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Pros and Cons of Live Kidney Donation in Prediabetics -A Critical Review and Way Forward

Kidney Donation in Prediabetes

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Abstract

There is shortage of organs including kidney worldwide. Along with deceased kidney transplantation, there is significant rise in live kidney donation. Prevalence of prediabetes (PD) including impaired fasting glucose (IFG) and impaired glucose tolerance (IGT), is on rise across the globe. Transplant teams frequently come across prediabetic kidney donors for evaluation to donate. Prediabetics are at risk of developing diabetes, chronic kidney disease (CKD), 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. 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 donation in prediabetics leading to more confusion among clinician. This increases the responsibility of transplant teams to take appropriate decisions in best interest of both donors and recipient. This review focuses on pathophysiological changes of PD in kidneys, potential complications of PD, other risk factors for development of type 2 diabetes, review of guidelines for kidney donation, potential role of diabetes risk score and calculator in kidney donor and way forward for 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: Increasing number of prediabetic kidney donors are encountered by transplant physicians. The decision to allow or not to allow these donors is always

challenging. Prediabetics are prone to multiple complications in the future including diabetes mellitus and CKD. Variability in recommendations by various organizations and societies about kidney donation in prediabetics lead to even further confusion in decision making. This extensive review focuses on evidence from both general population and kidney donors regarding kidney donation in prediabetics. This review will help clinicians to take well inform decisions and to identify future direction for further research and need for a uniform position statement by international transplant societies like The Transplantation Society (TTS) or International Society of Nephrology (ISN).

INTRODUCTION

The global prevalence of PD is high. PD increases 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 family history of diabetes make prediabetics riskier to donate. There is limited research on the impact of PD in kidney donors and there is need for prospective long term follow up studies. The combination of IFG and IGT has greater association with CKDS, cardiovascular events, stroke and peripheral neuropathy and should not make donation. Those with isolated IFG should be evaluated for other risk factors of diabetes with the usage of a validated risk calculator. Isolated IFG with no other risk factors may donate after appropriate long term lifestyle modifications. There is variability in recommendations among transplant community regarding kidney donation in prediabetics and there is a need to build up consensus to ensure uniform practice and better outcomes for both donors and recipients.

CONCLUSION

PD is described as high blood glucose level which does 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, an HbA1c level of 6.5% or greater, or a 2-hour 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-hour 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 IFG cutoff at 110 mg/dL (6.1 mmol/L) [1]. The global prevalence of PD reported in literature has been variable due to variety of reasons. Firstly, definition of PD by WHO and American Diabetes Associations has been different and as a result prevalence varied among different studies depending on the definition being used. Secondly, studies used different parameter such as fasting glucose, glucose tolerance test or glycosylated hemoglobin to define prediabetes which could have led to variable prevalence. Rooney MR *et al* used WHO definition of PD and reported, the global prevalence of IGT in 2021 as 9.1% (464 million) and it was projected to go up to 10 % (638 million) in 2045. Similarly, the global prevalence of IFG in 2021 was 5.8% (298 million) and it was projected to increase to 6.5% (414 million) in 2045 [2]. Bullard KM and his colleagues used American Diabetes Association definition and reported the prevalence of PD in adults aged ≥ 18 years as 29.2% in 1999-2002 which increased to 36.2% in 2007-2010 in US population [3]. A study from China used American Diabetes Association 2010 definition, and reported prevalence as 50.1% [4]. Around 5–10% of people with PD develop DM annually [3,4] 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 the 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 increase risk of ESRD [12,13]. Prediabetic

kidney donors have a seven-fold increase 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 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 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, blood pressure and insulin status [19]; with subsequent development of microalbuminuria. A Korean study reported odd ratio of 2.57 in 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 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 cardiovascular events and CKD [23]. Furthermore, presence of microalbuminuria in donors with PD could result in 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 F *et al* were the first to describe the histological manifestation of PD through an analysis of 23 patients who had diffuse thickening of 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 on follow-up [24]. The authors speculated that isolated diffuse thickening of glomerular capillary basement membrane may be a renal lesion in PD. Thickening of 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 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 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 glomerulonephritides [29-31]. However late CKD in kidney donors is due to denovo DM [29,32] and hypertensive nephrosclerosis [33]. PD has been implicated in hyperfiltration [16,17,18] and development of microalbuminuria [21,22] in the general population which are usually early manifestation of renal injury. Though the risk of conversion from PDM 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 S *et al* 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 [34]. Hebert SA *et al* and

