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Kidney Pancreas Transplant, a Brief Comprehension to Care

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Abstract

Surgical treatments for Insulin Dependent Diabetes Mellitus (IDDM) complicated with Advanced Chronic Kidney Disease (CKD) have emerged with the hope of providing a better sustainable quality of life. This article aims to highlight the utility of kidney and pancreas transplant in the management of IDDM with renal failure. There are different surgical methodologies, of which Simultaneous Pancreas And Kidney Transplantation (SPK) has been the most promising; in terms of graft survival and decreasing the need for a second surgical intervention in terms of kidney transplant. However, long waiting lists to find matching donors and post-operative complications are the most challenging obstacles. All recipients shall be screened for anti-HLA antibodies, non-HLA antibodies and Coronary Heart Disease (CHD). The presence of CHD poses a mortality risk post-surgery. Recipient selection requires a meticulous insight based on the insulin requirements, with the fact that not all will achieve insulin independence. A donor's risk factors must be estimated by the Pancreas Donor Risk Index (PDRI), the higher the score lower the chances of graft survival. Pancreatic graft failure has no unanimously agreed definition of rejection and is dependent on a variety of donor and recipient factors. Close follow up and a high index of suspicion for any unexplained signs or symptoms is required to detect early allograft rejection, and the consideration of other surgical and medical etiologies is also required. This mini review will discuss various options for the management of insulin dependent diabetics whose diabetes remain uncontrolled with maximal efforts and have developed advanced chronic kidney disease pending renal replacement.

Keywords: Insulin dependent diabetes mellitus, Chronic kidney disease, Kidney pancreas transplant.

Abbreviations: CHD-Coronary Heart Disease, CMV-CytoMegalovirus, CKD -Chronic Kidney Disease, CVS-Cardiovascular System, eGFR-Estimated Glomerular Filtration Rate, IDDM-Insulin Dependent Diabetes Mellitus, PDRI-Pancreas Donor Risk Index, rATG- Rabbit Anti-Thymocyte Globulin, SIRS-Systemic Inflammatory Response Syndrome, UNOS-United Network for Organ Sharing.

Diabetes is a major etiologic factor towards chronic kidney disease leading to end stage renal disease causing a major health care burden globally. Prevalence of diabetic kidney disease is almost 25-30% at present, with a progressive rise due to the complex nature of this disease and poor understanding of the patients. Diabetes has been detected in almost half of the USA end stage kidney disease population with higher incidence of Type 1 as compared to Type 2 diabetes [1,2]. Uncontrolled insulin dependent diabetes complicated with chronic kidney disease and an Estimated Glomerular Filtration Rate (GFR) of less than 20ml/min have the following options to undergo:

- Simultaneous Pancreas Kidney Transplant (SPK)
- Pancreas Transplant Alone (PTA)
- Segmental Pancreas And Kidney Transplant (SPKT)
- Review Of Anti-Diabetic Treatment (RADT)
- Islet Cell Transplantation (ICT)
- Pancreas Transplant After Kidney Transplant (PAKT)

The definitive approach to support this particular population is a combined kidney pancreas transplant. Based on this approach this article will outline the basic principles of these transplants, and recipient and donor evaluation in order to assist a renal physician to deal with such a population holistically. Amongst these options, the preferred management is to proceed to SPK transplantation. An ideal candidate for this procedure is the one who has treatment refractory IDDM, along with progressively advancing CKD. A major limitation is the availability of these allografts. As kidney and pancreas transplants are obtained from the deceased donor, there is a longer waiting time compared to those requiring kidney transplantation alone. In some cases, kidneys are obtained from live donors and pancreas from the deceased. Another approach is to take both the allografts from a living donor where a segment of the pancreas is taken along with the kidney.

Pancreas transplantation alone is also an option, but it is usually considered in those whose kidney function is substantial either through the functioning renal allograft or from the native kidneys. PTA is not a preferred option with advanced CKD, because the use of immunosuppression to protect pancreatic allograft will expedite deterioration of existing CKD, hastening the need for renal replacement therapy. The recipient will be at risk of needing dialysis or renal allograft soon after pancreas transplantation alone. This will subject him or her to another surgery, putting the existing pancreatic allograft at risk due to procedure related complications. Despite knowing this fact, some centers encourage pancreatic transplantation alone, and put the patient on the list for interval kidney transplant.

For SPK transplantation, methods include segmental pancreatic graft from the deceased donor, or a live donor, usually placed on the right side, whereas a donor kidney can be placed on either side. The right side remains favored due to the right ward location of the inferior vena cava, and easier anastomosis with iliac vessels. Pancreatic drainage can be done through the anastomosing duct with the duodenum, stomach, or bladder. Enteric route drainage has resulted into lesser complication rates in terms of leaks and acidosis. Bladder route drainage has an advantage of detecting pancreatic allograft rejection. Islet cell transplantation is a highly specialized technique being practiced in very few centers around the globe. It requires a large number of islet cells procured from a cadaveric donor pool. After processing, these are injected into the portal vein by percutaneous ultrasound guided catheter, without any surgery.

