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Management of Diabetic Patient with CKD 5 and Progressive Diabetic Complications: A Case-Based Review

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ABSTRACT

A 56 year old CKD 5 patient due to diabetic nephropathy (biopsy proved) presented to our hospital in transplant clinic for transplant assessment. She is not yet on dialysis and her current eGFR is 20 ml/min. She was diagnosed at the age of 29 to have diabetes. It is not clear from notes whether she is type 1 or type II DM. She is currently on insulin with frequent episodes of hypoglycemia unawareness, particularly during last three years. Her kidney function started to deteriorate 9 years from diagnosis of her diabetes. Her plain X-Ray pelvis is shown below. She has no DSA and has a family member (28 years old lady whose blood pressure is well controlled by one agent, but no more available information) who expressed her interest to donate a kidney for her.

Our team is intended to discuss her possible options of diabetic control and the outcome of each option, addressing graft (s) survival, patient survival, as well as the postoperative complications. We need also to council the potential donor regarding the procedures of kidney donation and to outline the workup of this potential donor. Furthermore, workup of this prospective recipient, as well as her prospective follow-up plan, might be generally outlined.

Keywords: Diabetic complications, Pre-emptive renal transplantation, Simultaneous pancreas and kidney transplant (SPK)

CASE ANALYSIS

The following data have been shown in the given scenario:

1. Post-menopausal lady 54 years old.
2. Stage 5 CKD with estimated glomerular filtration rate (eGFR)=20 ml/min. Not yet on dialysis (DX).
3. Possibility of pre-emptive renal transplantation (RTx).
4. Type I/II DM on insulin therapy with hypoglycemia unawareness for 3 years.
5. Plain-x-ray: evidence of vascular calcification in her deep pelvic vessels.
6. Absence of evidence of DSA.
7. Recipient data: female, 28 years old, with controlled hypertension (HT) with single agent.

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DISCUSSION

Possible options of diabetic control: the outcome of each option addressing graft (s) survival, patient survival and postop complications:

This post-menopausal diabetic lady, with CKD 5, possibly suffered from type I prolonged and uncontrolled DM as appeared in her recurrent episodes of unawareness of hypoglycemia due to associated autonomic neuropathy. Episodes of hypoglycemia appeared due to decreased insulin requirements owing to her progressing renal failure (eGFR)=20 ml/min). So, this lady is currently in need for a healthy kidney associated with a suitable option for her diabetic complications. Fortunately, one of her relatives is ready to offer her a kidney. Consequently, the following therapeutic options may be offered for diabetic control [1]:

1. SPK (Simultaneous kidney-pancreatic transplantation).
2. PAK (Pancreas after kidney transplantation) (poor option).
3. Pre-emptive kidney transplantation (KTx) alone (indirect therapy).

The American Diabetes Association (ADA) have addressed the following criteria [2]

- **SPK (Figure 1):** for type I DM, transplant recipient (TR) with ESRD who have had or plan to have a KTx are candidates for pancreas transplant. Successful transplant of a pancreas will definitely improve glycaemia levels and may improve also kidney allograft survival. Most pancreatic transplants are performed in patients with DM complicated with ESRD. Majority of these patients receive SPK rather than PAK [3].