his colleagues also did not find increased risk of CKD in donors with PD [35]. 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 [36]. About 40% of diabetics will develop CKD in their life span [37]. Microalbuminuria and hyperfiltration develops in 5-10 years after the initial diagnosis of DM (or PD). Macroalbuminuria develop in another 15 years and ESRD will ensue in 19 years from diagnosis of diabetes [38]. 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 [34] to 10.4 years [14], which may have missed capturing patients with late onset DM and diabetic kidney disease.

There are many studies done in general population on PD and risk of CKD 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 with those having 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 [39]. Selvin E *et al*, 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 hazard ratio of 1.12 (0.94–1.34) and 1.39 (1.04–1.85) for development of CKD. The corresponding hazard ratio for ESRD were 1.51 (0.82–2.76) and 1.98 (0.83–4.73), respectively [40]. In a study from Korea [20], the odd ratio for microalbuminuria and CKD in individual with PD having impaired fasting were 1.54 (95% confidence interval: 1.02-2.33) and 1.58 (1.10-2.25). The odd ratio 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 [41]. Redon J and his colleagues [42] 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 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 factor for CKD and 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 for IFG was 0.97 (95%CI: 0.75–1.25) and that 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 [43]. In secondary analysis of the Systolic Blood Pressure Intervention Trial (SPRINT), 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 [44]. Similarly, a study from Japan though found association of PD with development of proteinuria but it failed to show any association between PD and CKD [45].

A meta-analysis of 9 cohort studies the participants of which were mainly Asians and Whites found increased risk of CKD in PD. Eight studies used definition of impaired fasting as 6.1-6.9 mmol/L and after adjustment for established risk factors, the relative risk 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 relative risk of CKD was 1.12 (95%CI 1.02–1.21) [46].

Table 1 showing association of PD with CKD

Reference

Journal /Year

Study type

Objective

Findings

[39] Fox CS *et al*

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.

[42] Redon J *et al*

J Am Soc Nephrol / 2006

Prospective multicenter, cross-sectional study

To assess the relationship between urinary albumin excretion (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 /minute 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 if diabetes (OR 1.23; 95%CI 1.04 to 1.45).

[41] Plantinga LC *et al*

CAJSN/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.

[34] Okamoto M *et al*

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.

[40] Selvin E *et al*

Diabetes / 2011

Prospective cohort and cross-sectional analyses of Atherosclerosis Risk in Communities (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 hazard ratios (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). Hazard ratio for ESRD were 1.51 (0.82–2.76) and 1.98 (0.83–4.73)

[43] Schöttker B *et al*

Prev Med / 2013

Prospective Study

1-To determine the risk for incident reduced kidney function in participants with pre-diabetes

2-To determine dose–response relationships of fasting glucose and HbA_{1c} 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(HbA_{1c}-defined pre-diabetes): 1.03 (95%CI: 0.86–1.23)).

[14] Chandran S *et al*

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 mL/min/1.73 m^2 vs. 67.3±16.6 mL/min/1.73 m^2, *P*=0.21) was similar between 2 groups

3- Urine albumin/ creatinine 9.76±23.6 mg/g vs. 5.91±11 mg/g, *P*=0.29) was similar between 2 groups.

[46] Echouffo Tcheugui JB *et al*

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.

[44] Bigotte Vieira M *et al*

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 [hazard ratio (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).

[45] Furukawa M *et al*

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 (odds ratio [OR] 1.233; 95% confidence interval [CI] 1.170–1.301]. No association was found with eGFR decline (OR 0.981; 95%CI 0.947–1.017).

