but not higher risk of proteinuria or ESKD

PD: Prediabetes; CKD: Chronic kidney disease; IGT: Impaired glucose tolerance; IFG: Impaired fasting glucose; UAE: Urinary albumin excretion; GFR: Glomerular filtration rate; eGFR: Estimated glomerular filtration rate; HR: Hazard ratios; ESRD: End stage renal disease; ARIC: Atherosclerosis risk in communities; OR: Odds ratio; ESKD: End-stage kidney disease; FPG: Fasting plasma glucose; RELIVE: Renal and lung living donors evaluation; BP: Blood press; HbA1c: Glycated hemoglobin; SPRINT: Systolic blood pressure intervention trial; DM: Diabetes mellitus.

involving small nerve fibers, were present in 13.3% of patients with diabetes, 8.7% of patients with IGT, 4.2% of patients with IFG and 1.2% of patients with normoglycemia[88]. The Prospective Metabolism and Islet Cell Evaluation study followed patients for peripheral neuropathy and at 3 years follow up. Authors found that prevalence was highest among individuals who progressed to diabetes (50%) and followed by those who developed PD (49%), compared to individuals with normoglycemia who have an incidence of 29%[89]. A meta-analysis found that there was a wide range of prevalence estimates from 2%-77%, but most studies included in this analysis reported a prevalence ≥ 10%[90]. Unfortunately, there is lack of data on peripheral neuropathy in prediabetic kidney donors.

Retinopathy

The prevalence of retinopathy has been different in various studies. In an epidemiological study done in Pima Indians, retinopathy was reported in 12% of patients with IGT[91]. Diabetes Prevention Program study who had elevated blood glucose, but no history of diabetes, showed that retinopathy was present in 7.9% in patients with PD[92]. Post hoc analysis of a systematic review[93] showed lower median retinopathy in patients with a normal glucose tolerance of 3.2% (interquartile range 0.3%-7.3%) compared to 6.6% (interquartile range 1.9%-9.8%) in prediabetics. Reduced retinal arteriolar dilatation has been in implicated as manifestation of retinopathy in PD[94]. The Maastricht Study using spectral domain optical coherence tomography found that macular thickness is reduced in PD even before the onset of diabetic retinopathy. Hypertension, abdominal obesity and hyperglycemia were found to be predictors of incident retinopathy across all glucose levels from normoglycemia to PD and diabetes[95]. Though the association of retinopathy in the general population is strong, this is again not thoroughly investigated in kidney donors with PD.

Dementia

Dementia has been a recognized complication of PD. Insulin and insulin-like growth factors have an important role in the vital functions of neurons including survival and neuron growth, gene expression, protein synthesis, myelin production and maintenance in oligodendrocytes, synapse formation and plasticity[96,97]. PD, like diabetes, is a state of hyperinsulinism with insulin resistance which affects the function of brain cells (neurons and glial cells) leading to neurodegeneration and dementia[98-100]. A study from Sweden has shown significant brain volume loss affecting predominantly white matter leading to progressive cognitive impairment over a period of 9 years in both PD and DM [101]. Similarly, another study in elderly women showed risk of the development of cognitive impairment among participants with IFG (OR 1.64) and DM (OR 1.79)[102]. Prediabetics in the Maastricht study participants were found to have more cerebral lacunar infarcts, white matter lesions and loss of brain volume when compared with normoglycemic participants[103]. Hyperglycemia is a continuum from normoglycemia to PD. Diabetes and increasing hyperglycemia across this spectrum in prediabetic and diabetics affected executive functions in the NHANES 2011-2014 cohort[104]. In another population-based study, PD and DM were associated with minor deficits in global cognitive function, processing speed and executive functioning and an inverse correlation between glucose level with cognitive abilities in non-diabetics was found[105].

Depression

PD has been linked to risk of depression in various studies[106,107], likely through insulin resistance. Insulin resistance in the brain induces mitochondrial and dopaminergic dysfunction leading to anxiety and depressive-like behaviors[108]. Two meta-analyses done on the association of PD with depression reported mixed findings; one metanalysis reported that the prevalence of depression is moderately increased in prediabetic and in undiagnosed diabetic patients[109] and the other found that prediabetics are not at a higher risk of depression[110]. Some studies have also shown that the combination of PD with depression increases the risk of progression to the development of diabetes[111-113]. Since anxiety, depression and regret have been reported in some kidney donors[114-116], therefore, it is important to understand the potential future neurological sequelae of PD.