All the options mentioned above are possible and are being practiced successfully around the world. SPK is the best option but availability of allografts; local expertise and center capability for performing this procedure are the main deciding factors to adopt the modality. Immunosuppression use is not much different as compared to other solid organ transplant. Anti Thymocyte globulin is used as an induction agent of choice as compared to basiliximab, along with methylprednisolone. Maintenance immunosuppression is preferred to be of tacrolimus based triple therapy with mycophenolate and prednisolone, targeting tacrolimus trough levels of 8 to 10 ng/ml during first three months and then 6 to 8 ng/ml afterwards [3].

Graft survival

Survival of pancreatic allograft is dependent on the graft function and co-morbidity of the host. There is no unanimously agreed definition of graft function. Different centers have their own parameters and definition of graft function. United Network for Organ Sharing (UNOS) USA has defined pancreatic graft failure if recipient require insulin >0.5units/kg/day for three months or more post-transplant. International Pancreas and Islet Transplant Association and the European Pancreas and Islet Transplant Association in 2018 defined graft function based on the factors which include insulin requirement, hypoglycemic events, glycosylated hemoglobin, insulin and C peptide levels. Reported five 5-year survival for SPK, PAK and PTA were 73%, 65% and 53% respectively. Graft survival is poor if obtained from older or obese donors, poorer with retrieval after cardiac death and poorer in pancreas transplantation alone compared to SPK. Studies from 2004 to 2015 have shown up to 10% risk of pancreatic allograft failure within three months post transplantation [4-9].

Complications

Complications are related to surgery, immunosuppression, infection, and rejection. SPK is a complex surgical procedure compared to PAK, PTA, and KTA and carries the highest rate of complications. The most vulnerable period is the first year after these procedures. The following are some of the most the well-known complications [10-13].

- Post-operative related issues such as wound infection, dehiscence, anastomotic leak which could result in peritonitis, ileus, and intra-abdominal compartment syndrome.
- Consequences of infection may lead to perpetuation of inflammatory cytokines, resulting in deterioration of the condition further developing Systemic Inflammatory Response Syndrome (SIRS), sepsis and shock leading to grave morbidity and mortality outcomes.
- Thrombosis of the pancreatic graft, especially pancreatic artery thrombosis. Risk factors include a state of hypotension peri or post operatively and prolonged ischemic time leading to ischemia reperfusion injury and technical issues. It is the most feared complication, and usually happens within the first week post transplantation, while deep venous thrombosis risk is highest in the first month of transplant.
- Failure of the graft which is usually manifested within the first three months post transplantation, with higher incidence in PTA than with SPK transplant. US reported incidence is 7% and 5% respectively. There is no unanimously agreed definition of this condition. Pancreatic allograft function failure is suspected when the recipient needs insulin for their diabetic control, persistent hyperglycemia and rise of glycosylated hemoglobin with suppressed C peptide level. Rejection is variable, can involve either of the two or both the allografts. Recipient urinary amylase is indicative of pancreatic allograft rejection. Rise in serum creatinine could point towards SPK allograft dysfunction provided both the organs have come from the same donor.
- Graft failure is dependent on donor and recipient factors. Donor associated risk has been calculated from the scoring system, termed Pancreas Donor Risk Index (PDRI). It is calculated based on the variables which include ethnicity, age, sex, BMI, cause of death, organ preservation time and serum Creatinine. PDRI has an inverse relationship the higher the score, the lower the predicted graft survival [14].
- Recipient factors which has worse allograft outcome include age more than 45 years, BMI >30 and Afro American descent [15-17].
- Infection remains an area of concern, especially recurrent urinary tract infections in the case of bladder drained pancreas transplant. Cytomegalovirus (CMV) is a greater risk when the donor is seropositive and the recipient negative, particularly in the setting of multiple immunosuppressive agents and the use of T cell depleting agents such as anti-thymocyte globulin (rATG) which is a commonly used induction agent. Another opportunistic infection based on the degree of immunosuppression is BK Virus, which needs periodic surveillance. Failure to detect this virus in a timely manner may result in loss of both the allografts [18].
- Hyperglycemia can be of multi factorial etiology and needs to be anticipated pre transplant and monitored closely post transplantation. Detection of the cause is important to rectify and could be a result of graft dysfunction, graft failure, immunosuppressive drugs such as tacrolimus, cyclosporine, steroids, and recurrence of autoimmunity. Calcineurin Inhibitors (CNI) damage beta cells resulting in reduced insulin synthesis and secretion. Steroids cause insulin resistance. Persistence of hyperglycemia at 1-year post transplant is known as New Onset Diabetes after Transplant (NODAT). Tacrolimus is considered more diabetogenic with incidence of 8.4% as compared to cyclosporine having 6% and sirolimus with incidence risk of 6.6%. Not all studies support higher diabetes risk with tacrolimus use [19-23].
- Metabolic acidosis is a particular concern with pancreatic drainage to the bladder. It is caused by sodium bicarbonate loss resulting in non-anion gap acidosis, hyponatremia, and dehydration. This condition can be managed with high dose supplemental sodium bicarbonate indefinitely, for as long as the pancreatic graft is bladder drained. To avoid this issue most pancreatic transplants are drained enterically. Enteric drainage has the advantage of almost no issues of acidosis and dehydration as were seen in bladder drainage. The advantage of enteric drainage has been supported over bladder drainage from a study published from a single center [21,24,25].
- Post-transplant Erythrocytosis (PTE) is a condition which is associated with solid organ transplants particularly SPK with bladder drainage. Enteric drainage SPK has solved this issue and it is negligible with this procedure. The most plausible explanation is the euvolemic state of the recipient with enteric drainage, thus no dehydration. The incidence of PTE is 8 to 15% and is suspected with persistent rise of hemoglobin >17g/dl and hematocrit >51% for six months or more, provided there is no element of chronic lung disease or malignancy. This condition is associated with malaise, headache, and thromboembolic events and may result in allograft loss. Angiotensin converting enzyme or receptor inhitor are the main stay of treatment provided all other causes have been ruled out. Venesection is advised if Hb remains more than 18.5g/dl [26-33].