[35] Hebert SA *et al*

Transplantation/2022

Retrospective data analysis of The Renal and Lung Living Donors Evaluation (RELIVE) study

To study mortality, proteinuria, and end-stage kidney disease (ESKD) according to donation fasting plasma glucose (FPG): <100 mg/dL,100–125 mg/dL, and ≥126 mg/dL

IFG was associated with a higher diabetes risk (adjusted hazard ratio, 1.65; 95% confidence interval [CI], 1.18-2.30) and hypertension (adjusted hazard ratio 1.35; 95%CI, 1.10-1.65; $P = 0.003$ for both), but not higher risk of proteinuria or ESKD.

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 diabetes mellitus, cardiovascular events, stroke, microvascular complications such as neuropathy and retinopathy and has been associated with dementia, depression, cancers and increase all-cause mortality [47,48]

1-Development of diabetes:

Risk of progression from PD to diabetes vary widely, due to differences in the definition of PD, heterogeneity of PD, social and physical environment [49,50]. The lower cut-off point for IFG, which is still used by WHO, is 6.1 mmol/L [51]. In 2003, this cut-off point was lowered to 5.6 mmol/L by the ADA [52]. As a result, there is variability in prevalence of PD and subsequent progression to diabetes. Around 10-50% of individuals will develop diabetes in next 5-10 years [53-55]. On the other hand, 30-60% will revert to normoglycemia within 1-5 years [53].

The risk of progression of PD to diabetes is less well studied in kidney donors. Various studies done in kidney donors reported incidence of diabetes as 1.5-7.4%. However, most of these studies were cross sectional in nature, having sampling bias with a lack of baseline glucose levels before donation [56-65]. The risk of diabetes in kidney donors with PD is 6 times more as compared to donor without PD [14]. In a retrospective review with 1826 kidney donors, patients with IFG (100-126) were compared with those with normal blood glucose (<100 mg/dL) and donors with fasting glucose ≥126 mg/dL [66]. 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 in 15.4 ± 10.9 years compared to 5.5% donors with IFG who developed diabetes 10.6 ± 8.8 Latter after donation.

2-Risk of cardiovascular diseases:

Post kidney donation living donors are prone to high blood pressure and proteinuria [67-70]. Proteinuria, hypertension and reduced glomerular filtration rate are known risk factors for cardiovascular events [71-73]. There are mixed findings regarding post donation risk of cardiovascular events. A recent long-term follow-up (11.3 years) of kidney donors showed that donors were at increased risk of ischemic heart disease when compared with healthy controls [74]. Conversely, there are also studies which did not find increased risk of cardiovascular events [75,76]. 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 have been gathered from the general population. PD has been implicated as a risk factor for cardiovascular diseases in a range of studies [77-79]. PD shows a 20% higher risk of developing cardiovascular disease as compared to those with normal blood sugar [80]. Insulin resistance, inflammation and endothelial dysfunction in PD are linked to more cardiovascular events [81]. IGT is more often associated with cardiovascular events than IFG [82-84], with overall similar

cardiovascular risk to type 2 diabetes mellitus in many landmark trials such as DECODE (Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe) [82], DECODA (Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Asia) [85] and Funagata Diabetes study [79]. Similarly, increase in glycosylated hemoglobin even within normal range has been shown to cause more cardiovascular mortality. In the EPIC Norfolk study, even a small increase of only 1% increase in HbA1c within the normal range caused increase in 10-year cardiovascular mortality [86]. Since PD causes insulin resistance, inflammation and endothelial dysfunction [81], KT physicians have to be more mindful on potential future cardiovascular risks.

3-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 is around 37% [87]. Two-hour IGT is a stronger predictor of stroke and cardiovascular events compared to IFG [82,88]. IGT has also been implicated in recurrent ischemic stroke and TIA and it increases risk of recurrent TIA and minor stroke by 2 folds [89]. 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 combination of IFG and IGT were independent risk factors for stroke [90]. 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.

4-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 development of diabetes [91]. PD has been linked to development of peripheral neuropathy in the general population, though its prevalence is varied in different studies. The 1999-2004 cohort from NHANES reported the relative risk of peripheral neuropathy of 1.1 in PD and 1.7 in diabetes [92]. 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 [93]. The MONICA/KORA study found that neuropathy was more common in patients with IGT when compared to control [94]. Authors of this study used Michigan Neuropathy Screening Instrument (MNSI) and found that neuropathy, predominantly 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 [94]. The Prospective Metabolism and Islet Cell Evaluation (PROMISE) 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%) followed by those who developed PD (49%) compared to individuals with normoglycemia who have an incidence of 29% [95]. 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% [96]. Unfortunately, there is lack of data on peripheral neuropathy in prediabetic kidney donors.