Cancers

PD has been reported to be associated with cancers in several studies[117-119]. A community-based study from China reported that glucose intolerance (PD & DM) was associated with stomach, colorectal, and kidney cancer in individuals aged < 65 year[120]. PD is associated with obesity and overweight, which are the recognized risk factors for cancer[121]. Hyperglycemia has been linked to the increased production of reactive oxygen species, reduced levels of antioxidant capacity, and increased levels of DNA damage which may be a potential mechanism of carcinogenesis in these patients [122]. A meta-analysis of 16 prospective studies found that PD was associated with an increased risk of cancer overall (RR 1.15; 95%CI: 1.06-1.23). The analysis also found that cancer of the stomach/colorectum, liver, pancreas, breast and endometrium were significantly associated with PD ($P < 0.05$). However, no association was found with cancer of the bronchus/Lung, prostate, ovary, kidney or bladder[121].

Kidney donors have a similar incidence of liver cancer, melanoma, breast cancer, and non-Hodgkin lymphoma 7 years post donation as compared to the general population. However, there is an increased incidence of colorectal cancer (adjusted incidence rate ratio 2.07, 95%CI: 154-2.79) and kidney cancer (2.97, 1.58-5.58) in kidney donors[123]. Given the evidence, kidney donors with PD, especially those who are overweight and are actively smoking, may be more prone to develop tumors post donation.

Nonalcoholic fatty liver disease

The prevalence of nonalcoholic fatty liver disease (NAFLD) is 48.25% in patients with PD[124]. In a study from United States, 44%-62% of the adults with PD had NAFLD[125] Prevalence in the general population is 26%, which is much

lower than PD[126]. Obesity associated insulin resistance increases free fatty acid levels which leads to more storage of fat in the liver. This leads to more hepatic insulin resistance and activation of inflammatory pathways and oxidative stress, which promote fibrosis in liver[127]. Subclinical chronic hepatic inflammation and insulin resistance has been shown to cause NAFLD in PD[128]. NAFLD has been linked with reduced GFR[129]. Living kidney donors do not have underlying kidney disease but have reduced GFR as a result of nephrectomy. However, a study reported that reduced kidney function after kidney donation is not associated with increased incidence or progression of NAFLD[130], but that data on prediabetic kidney donors is lacking. Looking at data from the general population, it will be interesting to evaluate the association between NAFLD and PD in kidney donors.

All-cause mortality

PD has been linked to increased all-cause mortality[131]. A study from Japan showed that PD was significantly associated with increased risk of death from all causes and cancer but not cardiovascular diseases[132]. PD along with hypertension not only caused increased all-cause mortality but also increased cardiovascular mortality[8]. Another recent metanalysis of 16 studies found that PD was associated with an increased risk of all-cause mortality[46]. Inactivity and obesity are common among PDs. Physical activity is of utmost important in prediabetics. A recent study showed that conversion of euglycemia along with physically activity was associated with a lower risk of death compared with persistent PD and physical inactivity[133]. Keeping these facts in mind, it is important to fully educate prediabetic kidney donors about physical activity prior to donation. Figure 1 showed potential complications which can happen in a kidney donor.

Other complications

Various other complications such as sleep disturbances[134], snoring[135], obstructive sleep apnea[136], increase fracture risk[137] and high mean platelet volume and platelet distribution width[138] have been reported in PD.

WHAT RISK FACTORS MAKE PD RISKIER?

Various risk factors, when present in prediabetics, make them prone to develop diabetes. KT should be cognizant of these risk factors before allowing a prediabetic kidney donor to donate. These risk factors are as follows:

Age

The elderly have a higher prevalence of diabetes and PD than young and middle-aged people[139,140]. Age is an important risk factor for the development of diabetes because of inflammation, mitochondrial dysfunction and abnormal lipid metabolism[141]. However, there are studies which showed that the majority of the PD either remained stable or reverted to normoglycemia[142,143]. Since PD is a continuous and cumulative risk, most transplant programs may discourage young prediabetics to donate.