Allograft rejection

Pancreas rejection presents with non-specific abdominal symptoms with elevation of amylase, lipase, other inflammatory markers, and an increased requirement of insulin. In the case of SPK transplantation, a rise in serum Creatinine can indicate pancreatic allograft rejection. Urinary amylase is a reliable indicator of rejection in bladder drained pancreas. Routine workup to investigate the cause is required and includes immunosuppressive drug levels, and radiological studies using ultrasound or CT imaging to rule out other abnormalities. To confirm rejection, pancreatic allograft biopsy is the definitive method which not only confirms rejection but defines its type and thus treatment is tailored accordingly. However, pancreatic allograft biopsy is not performed as a routine, and would be considered after kidney biopsy. There is also no recommendation of protocol biopsy for pancreatic allograft rejection [34,35].

Recipient Workup

Along with standard recipient workup based on the 2014 criteria for pancreas allocation system, selection of candidates for suitability of pancreas transplantation includes recipient age, GFR, body mass index (BMI) and insulin requirement. After qualifying initial scoring then further evaluation is performed.

Age: The database of United Network for Organ Sharing (UNOS) USA of pancreatic transplant recipients from 1996 to 2012 has shown better graft survival in recipients younger than 50 years and worse in 6o years or older. Patients aged 45-65 years are considered for pancreas transplantation provided there are no significant co-morbidities [36].

eGFR: For patients with type 1 diabetes and eGFR <20ml/min, SPK transplant is a preferred consideration. Otherwise, dialysis dependent candidates are accepted at any point of time, provided they meet the criteria.

Insulin requirement: Insulin dose is calculated, and C peptide levels are measured in order to assess the need and benefit of pancreatic transplant. Pancreas transplantation is considered beneficial in those who are insulin dependent with C peptide <2ng/ml. Generally, it is believed that those who require higher insulin >1 unit/kg/day may not achieve insulin independence post pancreas transplant. The reason being the possibility of insulin resistance or presence of antibodies against insulin producing islet cells. Recurrent episodes of Hypoglycemia, or hypoglycemia unawareness, merit urgent transplantation.

BMI: For SPK transplantation, the acceptable BMI limit is 30. This is less than KTA, which allows transplantation up to BMI 36-40, based on the center. The reason for a lower BMI limit in pancreas recipients is to have a lower risk of complication, better wound healing, less insulin resistance and lower post-transplant diabetes risk [37-39].

Cardiovascular Evaluation

The Cardiovascular System (CVS) is a major contributor of post-transplant morbidity and mortality if not evaluated properly pre-operatively. CVS assessment comprises of invasive and non-invasive tools. The selection of required investigations depends on the risk factors including diabetes duration and complications such as retinopathy, nephropathy, neuropathy, hypertension, dyslipidemia, age, sex, smoking status, dialysis duration and previous history of Coronary Heart Disease (CHD). CHD by definition includes history of myocardial infarction, coronary artery bypass grafting or stenting. High risk candidates for SPK or PAK are screened for CVS with invasive coronary angiogram in order to rectify any lesion detected prior to transplant. One-year mortality risk in SPK and PAK with CHD is 20% higher. All on dialysis must go for invasive coronary angiography due to significant false negative rate with non-invasive exercise tolerance tests [40-44].