5-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 [97]. 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 [98]. Post hoc analysis of a systematic review [99] showed lower median retinopathy in patients with 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 [100]. The Maastricht Study using spectral domain optical coherence tomography found that macular thickness is reduced in PD even before 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 [101]. Though the association of retinopathy in general population is strong, this is again not thoroughly investigated in kidney donors with PD.

6-Dementia

Dementia has been a recognized complication of PD. Insulin and insulin-like growth factors have important role in vital functions of neurons including survival and growth of neurons, gene expression, protein synthesis, myelin production and maintenance in oligodendrocytes, synapse formation and plasticity [102,103]. PD, like diabetes, is a state of hyperinsulinism with insulin resistance which affects function of brain cells (neurons and glial cells) leading to neurodegeneration and dementia [104-106]. 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 [107]. Similarly, another study in elderly women, showed risk of development of cognitive impairment among participants with IFG (odd ratio 1.64) and DM (odd ratio 1.79) [108]. Prediabetics in the Maastricht study participants found to have more cerebral lacunar infarcts, white matter lesions and loss of brain volume when compared with normoglycemic participants [109]. The hyperglycemia is a continuum from normoglycemia to PD and then diabetes and increasing hyperglycemia across this spectrum in prediabetic and diabetics affected executive functions in NHANES 2011–2014 cohort [110]. 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 [111].

7-Depression:

PD has been linked to risk of depression in various studies [112,113], likely through insulin resistance. Insulin resistance in brain induces mitochondrial and dopaminergic dysfunction leading to anxiety and depressive-like behaviors [114]. Two meta-analyses done on association of PD with depression reported mixed findings; one metanalysis reported that prevalence of depression is moderately increased in prediabetic and in undiagnosed diabetic patients [115] and the other found that prediabetics are not at higher risk of depression [116]. Some studies have also shown that the combination of PD with depression increases risk of progression to development of diabetes [117-119]. Since

anxiety, depression and regret have been reported in some kidney donors [120-122], therefore, it is important to understand the potential future neurological sequelae of PD.

8-Cancers

PD has been reported to be associated with cancers in several studies [123-125]. A community-based study from China reported that glucose intolerance (PD & DM) was associated with stomach, colorectal, and kidney cancer in individuals with age <65 years [126]. PD is associated with obesity and overweight, which are the recognized risk factors for cancer [127]. Hyperglycemia has been linked to increase 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 [128]. 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 [127].

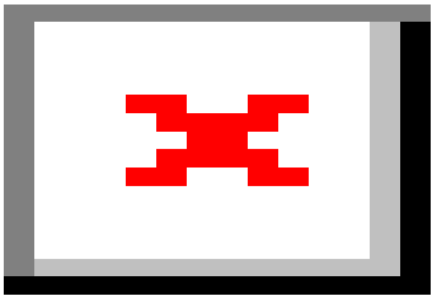
Kidney donors have a similar incidence of liver cancer, melanoma, breast cancer, and non-Hodgkin lymphoma post donation 7 years as compared to general population. However, there is increased incidence of colorectal cancer (adjusted incidence rate ratio 2.07, 95%CI 154– 2.79) and kidney cancer (2.97, 1.58–5.58) in kidney donors [129]. 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.

9-Nonalcoholic fatty liver disease (NAFLD)

The prevalence of NAFLD is 48.25% in patients with PD [130]. In a study from USA, 44-62% of the adults with PDM had NAFLD [131]. Prevalence in general population is 26% which is much lower than PDM [130]. Obesity associated insulin resistance increases free fatty acid levels which lead 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 the fibrosis in liver [133]. Subclinical chronic hepatic inflammation and insulin resistance has been shown to cause NAFLD in PDM [134]. NAFLD has been linked with

reduced GFR [135]. 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 [136]., but data on prediabetic kidney donors are lacking. Looking at data from general population it will be interesting to evaluate the association between NAFLD and PD in kidney donors.