Obesity

Obesity is a potentially modifiable risk factor for diabetes[144]. Obesity is characterized by insulin resistance which is manifested by decreased insulin-stimulated glucose transport and metabolism in adipocytes and skeletal muscle and by impaired suppression of hepatic glucose output[145]. Individual adipose cell type composition, adipose mitochondrial gene expression and body fat percentage have been shown to predict insulin resistance in both prediabetics and obese individuals[146]. Excess visceral fat and insulin resistance, rather than general adiposity, were found to be associated with the development of PD and diabetes[147].

Kidney donors with BMI ≥ 25 kg/m^2 at the time of donation are prone to develop significant weight gain over 1-year post-donation[148]. Praga *et al*[148] found that kidney donors with higher BMI had a greater risk for the development of proteinuria and renal dysfunction[149]. Similarly, another study also found a significant relationship between increasing BMI and the rate of kidney insufficiency after kidney donation[150]. Therefore, prediabetics with obesity should be evaluated carefully due to the risks of the development of diabetes, proteinuria and renal dysfunction.

Smoking

Smoking has been shown to decrease insulin action and increased insulin resistance in experimental settings[150]. Coronary artery risk development in young adults (CARDIA-study) studied the effect of active and passive smoking on glucose intolerance. At a 15-year follow-up, glucose intolerance was highest among smokers (21.8%), followed by passive smokers who never smoked (17.2%) and ex-smokers (14.4%), compared to 11.5% in individuals who never smoked[151]. Another study found that 5-10 pack-years of smoking increased odds of PD by 2-fold, which is reversible with smoking cessation[152]. Smokers are 30% to 40% more likely to develop diabetes compared to non-smokers[153]. Various studies have shown strong associations between cigarette smoking and the development of DM[154-157]. Smoking is common in kidney donors, though pre-donation education usually reduces incidence of smoking[158]. Active or passive smoking in kidney donors may lead to higher serum creatinine compared to non-smokers[158,159]. Therefore, prediabetic kidney donors with a history of smoking should be advised to stop and be evaluated thoroughly for future risk of DM.

Ethnicity/race

Certain ethnicities are more prone to developing diabetes and its complications. The United States is populated by multiple ethnic groups. The rate of diagnosis of diabetes is 14.5% in American Indian/Alaskan Natives, 12.1% in non-

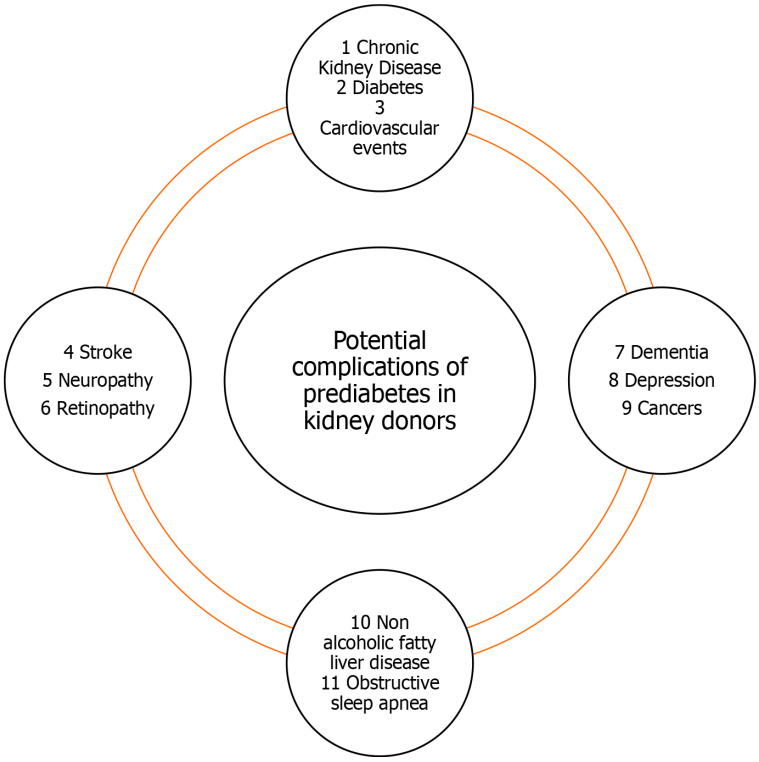

Figure 1 Showing potential complications of prediabetes in kidney donors.