Peripheral Vascular Disease (PVD) Evaluation

Long standing diabetes has a particular effect on the vasculature causing calcification, especially when there is history of intermittent claudication or evidence of vascular disease. Non contrast CT imaging of the vessels is usually performed as a routine to estimate total calcium score and to detect calcification. Iliac and femoral vessels are the sites of graft anastomosis. A thorough history including symptoms of vascular insufficiency needs to be sought. Based on the claudication history and vascular calcification, angiography is to be performed and consideration of required re-vascularization therapy. Special consideration is required in particular for angiography as there is a higher risk to develop contrast induced nephropathy for those who are not on dialysis support yet.

Surgical Consideration

The optimum procedure for a particular recipient is planned based on the availability of the organ. Pancreatic drainage whether bladder or enteric is based on the local expertise. There is no difference in survival advantage but in terms of complication enteric drainage is superior to bladder drainage SPK [45-49].

HLA matching

All recipients are screened for Human Leukocyte Antigen (HLA) and antibodies are detected by various sophisticated tests, sensitivity, and specificity of which has been transformed over a period of time. Antigens are defined molecularly through DNA analysis, providing description of antigens at allelic-level. Anti-HLA antibodies are being detected by flow cytometry, solid-phase immunoassays, and single-antigen bead assays such as Luminex. Non-HLA antibodies can also be detected by these assays. Long term graft survival is better with better matched HLA but this advantage vanishes with cold ischemic time of more than 36 hours [50-54].

Donor evaluation

Organ Procurement and Transplant Network (OPTN) suggest that live donors should be interviewed by a social worker and transplant coordinator, followed by psychology and psychiatry team. Clinical assessment must be performed by a physician, transplant surgeon and initiation of laboratory workup based on the details available from the past medical, surgical, family, drug, and social history. A donor must be provided with an independent donor advocate, whose job it is to make sure that the donor has been provided with adequate information including pros and cons of the donation and transparency of the transplant process. After obtaining consent for donation blood grouping, HLA typing, and PRA analysis is commenced. A donor may need to be educated about the paired exchange program [55].

The summary points of Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guideline on the evaluation and care of living kidney donors (Transplantation 2017) are as follows:

- There should be a comprehensive screening for active or latent infections including hepatitis viruses, cytomegalovirus and Epstein Barr virus, tuberculosis, and syphilis.
- Diabetes status must be evaluated meticulously with oral glucose tolerance test and suitability should be assessed on a case-by-case basis, along with other risk factors. Age less than 18 years is a contraindication for donation but there is no upper age limit, provided there are no other risks.
- Albuminuria >150mg/day is an exclusion criteria for donation [56].
- Hematuria >10 RBC/ HPF are not accepted but few centers may accept following detailed urological evaluation with cystoscopy and kidney biopsy.
- Hypertensive donors can be accepted whose blood pressure is controlled with one or two antihypertensive agents without evidence of target organ damage [57].
- Based on a 2005 survey, the majority of US transplant centers accept a donor with history of nephrolithiasis provided the absence of stones and normal metabolic studies. Metabolic

abnormalities associated with stone risk include very low citrate and very high calcium or oxalate [52].

- Donor BMI criteria is variable among centers [58].
- Organ donation is contraindicated from individuals with a history of hematologic malignancies, melanoma, choriocarcinoma, monoclonal gammopathy, and testicular, lung, and breast cancers [59].

Follow up of the recipient

Once the allograft recipient is discharged from the hospital, they need close follow up. The frequency of this is guided by local resources and center policy and capabilities. It is usually initially twice a week for three months, then every two weeks for three months, followed by monthly for four to six months. The purpose is to monitor immunosuppressant drug levels and toxicity, inter current illness or opportunistic infection, diabetes monitoring with other electrolytes and early detection of rejection. During this time period the recipient is also assessed for general wellbeing, psychosocial improvement, quality of life and compliance. Meanwhile the recipient can be educated in the importance of compliance and self-care. The concerns of the patient can be addressed, and they are encouraged to report any unusual signs or symptoms immediately.

Conclusion

SPK is currently the best surgical modality for IDDM with advanced CKD. All patients posted for SPK must be eligible, and therefore need thorough evaluation. This surgical modality carries a risk of multiple complications and they need to be fully explained to the patient. Graft failure is the most feared complication. The definition of graft failure varies from different centers, and its prognosis is highly dependent on various donor and recipient factors. However, there are no protocols developed to confirm rejection, and therefore, frequent follow-ups to screen for rejection and other complications are required, and it is a real challenge in terms of diagnosis and management.

Conflict of Interest

There is no conflict of interest to declare.

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