Figure 1:



9-All cause mortality:

PD has been linked to increased all-cause mortality [137]. A study from Japan showed that PD was significantly associated with increased risk of death from all causes and cancer but not cardiovascular diseases [138]. PD along with hypertension not only cause increased all-cause mortality but also increased cardiovascular mortality [8]. Another recent metanalysis of 16 studies found that PDM was associated with increased risk of all-cause mortality [139]. 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 [140]. Keeping these facts in mind, it is important to fully educate prediabetic kidney donor about physical activity prior to

donation. Figure 1 showed potential complications which can happen in a kidney donor.

10- Other complications:

Various other complications such as sleep disturbances [141], snoring [142], obstructive sleep apnea [143], increase fracture risk [144] and high mean platelet volume and platelet distribution width [145] 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 follow:

1-Age:

Elderly has a higher prevalence of diabetes and PD than young and middle-aged people [146,147]. Age is an important risk factor for development of diabetes because of inflammation, mitochondrial dysfunction and abnormal lipid metabolism [148]. However, there are studies which showed that majority of the PD either remained stable or reverted to normoglycemia [149,150]. Since PD is a continuous and cumulative risk, most transplant programs may discourage young prediabetics to donate.

2-Obesity

Obesity is a potentially modifiable risk factor for diabetes [151]. 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 [152]. 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 individual [153]. Excess visceral fat and insulin resistance rather than general adiposity were found to be associated with development of PD and diabetes [154].

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 [155]. Praga *et al* found that kidney donors with higher BMI had a greater risk for the development of proteinuria and renal

dysfunction [156]. Similarly, another study also found significant relationship between increasing BMI and the rate of kidney insufficiency after kidney donation [157]. Therefore, prediabetics with obesity should be evaluated carefully due to risks of development of diabetes, proteinuria and renal dysfunction.

3-Smoking

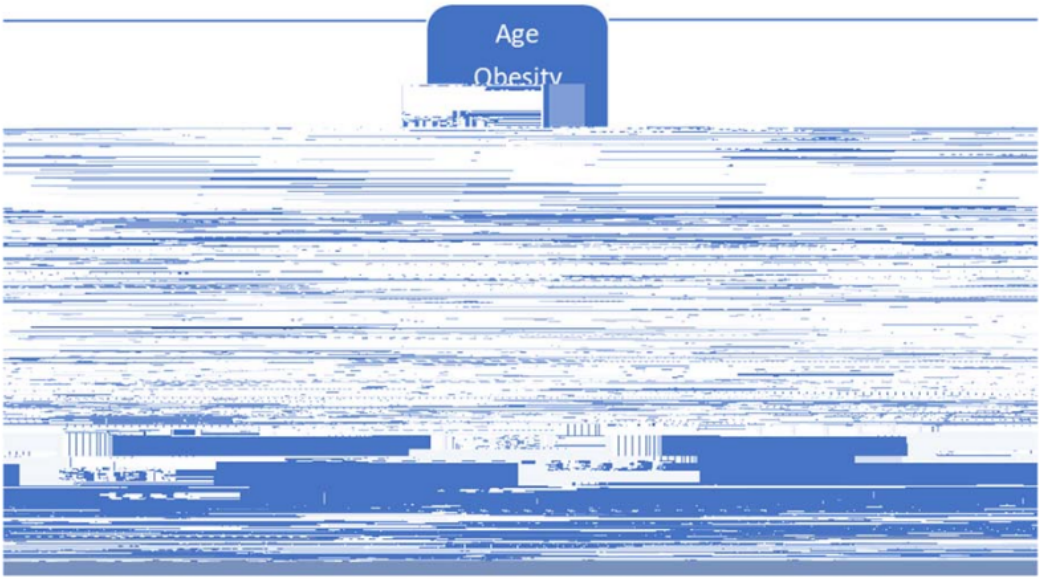
Smoking has been shown to decrease insulin action and increased insulin resistance in experimental setting [157]. Coronary artery risk development in young adults (CARDIA-study), studied effect of active and passive smoking on glucose intolerance. Over 15 years follow up glucose intolerance was highest 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 smoke [158]. Another study found that 5-10 pack-years of smoking increased odds of PD by 2-fold, which is reversible with smoking cessation [159]. Smokers are 30 to 40% more likely to develop diabetes as compared to non-smoker [160]. Various studies have shown strong association between cigarette smoking and development of DM [161-164]. Smoking is common in kidney donor, though pre-donation education usually reduces incidence of smoking [165]. Active or passive smoking in kidney donors may lead to higher serum creatinine compared to non-smoker [166,167]. Therefore, prediabetic kidney donors with history of smoking should be advised to stop and be evaluated thoroughly for future risk of DM.