Hispanic blacks, 11.8% in Hispanics, 9.5% in Asian Americans and 7.4% in non-Hispanic whites. Among Asian Americans, 12.6% of Asian Indians have diabetes, followed by Filipinos (10.6%) and Chinese (5.6%). Among Hispanic adults, 14.4% have diabetes followed by 14.4% Puerto Ricans[160]. Similarly, in the United Kingdom, the prevalence of type 2 diabetes is indeed higher among Asian, Black and minority ethnic groups[161]. Health Survey for England found reported prevalence of type 2 diabetes in Black Caribbean (9.5% men, 7.6% women), Indian (9.2% men, 5.9% women), Pakistani (7.3% men, 8.4% women), and Bangladeshi (8.0% men, 4.5% women) people[161]. The percentage of change in the number of people with diabetes between years 2000 to 2030 has been 97% for Sub-Saharan Africa, 67% for Middle East, and 42% for Asia and Islands[162]. The propensity for development of diabetes among various ethnic groups should be kept in mind before allowing a pre-diabetic kidney donor to donate his kidney.

Gestational diabetes

Gestational diabetes has been an important recognized risk factor for future development of diabetes. Insulin resistance along with pancreatic β-cell dysfunction has been proposed as a mechanism for gestational diabetes[163]. The risk of the development of diabetes is 7-10 times higher in women with gestational diabetes[164,165]. After the diagnosis of gestational diabetes, rapid conversion to overt diabetes is seen within 5 years, with a slower progression subsequently [166]. Furthermore, women with gestational diabetes are at higher risk of developing metabolic syndrome[167,168] and are at increased risk of cardiovascular events[167]. It should also be kept in mind that subsequent pregnancy post-donation makes female donors more prone to a higher risk of preeclampsia, gestational hypertension and preterm birth [169]. Therefore, female kidney donors with PD and a history of gestational diabetes should be thoroughly assessed for risk *vs* benefits.

Metabolic syndrome

The combination of glucose intolerance, hypertension, dyslipidemia and obesity is known as metabolic syndrome[170]. In the Beaver Dam study, the OR for the incidence of diabetes was 9.37 if three abnormalities of metabolic syndrome were present. The OR went up to 33.67 if four or more abnormalities were present[171]. In the Framingham Heart Study Offspring Study, the RR for type 2 diabetes increased with the number of metabolic syndrome components[171]. The West of Scotland Coronary Prevention Study used National Cholesterol Education Program definition for metabolic syndrome with or without the inclusion of C-reactive protein. The study found a RR for diabetes at 7.26 with three abnormalities of metabolic syndrome. The RR went up to 24.4 for four more abnormalities of metabolic syndrome[172]. The British Regional Heart study found the RR for diabetes to be at 4.56 for three abnormalities. The RR for the development of diabetes went up to 10.88 for four more abnormalities[173].

IFG is one of the components of metabolic syndrome. Various studies have shown that IFG is one of the strongest predictors of the development of diabetes compared to the other elements of metabolic syndrome. In a study from Finland[174], the HR for the development for IFG was 5.16, which was the highest when compared with obesity (HR 1.75), triglyceride (HR 1.34), High density liptein-cholesterol (HR 1.60) and blood pressure (HR 1.87). The Framingham Offspring Study showed that individuals with metabolic syndrome which included IFG showed a high RR of 11, which

was much higher than the RR of 5 in individuals for whom IFG was excluded in analysis[175].