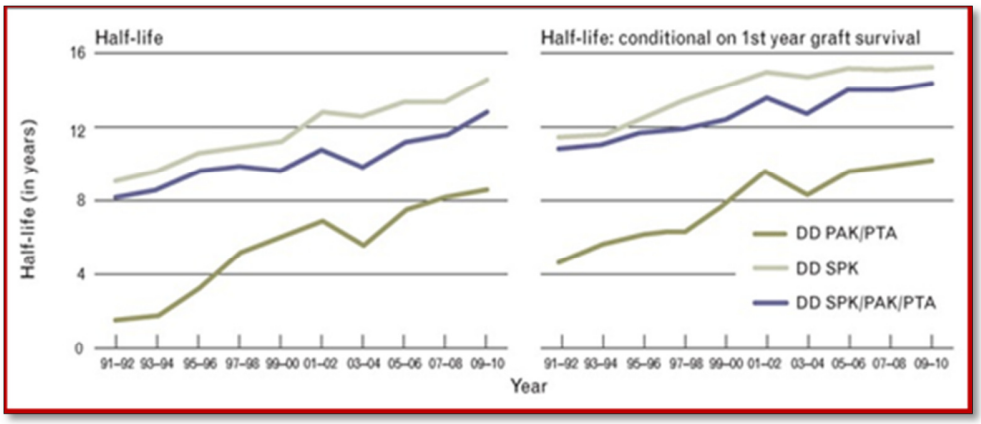

Figure 1. Improving results of SPK transplantation in the USA. The half-life for an SPK is now approximately 14 years. *PAK: Pancreas After Kidney; PTA: Pancreas Transplant Alone; SPK: Simultaneous Pancreas Kidney*
Reproduced with permission from Redfield et al. [1]

The current status of the techniques in SPK transplantation is yielding superior and continuous improving results. So, the first option for this patient is SKT. PAK and Islets after kidney are poorer option but pancreas alone or Islets alone NOT an option. Apart from SPK transplantation, other treatment options include:

- **Live donor kidney transplant (pre-emptive transplantation):** A kidney transplant from a young relative live donor is a very good option, as they tend to work straight away, and usually work for longer than a kidney from a deceased donor. However, without a pancreas, in addition to diabetic complications, our patient will still have diabetes. Furthermore, the impact of the immunosuppressive medications post-transplant may make the recipient's blood sugar control even worse.
- **Live donor kidney transplant followed by a pancreas transplant (PAT):** This is a poor option. A pancreas transplant from a deceased donor can take place 12 to 18 months after a live donor kidney transplant. Considering that the transplanted pancreas and kidney came from different donors, the risk of the expected rejection for the pancreas is currently higher. The average survival of a pancreas transplanted after a live donor kidney transplant is 3-5 years. This is much less than a pancreas transplanted as a part of an SPK transplant (10-14 years) **(Figure 1)** [2].

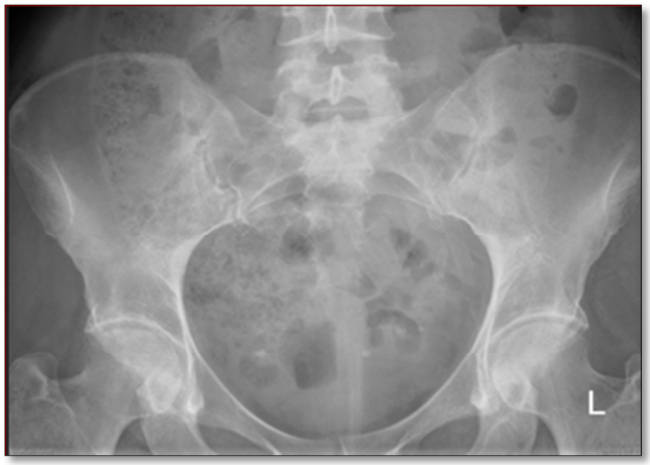

Figure 2. Vascular calcification is evident in plain pelvic X-ray.

Outcomes: Mortality, morbidity, and results of transplant may vary with the operative experience as well as with patient selection.

Patient survival:

1. According to 2004 to 2015 registry data, patient survival rates for SPK, PAK, or PTA ranged from: 96-99% within 1 year, 89-91% at 5 years, at 70-80% at 10 years postoperatively [4-6]. Most deaths that occur within the first 3 months post-transplant were due to cardiovascular (CVS) or cerebrovascular disc.
2. Few data exist about survival benefit for transplant compared with waitlisted patients. The following data relies on retrospective studies of transplantation registries from 1995 to 2003:

- **SPK** survival of TR was much better than that of waitlisted patients who remain on DX [7]. The decreased mortalities is partially due to the apparent survival benefit conferred by KTx alone (KTA; even without pancreas transplant) compared with DX.