4-Ethnicity /Race

Certain ethnicities are more prone to develop diabetes and its complications. United State is populated by multiple ethnic groups. The rate of diagnosis of diabetes is 14.5% in American Indian / Alaskan Natives, 12.1% of non-Hispanic blacks, 11.8% of Hispanics, 9.5% of Asian Americans and 7.4% of 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% of Mexican American have diabetes followed by 14.4% in Puerto Ricans [168]. Similarly in UK, prevalence of type 2 diabetes is indeed higher among Asian, Black and minority ethnic groups [169]. 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) [170]. Percentage of change in number of people with diabetes between years 2000 to 2030 has been 97 percent for Sub-Saharan Africa, 67 % for Middle East, and 42% for Asia and Islands [171]. 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.

Figure 2



5-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 [172]. The risk of development of diabetes is 7-10-folds higher in women with gestational diabetes [173,174]. After the diagnosis of gestational diabetes, rapid conversion to overt diabetes is seen within 5 years, with a slower progression subsequently [175]. Furthermore, women with gestational diabetes are at higher risk of developing metabolic syndrome [176] and are at increased risk of cardiovascular events [177]. It should also be kept in mind that

subsequent pregnancy post donation, make female donors more prone to higher risk of preeclampsia, gestational hypertension and preterm birth [178]. Therefore, female kidney donors with PD and history of gestational diabetes should be thoroughly assessed for risk *vs* benefits.

6 -Metabolic syndrome

The combination of glucose intolerance, hypertension, dyslipidemia and obesity is known as metabolic syndrome [179]. In the Beaver Dam study, the odd ratio for incidence of diabetes was 9.37 if three abnormalities of metabolic syndrome were present. The odd ratio went up to 33.67 if four or more abnormalities were present [180]. In the Framingham Heart Study Offspring Study, the relative risk for type 2 diabetes increased with the number of metabolic syndrome components [184]. The West of Scotland Coronary Prevention Study used NCEP definition for metabolic syndrome with or without the inclusion of C-reactive protein. The study found, relative risk for diabetes 7.26 with three abnormalities of metabolic syndrome. The relative risk went up to 24.4 for four more abnormalities of metabolic syndrome [181]. The British Regional Heart study found the relative risk for diabetes as 4.56 for three abnormalities. The relative risk for development of diabetes went up to10.88 for four more abnormalities [182].

IFG is one of the components of metabolic syndrome. Various studies have shown that IFG is one of the strongest predictors of development of diabetes compared to the other elements of metabolic syndrome. In a study from Finland [183] hazard ratio for development for impaired fasting glucose was 5.16 which was highest when compared with obesity (hazard ratio 1.75), triglyceride (hazard ratio 1.34), HDL-cholesterol (hazard ratio 1.60) and blood pressure (hazard ratio 1.87). The Framingham Offspring Study showed that individuals with metabolic syndrome which included IFG showed a high relative risk of 11 which was much higher than the relative risk of 5 in individuals in whom IFG was excluded in analysis [184].

Development of metabolic syndrome has been studied in kidney donors. An analysis of 2,018 Living kidney donor 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 [185]. However, in another study more donors develop new onset metabolic syndrome as compared to controls [186]. Martín-Alemañy Geovana *et al* reported that living kidney donors had a high frequency of cardiometabolic risk factors and metabolic syndrome at the time of donation, which significantly increases over time [187]. In fact, metabolic syndrome was found to be a major barrier to kidney donation in one of the studies [188]. Therefore, one should carefully evaluate potential donors with PD and metabolic syndrome as they may be at risk of developing DM and cardiovascular complications.