The development of metabolic syndrome has been studied in kidney donors. An analysis of 2018 Living kidney donors, when matched with control non-donors, found that the living kidney donors showed a lower absolute prevalence for all metabolic risk factors, except for those who were either overweight or obese[176]. However, in another study, more donors developed new onset metabolic syndrome compared to the control group[177]. Martín-Alemañy *et al*[178] reported that living kidney donors had a high frequency of cardiometabolic risk factors and metabolic syndrome at the time of donation, which significantly increased over time[178]. In fact, metabolic syndrome was found to be a major barrier to kidney donation in one of the studies[179]. Therefore, one should carefully evaluate potential donors with PD and metabolic syndrome as they may be at risk of developing DM and cardiovascular complications.

Family history

Family history is one of the recognized risk factors for the development of type 2 diabetes. Familial predisposition is usually due to a combination of environmental and behavioral risk factors with genetic propensity due to various genes [180,181]. The prevalence of diabetes among individuals who have a first-degree relative with diabetes was 14.3% and it was significantly higher than individuals without a family history (3.2%)[180]. The authors classified family history risk categories of diabetes as high (at least two generations have first degree relative with diabetes), moderate (one generation of first-degree relatives with diabetes) and average (no first-degree relatives with diabetes). The prevalence rates of diabetes were 32.7% in a high-risk family, 20.1% in a moderate risk family and 8.4% in an average risk family[182]. Therefore, family history risk categories of diabetes have a significant and graded association with the prevalence of diabetes. In the EPIC-InterAct study, the authors investigated the association between a family history of diabetes among different family members and the incidence of type 2 diabetes and also studied the extent of genetic, anthropometric and lifestyle risk factors in familial predisposition. The study found that lifestyle, anthropometric and genetic risk factors contributed only minimally, with most of the risk being attributed to positive family history[183]. The Health Examinees-Gem study was done in Korea and aimed to find associations between a family history of diabetes with adherence to regular exercise, healthy diet and body composition, and clusters of healthy behaviors. The participants of the study were found to be strictly adherent to exercise and healthy diet but were found to not have a normal body composition[184]. Therefore, prediabetic kidney donors should always be evaluated with respect to their detailed family history of DM or PD. Figure 2 shows potential risk factors of the development of diabetes in a prediabetic kidney donor.

WHAT GUIDELINES RECOMMEND KIDNEY DONATION IN PD?

The Amsterdam Forum on the Care of the Living Kidney Donor (2006)[185] recommends to exclude individuals with a history of diabetes or fasting blood glucose ≥ 126 mg/dL (7.0 mmol/L) on at least two occasions[or 2-h glucose with oral glucose tolerance test ≥ 200 mg/dL (11.1 mmol/L)], but do not have any recommendations for PD[185].

Caring for Australian and New Zealanders with Kidney Impairment (CARI) guidelines[186] recommend checking fasting blood sugar twice in all kidney donors. Those with sugar ≥ 7 mmol/L on both occasions are considered diabetic and this is considered to be an absolute contraindication. The guidelines used the criteria of IFG as 6.1-6.9 mmol/L. Any donor with at least one occasion of IFG should have a 2 h oral glucose tolerance test. Those with normal fasting sugars were allowed to donate. Patients at high risk for the development of type 2 DM were advised to have an oral glucose tolerance test. The characteristics of high risk for developing type 2 diabetes mentioned in CARI guidelines included family history, age > 45 years, being an Aboriginal or Torres Strait Islander and obesity. If the 2-h glucose of an oral glucose tolerance test result is ≥ 11.1 mmol/L then the patient is considered diabetic and this is an absolute contra-indication to a living kidney donation. Donors with IGT and a blood sugar between 7.8-11.0 mmol/L are considered not fit to donate. Donors with glucose tolerance < 7.8 mmol/L are normal and considered to not be a contraindication to donation. Furthermore, a past history of gestational diabetes was considered as contraindication to donation.

The American Society of Transplantation (AST)[187] states that the risk of DM in donors with PD is higher than that for a healthy donor. PD also increases the future risk of diabetic kidney disease. United Network of Organ Sharing excludes donors with diabetes from donation whilst AST recommend potential donors with PD to do lifestyle modifications. The AST recommends changes in diet, to do more exercise and to lose weight to achieve euglycemia and reduce the risk for future DM[187].