Graft survival: According to 2004-2015 registry data, early allograft failure (within 90 days) reported in about 8-9.4% of patients [4]. 5 years pancreas graft survival for SPK, PAK and PTA was approximately 73, 65 and 53%, respectively [5]. Pancreas graft survival is reported to be inversely related to several donor varieties, including: age, body mass index as well as CVS death. TR of pancreas alone whose organs came from donors with poor donor risk indices usually experience lower rate of graft survival as compared to TR of SPK (77 vs. 88% at one year) [6,8]. Recognition of pancreas graft survival has been variably defined by different transplantation centers (e.g. complete insulin independence, continuity of C-peptide production) [5]. A stable universal definition may help the evolution of robust future outcomes studies. In US, the United Network for Organ Sharing has postulated a new definition of graft failure that includes: use of insulin ≥ 0.5 units/kg/days for 90 consecutive days [5,9]. In 2018, a classification of graft function was addressed by the International Pancreas and Islet Transplant Association and the European Pancreas and Islet Transplant Association [10].

Vascular calcification (VCL): One of the remarkable finding in this recipient preparation is the presence of evident VCL in her radiographic examination. VCL can be simply assessed by plain radiology of the aorto-pelvic area **(Figure 2)**. Considering the silent nature of this disease as well as its devastating Sequalea in renal TR, this investigation has gaining much popularity [11]. Moreover, VCL is categorized as a strong predictor of post-transplant all-cause and CVS mortality. Arterial calcification can be seen in the intima or the media. Sequalea and difference between both locations are summarized **(Table 1 and Figure 3)**.

Table 1. Vascular calcification

Items	Intimal calcification	Medial calcification
Appearance (aorto-iliac plain X-ray)	Not linear	*Linear* calcification, (railroad calcifications)
Hemodynamic impacts	Compromise blood flow, leading to tissue ischemia and necrosis	Arterial stiffening and decreased vascular compliance
Outcome	Worse: Strong predictors of death in HDX patients	Worse: Strong predictors of death in HDX patients

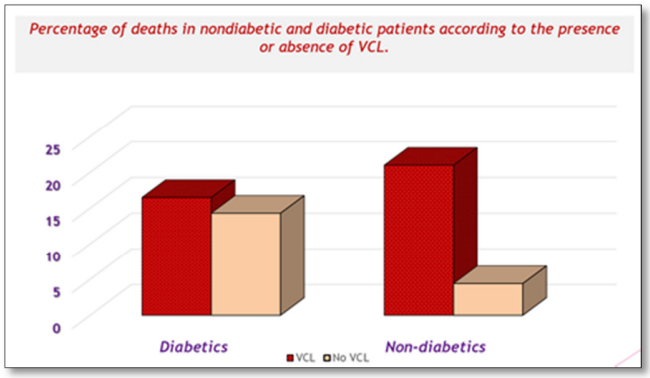

Figure 3. Significant interaction between VCL and diabetes prior to RTx, as calculated by the Cox regression analysis. In particular, the effect of VC on mortality was restricted to non-diabetic patients, i.e., those with VC had a significantly higher mortality rate than patients without VCL (21 vs. 9%; P=0.0001). By contrast, these differences were not observed in diabetic patients (16.5 vs. 14.3%; P=0.656)
Source: Adapted from Hernandez et al. [11]

Post-operative complications

Graft loss: Causes of pancreas graft loss vary with the time after transplant. Early graft loss, that can be defined as loss occurring within hours or days post operatively, it is usually results from (thrombosis, leaks, bleeding, infection and pancreatitis) (these complications are usually called technical failures). One series reported 211 TR undergoing pancreas transplant, technical graft failure was observed in 23 TR (11%), with the most common reported cause was due to thrombosis. Risk factors for technical failure include [obese donor/recipient and delayed preservation time of the donor organ]. Later graft loss, i.e., several weeks later, is more common and usually attributed to immunologic rejection [6,12,13].

The absence of a uniformly agreed criteria of allograft failure is currently impeded the proper estimation of pancreatic graft outcome. While some centers deny the failure of the allograft as long as C-peptide production persists, other centers document graft failure only with loss of recipient's independence on insulin. However, the OPTN/UNOS Pancreas Transplantation Committee has currently summarized the following criteria for pancreas allograft failure, to be implemented in the near future **(Box 1)** [14,15].

- Removal of the transplanted pancreas
- Re-registration for a pancreas transplant
- Registration for an islet transplant after receiving a pancreas transplant
- Insulin use of ≥ 0.5 units/kg/day for a consecutive 90 days
- Death of the recipient.