7.Family history

Family history is one of the recognized risk factors for 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 [189,190]. 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%) [189]. 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 high-risk family, 20.1% in moderate risk family and 8.4% in average risk family [191]. Thus 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 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 [192]. The Health Examinees-Gem (HEXA-G) study was done in Korea, aims to find associations of 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 [193]. Therefore, a prediabetic kidney donors should always be evaluated with a detailed family history of DM or PD. Figure 2 shows potential risk factors of development of diabetes in a prediabetic kidney donor.

WHAT GUIDELINES RECOMMEND ABOUT KIDNEY DONATION IN PD?

The Amsterdam Forum on the Care of the Living Kidney Donor (2006) [194], 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-hour glucose with oral glucose tolerance test ≥ 200 mg/dL (11.1 mmol/L)) , but do not have any recommendations for PD [194].

CARI guidelines [195] recommend to check fasting blood sugar twice in all kidney donors. Those with sugar ≥7 mmole/L on both occasions are considered as diabetic and is considered absolute contraindication. The guidelines used 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 diabetes mellitus were advised to have oral glucose tolerance test. The characteristics of high risk for developing type 2 diabetes mentioned in CARI guidelines included family history, age > 45 years, Aboriginal or Torres Strait Islander (ATSI) and obesity. If the 2-hour 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 living kidney donation. Donors with IGT having blood sugar between 7.8–11.0 mmol/L are considered not fit to donate. Donors with glucose tolerance <7.8 mmol/L is normal and was considered to be not a contraindication to donation. Furthermore, a past history of gestational diabetes was considered as contraindication to donation.

American Society of Transplantation (AST) [196] states that the risk of DM in donors with PD is higher than for a healthy donor. PD also increases the future risk of diabetic kidney disease. UNOS (United Network of Organ Sharing) excludes donor 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 risk for future DM [196].

British Transplantation Society (BTS) and UK Renal Association published their guidelines in 2018 [197]. 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 oral glucose tolerance test, in prospective donors with an increased risk of type 2 diabetes such as family history of diabetes, history of gestational diabetes, ethnicity or obesity. If oral glucose tolerance test shows persistent IFG or IGT, then careful assessment should be done clinically using the diabetes risk calculator [198]. Unlike other guidelines, these guidelines do not exclude diabetic completely. Diabetics can be taken as donor provided there is no target organ damage and cardiovascular risk factors such as obesity, hypertension or hyperlipidemia are optimally managed. Furthermore, through assessment should be done to know lifetime risk of cardiovascular and progressive CKD in the presence of a single kidney.

KDIGO published its guidelines for care of live kidney donor in 2019.The guidelines suggest to take history of diabetes mellitus, gestational diabetes, and family history of diabetes. Blood sugar status should be assessed by doing fasting blood glucose and/or glycated hemoglobin (HbA1c) before donation. The guidelines also recommend to do two-hour glucose tolerance testing or HbA1c testing in donor candidates with elevated fasting 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 individual basis keeping in view their future risk. Furthermore, KDIGO guidelines recommend that donor with PD and DM should be explained that their condition may progress and could result in end organ damage [199].

European Best Practice Guidelines published in 2015, recommended that DM is a contra-indication to donation, other than in exceptional circumstances (1D) and IGT is not an absolute contra-indication to donation (2C) [200].

Looking at these guidelines, there is variability in recommendation for donation 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 literature. American Society of Transplantation guidelines has mentioned about using diabetes risk calculator to provide accurate and individualized risk for future development of diabetes [196 ,201]. The Renal Association and British Transplantation Society also recommend diabetic risk calculator [197, 198]. The University of Minnesota, developed an apparatus that predict risk of hypertension, type 2 diabetes, 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, e GFR, serum creatinine, (capillary or serum) glucose, body mass index, systolic blood pressure, diastolic blood pressure, family history of hypertension and dyslipidemia. It also took into consideration relationship to recipient and whether recipient has type 1 or type 2 DM. Unfortunately, prediction for hypertension and diabetes may not be valid for non-White donors [202].