The British Transplantation Society (BTS) and United Kingdom Renal Association published their guidelines in 2018 [188]. All potential living kidney donors must have a fasting plasma glucose done. A fasting plasma glucose concentration between 6.1-6.9 mmol/L is suggestive of IFG and an oral glucose tolerance test should be undertaken in these donors. These guidelines also recommend an oral glucose tolerance test in prospective donors with an increased risk of type 2 diabetes such as a family history of diabetes, history of gestational diabetes, ethnicity or obesity. If an oral glucose tolerance test shows persistent IFG or IGT, then careful assessment should be clinically done using the diabetes risk calculator[189]. Unlike other guidelines, these guidelines do not exclude the diabetic completely. Diabetics can be taken as donors provided there is no target organ damage and cardiovascular risk factors such as obesity, hypertension or hyperlipidemia are optimally managed. Furthermore, thorough assessment should be done to ascertain the lifetime risk of cardiovascular and progressive CKD in the presence of a single kidney.

The Kidney Disease: Improving Global Outcomes (KDIGO) published its guidelines for the care of live kidney donors in 2019. The guidelines suggest to take a history of DM, gestational diabetes, and family history of diabetes. Blood sugar status should be assessed by checking fasting blood glucose and/or HbA1c before donation. The guidelines also recommend doing a two-hour glucose tolerance testing or HbA1c testing for donor candidates with elevated fasting

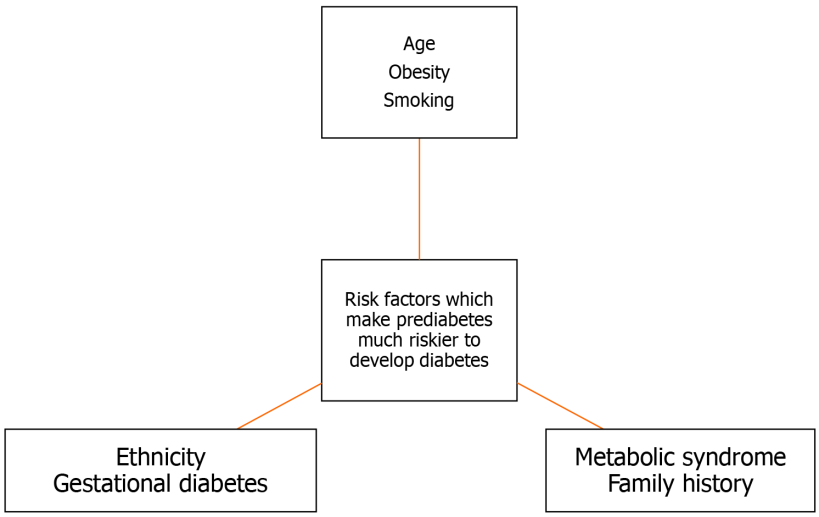

Figure 2 Showing risk factors for development of diabetes.

blood glucose, history of gestational diabetes, or family history of diabetes in a first-degree relative. Decisions regarding donors with PD or DM should be taken on an individual basis, keeping in view their future risk. Furthermore, KDIGO guidelines recommend that donors with PD and DM should be explained that their condition may progress and could result in end organ damage[190].

European Best Practice Guidelines, published in 2015, recommended that DM is a contra-indication to donation, other than in exceptional circumstances (1D), and that IGT is not an absolute contra-indication to donation (2C)[191].

Looking at these guidelines, there is variability in recommendation for donations in prediabetics and there is a need to build a uniform consensus among the transplant community across the globe.

USE OF DIABETES RISK SCORE AND RISK CALCULATORS IN KIDNEY DONORS

Various diabetes risk scores and risk calculators have been reported in the literature. The AST guidelines have mentioned the diabetes risk calculator provides accurate and individualized risk for future development of diabetes[187-192]. The Renal Association and BTS also recommend a diabetic risk calculator[188,189]. The University of Minnesota developed an apparatus that predicted risk of hypertension, type 2 diabetes, and reduced e GFR using data of living kidney donor program from 1963 through 2017 with a median follow up of 22.8 years. It requires donor age, sex, race, smoking status, estimated GFR, serum creatinine, (capillary or serum) glucose, BMI, systolic blood pressure, diastolic blood pressure, family history of hypertension and dyslipidemia. It also took into consideration the relationship to the recipient and whether the recipient has type 1 or type 2 DM. Unfortunately, prediction for hypertension and diabetes may not be valid for non-white donors[193].