Box 1. Criteria for pancreas allograft failure for future implementation.

Rejection: In old reports pancreas transplantation may be rejected within few days or after many years post-transplant. Incidence of acute allograft rejection of pancreas may approach 60-80% of pancreatic grafts. However, Alemtuzumab and Tacrolimus based steroid free regimes are reported to have very low early rejection rates [16-18]. Management of rejection includes patient hospitalization with intensifying the immunosuppressive load. Methodologies applied to manage acute rejection of pancreas transplant alone are similar to that used in kidney-pancreas transplant.

Indices of rejection, however, include:

1. Increasing blood glucose levels.
2. Increasing serum amylase levels.
3. Diminished urinary amylase excretion (pancreatic exocrine function).

These aforementioned markers are less sensitive than a rise in S. Cr if a concurrent renal allograft is transplanted. Raised fasting blood glucose, however, is considered a relatively late indicator of graft deterioration, and the elevated serum enzymes, e.g. amylase, are nonspecific indicators of rejection. If rejection is a possibility, a cystoscopic-guided transduodenal pancreatic biopsy is ultimately the preferred technique for a definite diagnosis.

Workup of the prospective recipient: Diabetic nephropathy is proved to be the most common cause of ESRD in the western countries. In the US diabetic nephropathy is the etiology of ESRD in about 23% of kidney TR.

- Kidney transplantation is generally the optimal therapy for diabetics with ESRD and is generally preferred than commencing dialysis.
- One of the vital factors affecting patient's outcome is the timing of transplantation. Patients proceeded into transplantation with no previous history of dialysis (preemptive transplantation) usually show decreased mortality rates as compared to those who have experienced dialysis before transplantation **(Figure 4)**.
- Diabetics with ESRD and candidate for transplantation: it is recommended that if possible, pre-emptive kidney transplantation rather than commencing dialysis followed by transplantation. Living-donor kidneys are generally superior to deceased-donor kidney.
- In view of considering pre-emptive transplant as the goal, diabetics should be referred to the responsible transplant center when (eGFR) approached <30 mL/min. So, our patient is little late, but generally she is candidate to proceed in pre-emptive transplantation.
- For cardiac clearance, coronary heart disease assessment is advised and to limit the risk of toxic effects of immunosuppression, diabetics with ESRD are better be evaluated for the presence of underlying coronary heart disease. Optimal approach is unclear. Accordingly, the following steps are suggested:

    1. Diabetic TR should be thoroughly evaluated as regard full detailed history, physical examination, ECG, and chest radiography.
    2. Diabetic with symptoms and signs suspicious for coronary heart disease or myocardial infarction should perform cardiac catheterization unless revascularization has been previously performed.
    3. If initial screening for coronary angiography has not been performed, patient should proceed with screening dobutamine stress echocardiography. If positive, decision to perform angiography and possible angioplasty or surgery is usually made in collaboration with her cardiologist.

Pre-emptive transplantation and living-donor versus deceased kidneys: Pre-emptive (i.e., before dialysis is indicated) KTx is generally recommended whenever possible, rather than commencing DX followed by transplantation after dialysis **(Figure 4)**. Robust evidence suggests that pre-emptive KTx can result in substantial improvement in patient survival as compared to transplantation following a period of DX [19,20]. Moreover, limited evidence also suggests that diabetics with CKD have a survival advantage with pre-emptive transplantation [20].

Thorough analysis of 73,103 patients registered in USRDS database that include 20,000 diabetics, compared with preemptive transplantation, there was a relative increase in post-transplant mortality risk of 21, 28, 41, 53 and 72% among those with waiting times of 6 to 12, 12 to 24, 24 to 36, 36 to 48 and over 48 months, respectively [19]. Similarly, relative to pre-emptive transplantation, waiting times of 0 to 6, 6 to 12, 12 to 24 and over 24 months conferred a 17, 37, 55 and 68% relative increase in post-transplant risk for death-censored graft loss, respectively. The association between mortality risk/allograft loss and increased time on DX was observed among all subgroups recognized by etiology of ESRD, including diabetics.