There are various risk scores models and risk calculators available. Prominent risk assessment tools include the Australian 5-year type 2 Diabetes Risk Assessment (AUSDRISK) [203], the Diabetes UK 10-year Know Your Risk [204], The Finnish Diabetes Risk Score (FINDRISC) [205], and the American Diabetes Association type 2 Diabetes Risk Test [206]. Age, gender, family history of diabetes, body mass index 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 UK calculator, on the other hand, include 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 UK calculators. Physical activity is included in the AUSDRISK and ADA calculators. FINDRISC diabetes calculator includes gender, weight, height, age, waist circumference, physical activity for more than 30 minutes, 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 prediction of risk of diabetes mellitus [207]. This systematic review found poor methods including pre-screening univariate variables, categorization of continuous risk predictors and 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 [208]. 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 future development of diabetes.

WHAT SHOULD BE THE WAY FORWARD?

There were about 88,751 patients on the waiting list till September 2023, to get a kidney as per Organ Procurement & Transplant Network (OPTN) data. Only 20,445 of the patients were transplanted till September 2023. About, 15824 kidneys were obtained from deceased donors and another 4,621 were from living donor. This reflects that approximately only 1/4th of the patients on the waiting list could get a kidney [209]. Because of global organs shortage 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 future risk of development of diabetes, development of CKD and other complications of PD have contributed the conundrum of using complex donors. As discussed, couple of studies with short term

duration (ranging from 88 months to 10.4 years) in kidney donors having PD did not find increased risk of CKD [14,34,35]. After progression of PD to DM, another approximately 19 years are needed for progression of microalbuminuria to macroalbuminuria and then to development of ESRD [38]. Keeping these facts in mind, to know the real sequalae of PD in a kidney donor, we need long term studies of at least 19 years of follow up.

Post donation, the prediabetics kidney donors are left with only one kidney. Most of the evidence regarding PD and its complication are derived from studies done in general population [20,40-42]. Development of diabetes and CKD are not the only worries. Other complications of PD including cardiovascular disease [77-79], stroke [82,87-90], neuropathies [91-96], retinopathy [97-101], dementia [102-111], depression [112-122], cancers [123-125], non-alcoholic fatty liver disease [130-134] and increased all-cause mortality [137-139] are well established in 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" [210]. 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 showing detailed risk *vs* benefits and alternative options other than transplant should be available for both donor and recipient to protect both of them equally. Unfortunately, the guidelines from various societies and organizations are variable leading to further confusion [194-197,199,200]. We feel that, while evaluating a potential prediabetic kidney donor, one has to look at overall risk of development of diabetes. Donor with impaired fasting glucose should undergo 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 gives great risk of developing renal dysfunction [20] and peripheral neuropathy [93]. Similarly, two hours IGT, has been a strong predictor of stroke and cardiovascular events [82,88]. Therefore, prediabetic kidney donor with impaired fasting glucose and IGT should be considered as high risk and may not be suitable candidate. 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 low risk case. IFG along with single or combinations of risk factors such as age, family history, ethnicity, smoking, obesity, gestational diabetes and metabolic syndrome may be considered as 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 that are willing to undergo long term life style modification and accept the risk.

RECOMMENDATION

We suggest the following recommendations:

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

Kidney donor with PD having abnormal IFG along with IGT are considered high risk even in the absence of other risk factors. If appropriate life style modification failed to revert 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. Presence of any risk factor in kidney donors along with IFG, make them high risk. Appropriate life style modifications are recommended to achieve euglycemia and possible donation in the future.

Locally well designed and validated risk score or risk calculator may be helpful in identifying high risk donor 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 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 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 need for enhanced medical follow up of kidney donor who has history of PD. They should have greater access to clinics, health club memberships, dietician and medications. Life style modification should be re-enforced through continuous education.

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

9-It will be interesting to assess the efficacy of sodium-glucose cotransporter-2 (SGLT2), glucagon like peptide 1 (GLP1), mineralocorticoid receptor antagonist (MRA) and RAS inhibitors in kidney donors with PD and its effect on long term renal and cardiovascular outcome

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

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