There are various risks score models and risk calculators available. Prominent risk assessment tools include the Australian 5-year type 2 Diabetes Risk Assessment (AUSDRISK)[194], the Diabetes United Kingdom 10-year Know your Risk[195], The Finnish Diabetes Risk Score (FINDRISC)[196], and the ADA type 2 Diabetes Risk Test[197]. Age, sex, family history of diabetes, BMI and history of hypertension are included in all the country-specific calculators. The ADA calculator does not include ethnicity but takes gestational diabetes into consideration. The AUSDRISK and United Kingdom calculator, on the other hand, take ethnicity but not gestational diabetes into consideration. The AUSDRISK also includes smoking, fruit and vegetable intake and personal history of elevated glucose level. Waist circumference is included in both the AUSDRISK and United Kingdom calculators. Physical activity is included in the AUSDRISK and ADA calculators. The FINDRISC diabetes calculator includes gender, weight, height, age, waist circumference, and physical activity for more than 30 min, vegetable and fruits intake, use of blood pressure medications, high glucose level in past, and family history of diabetes in two generations. A systematic review done in 2011 identified 43 risk models for the prediction of the risk of DM[198]. This systematic review found poor methods including pre-screening univariate variables, the categorization of continuous risk predictors and the poor handling of missing data which could jeopardize model development. The other problem found was universal validation. Most risk scores show overall good results in predicting DM in populations for whom they were developed. However, the performance of these risk scores is more heterogeneous and generally weaker in external populations[199]. Unfortunately, most of these risk detection models have not been validated in kidney donors. It may be reasonable to use a well validated local risk calculator or risk score for all prediabetic kidney donors in that particular area to provide more accurate and individualized risk for the future development of diabetes.

WHAT SHOULD BE THE WAY FORWARD?

There were about 88751 patients on the waiting list for a kidney until September 2023, as per Organ Procurement & Transplant Network data. Only 20445 of the patients were transplanted until September 2023[200]. About 15824 kidneys were obtained from deceased donors and another 4621 were from living donors. This reflects that approximately only a quarter of the patients on the waiting list could get a kidney. Because of a global organ shortage and unmet needs for kidneys, many centers accept increasingly complex live donors including prediabetics. The lack of evidence for long-term outcomes for pre-diabetic kidney donors for the future risk of development of diabetes, development of CKD and other complications of PD have contributed to the conundrum of using complex donors. As discussed, a couple of studies with short term duration (ranging from 88 months to 10.4 years) in kidney donors having PD did not find an increased risk of CKD[14,33,34]. After progression of PD to DM, approximately another 19 years are needed for progression of microalbuminuria to macroalbuminuria and then to development of ESRD[37]. Keeping these facts in mind, to know the real sequelae of PD in a kidney donor, we need long term studies of at least 19 years to effectively follow up.

Post donation, the prediabetic kidney donors are left with only one kidney. Most of the evidence regarding PD and its complications are derived from studies done in the general population[20,39,41]. Development of diabetes and CKD are not the only worries. Other complications of PD including cardiovascular disease[7,72,73], stroke[76,81-84], neuropathies [85-88,90,122], retinopathy[91-95], dementia[96-101,103-105], depression[106-116], cancers[117-119], non-alcoholic fatty liver disease[124-128] and increased all-cause mortality[46,131,132] are well established in the general population. Therefore, it is the responsibility of the transplant team that there should be no maleficence and every effort should be taken to follow the ethical principle "first do no harm"[201]. Every effort should be made to avoid any subtle form of coercion from the family in case of live related kidney donation. A well-informed consent form showing detailed risk *vs* benefits and alternative options other than a transplant should be available for both the donor and recipient to protect both of them equally. Unfortunately, the guidelines from various societies and organizations are variable, leading to further confusion[185-187,190,191]. We feel that, while evaluating a potential prediabetic kidney donor, one has to look at overall risk of development of diabetes. Donors with IFG should undergo a glucose tolerance test and, if IGT is detected, then great care should be taken to further evaluate these donors. The combination of IFG and IGT poses a great risk of developing renal dysfunction[20] and peripheral neuropathy[88]. Similarly, two hours IGT has been a strong predictor of stroke and cardiovascular events[76,83]. Therefore, prediabetic kidney donors with IFG and IGT should be considered as high risk and may not be suitable candidates. Those with isolated IFG with normal glucose tolerance should be further evaluated. If they have no risk factors (age, ethnicity, smoking, obesity, gestational diabetes and metabolic syndrome) they may represent a low-risk case. IFG along with a single or combination of risk factors such as age, family history, ethnicity, smoking, obesity, gestational diabetes and metabolic syndrome may contribute to the status of a high-risk donor. A well designed and validated local risk score or calculator may be used in these cases. Those with high risk should be excluded and those with low risk may be accepted provided they are willing to undergo long term lifestyle modification and accept the risk.