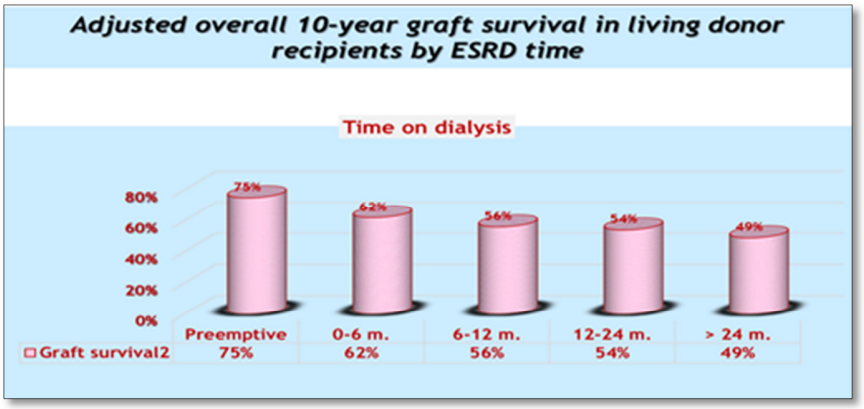

Figure 4. Comparison of renal allograft survival according to longevity on dialysis.
Source: Adapted from: Meier-Kriesche et al. [21]

The workup of the potential donor: Fortunately, this lady has a family member, 28 years old pre-menopausal female who's enthusiastic to donate her one kidney. The only positive information with this lady (the donor), is that she

has hypertensive disease that is well controlled by only one medication. However, evaluation of this donor includes:

- **The presence of past history of hypertension:** This mandates thorough evaluation and detailed questionnaire. The hypertensive donor on two or more medications is generally excluded [20]. But if she is controlled by one medication, she may continue in the process of donor workup only with absence of any evidence of end organ damage. Of note, a 2007 survey, 41% of centers may consider donors with well-controlled HT on one medication and only 8% will consider donors on two medications [22]. For donors on one antihypertensive drug, the following conditions should be guaranteed:
    1. Absence of microalbuminuria.
    2. Absence of obesity and dyslipidemia.
    3. Cardiac clearance with absent left ventricular hypertrophy (LVH).
    4. Clearance of ophthalmologic changes characteristic of HT in funduscopic examination.

Control of blood pressure (BP) should be documented at least in the last six months prior to the start of evaluation with availability of strict follow up of her BP after donation. Considering that evolution of HT and CKD in African Americans as well as Hispanics ethnicities post-donation [23], hypertensive disease may show poorer outcomes in these ethnicities, so that exclusion of large percentage of this population should be expected.

There is universal agreement the (2017 KDIGO guidelines) that the definition of normal blood pressure is confined by the local guidelines related to the general population in region/country where the donation is arranged [24]. Diagnosis of hypertension, however, is mainly established by the OPD measurement of BP and strict follow up. In case of reluctant diagnosis about HT diagnosis (variable readings or high normal), further evaluation can be accomplished through ambulatory blood pressure monitoring (ABPM) or through repetition of the standard measuring [24].

According to the OPTN policy (The Organ Procurement and Transplantation Network), there is general agreement that uncontrolled hypertension, or the presence of HT that is associated with an evidence of end-organ damage (mentioned above), is considered an absolute contraindication to living kidney donation [25]. Our donor here, in this scenario has her BP controlled with only one medication, so it is mandatory to clear her target end-organs from any HT detrimental complications. The criterion of acceptance of a donor with controlled HT, however, is not universal. One series in 2005 showed that 47% and 41% of kidney centers in the US have excluded donors taking any antihypertensive drug or treated with more than one drug, respectively [26].

For donors, at least two BP readings on two separate occasions should be performed [27]. If she has any elevated BP reading she must sent for 24 h ABPM to rule out white coat hypertension or to confirm the abnormal finding.