RECOMMENDATION

We suggest the following recommendations:

There is a need for greater consensus amongst regional societies to call for unified position statements regarding kidney donation in donors with PD, through international transplant societies like The Transplantation Society or International Society of Nephrology.

Kidney donor with PD and abnormal IFG along with IGT are considered high risk even in the absence of other risk factors. If appropriate lifestyle modification fails a reversion to euglycemia, they then should not donate.

Kidney donors with isolated IFG with normal IGT should be evaluated for other risk factors such as age, family history, ethnicity, smoking, obesity, gestational diabetes and metabolic syndrome. The presence of any risk factors in kidney donors, along with IFG, make them high risk. Appropriate lifestyle modifications are recommended to achieve euglycemia and possible donation in the future.

A locally well designed and validated risk score or risk calculator may be helpful in identifying high risk donors and should be used to identify high risk donors.

All kidney donors with PD should be advised about modifiable risk factors such as smoking, weight loss and correction of any component of a metabolic syndrome, if present.

Comprehensive risk explanations should be done. The donor should be aware of possible development of diabetes and various complications of PD, including CKD and cardiovascular events. Both the donors and recipient should know about alternative therapies such as hemodialysis and peritoneal dialysis. Donors with a poor track record or history and who are unable to lose weight or quit smoking should be excluded through collaboration with donor advocacy or social workers.

In case if donation is made, there is a need for an enhanced medical follow up of a kidney donor who has history of PD. They should have greater access to clinics, health club memberships, a dietician and medications. Lifestyle modification should be re-enforced through continuous education.

There is a need for long-term well designed prospective studies in kidney donors with PD to know the long-term risk of diabetes and the various complications associated with PD.

It will be interesting to assess the efficacy of sodium-glucose cotransporter-2, glucagon like peptide 1, mineralocorticoid receptor antagonist and renin angiotensin inhibitors in kidney donors with PD and the effect of this on long term

renal and cardiovascular outcomes.

Most of the knowledge regarding PD and the risk of DM and other complications is derived from studies done in the general population. Unfortunately, there is limited work done in kidney donors with PD. Most of these studies are retrospective in nature, with a small sample size and a shorter follow up. As a result, this is one of the limitations of our review.

CONCLUSION

The global prevalence of PD is high. PD increases the risk of DM, CKD, cardiovascular events, stroke, neuropathy, retinopathy, dementia, depression, cancer, non-alcoholic fatty liver disease and increases all-cause mortality. Increasing age, obesity, smoking, certain ethnicities, gestational diabetes, metabolic syndrome and a family history of diabetes make it riskier for prediabetics to donate. There is limited research on the impact of PD in kidney donors and there is a need for prospective long term follow up studies. The combination of IFG and IGT has greater association with CKD, cardiovascular events, stroke and peripheral neuropathy, and patients with these issues should not make donations. Those with isolated IFG should be evaluated for other risk factors of diabetes with the use of a validated risk calculator. Those with isolated IFG and no other risk factors may donate after appropriate long term lifestyle modifications. There is variability in recommendations among the transplant community regarding kidney donation in prediabetics and there is a need to build up a consensus to ensure uniform practice and better outcomes for both donors and recipients.

FOOTNOTES

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