Kidney function: OPTN policy requires estimation of kidney function, either by measured GFR or a 24 h Cr Cl (creatinine clearance) [25]. KDIGO recommends the use of eGFR from serum creatinine concentration (S. Cr) for initial assessment, which should be followed by confirmation with one or more additional estimations: measured GFR, 24 h Cr Cl, eGFR from the combination of S. Cr. and cystatin C (eGFRcr-cys) or repeat eGFR [24]. The last option (i.e., repeat eGFR) is the least preferred one. However, utilizing eGFR alone is not recognized by OPTN policy, but screening with eGFR confirmed by 24 h Cr Cl or measured GFR can be efficacious and more policy compliant.

Identification of renal anatomy: accepting donor with anatomical aberrations is now considered only a relative CI by most transplant centers. Renal imaging prior to nephrectomy can be performed through US, DSA, CT and MRA. With final evaluation, all donors should have a full-detailed assessment of vascular/ureteric anatomy, usually CT or MRI testing.

Informing the risk: An honest and deep discussion with the donor with clear explanation by the transplant team in regard to the potential risks of donation as well as her health status if she had pregnancy with a solitary kidney and if she currently had children or not [28].

Post-transplantation care and follow up

Several complications involving kidney TR may occur in all diabetics that include: allograft rejection, increased risk of infection and malignancy. We will focus here in this scenario on some of these issues related to diabetics after SPK. Further complications affecting all diabetics, e.g. gastroparesis, autonomic neuropathy, peripheral neuropathy, and foot ulcers, are discussed elsewhere.

Allograft rejection: The actual incidence of allograft rejection in diabetic TR has not been well evaluated. In small series, risk of acute allograft rejection was reported to be similar among diabetic and non-diabetic TR [29,30]. However, Alemtuzumab and Tacrolimus based steroid free regimes have been reported to have very low early rejection rates [16-18].

Malignancies: Despite paucity of data about the real incidence of malignancies, it appears to be similar in TR with and without diabetic disease [31]. However, some series reported an increased incidence of malignancies in TR receiving SKP as compared to kidney transplant alone. It is not clear whether this may be related to the increased immunosuppressive burden among such cohort of recipients.

Viral infection: Viral infections in diabetics post-transplant are discussed elsewhere.

Urinary tract infection: Although the use of post-transplant prophylactic antibiotics is widely applied, UTI still represents a common complication among TR. However, the incidence of post-transplant UTI is reported to be more common in diabetics as compared to non-diabetics [32,33]. This may be attributed in part to the high incidence of neurogenic bladders among diabetic TR. Prophylactic therapy among diabetic TR is appeared to be similar to that in non-diabetic recipients. Among TR with or without diabetes, it is recommended to cover with an antimicrobial agent to guard against UTI.

Recurrent diabetic nephropathy: Most diabetic TR may develop histological changes of diabetic nephropathy recurrence that appear in some recipients within one-year post-transplant. However, diabetic nephropathy is rarely complicated by graft failure [34]. Disease recurrence in the allograft can be theoretically prevented through optimizing glycemic control. Interestingly, one single randomized trial of type 1 diabetic recipient reported that intensive insulin therapy at time of transplant was associated with less pathological alterations related to diabetic nephropathy on 5-years follow up kidney biopsies. Recurrent diabetic nephropathy, however, can be prohibited through successful kidney-pancreas transplant.

Glycemic control: The optimum glycemic control may be hampered immediately post-transplant, partly due to insulin resistance as well as due to diminished insulin secretion induced by steroids therapy in addition to the effect of other immunosuppressive medications. The importance of glycemic control on TR outcomes has been elucidated in a study of type I DM TR who underwent SKP or living-donor kidney between 1983 and 2012 [35]. In a median follow-up of about 8 years, the adjusted hazard ratio (HR) for CVS disease-related death in SPK compared with living-donor kidney was 0.63. This outcome has been exaggerated in those with a functioning SPK transplant.

CONCLUSION

With the development of devastating diabetic complications, management of which should take the first priority. With a pancreatic graft life span approaching 14 years, this lady would get many benefits with SKP transplant. However, if early deceased donor transplantation is not available due to, for example, a very long waiting list, a preemptive living related donor transplant will be a reasonable therapeutic option, unless there was a clear contraindication. PAK and Islets after KTx are alternative options, but pancreas alone or Islets alone would be inadvisable in this case due to its associated sensitization which would make future kidney transplantation difficult.

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