Transplant Options for the Management of Diabetic Nephropathy

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ABSTRACT

Kidney transplantation remains the most effective treatment for end stage renal disease with the best long-term outcome irrespective of the aetiology for most patients. Patients with diabetic nephropathy however present a challenge in that, whilst the renal status normalizes with the renal transplant, a persisting poor glycaemic control may ultimately jeopardize the health of the transplanted kidney. Hence there is a strong need for an adequate long term glycaemic control in these patients. The advent of safe pancreatic transplantation has offered the hope of a more effective long term glycaemic control in diabetics over the use of insulin and medications. It is important that in the treatment of patients with diabetic nephropathy, attention should not only be given to possible renal transplantation, in addition, it is vital that consideration be also given to the possible pancreatic transplant options that may offer this group of patients adequate glycaemic control in the long term. In this write up, the authors look at the various pancreatic transplant options available in the treatment of diabetic nephropathy.

Keywords: *Diabetic nephropathy, kidney transplantation, pancreatic transplantation*

INTRODUCTION

Kidney transplantation remains the most effective treatment for end stage renal disease with the best long-term outcome irrespective of the aetiology for most patients. Patients with diabetic nephropathy however present a challenge in that, whilst the renal status normalizes with the renal transplant, a persisting poor glycaemic control may ultimately jeopardize the health of the transplanted kidney. Hence there is a strong need for an adequate long term glycaemic control in these patients. The advent of safe pancreatic transplantation has offered the hope of a more effective long term glycaemic control in diabetics over the use of insulin and medications.

The various options of pancreatic transplantation are now generally considered for patients with type 1 diabetes as these are the patients with reduced endogenous insulin and normal insulin sensitivity. Recently however, some authorities now consider some subset of type 2 diabetes patients for pancreatic transplantation, provided a set of parameters are met such as patients having a BMI of less than 30kg/m^2, and requiring insulin less than 1.5U/kg per day. [1]

In this review, we look at the various transplant options available to patients with diabetic nephropathy.

Transplantation Options For The Treatment Of Diabetic Nephropathy

The optimal management of a patient with diabetic nephropathy will depend on whether the patient has type 1 or type 2 diabetes, and on the stage of the renal impairment. Though it may be sometimes

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difficult to differentiate between the two types of diabetes,[2] the use of clinical features such as age at presentation, the nature of the onset, presence or absence of ketosis and family history may help in deciding which type of diabetes the patient has. For example, the most likely diagnosis in a diabetic with frequent episodes of hypoglycaemia unawareness will be type 1 diabetes mellitus. It is also possible to confirm a case of type 1 diabetes mellitus by assessing the C- peptide levels. It is always good to interpret the C- peptide levels with a diabetologist.[3]
The options of managing diabetic nephropathy will have to take into consideration the stage of the chronic kidney disease with the estimated glomerular filtration rate (eGFR). In severe cases with eGFR less than 20mls/ml, a pre-emptive kidney transplant may be considered as its clear advantages have been documented especially in patients receiving living donor transplant.[4, 5] The optimal management of a patient with diabetic nephropathy should take care of both the diabetic control and the treatment of any end stage chronic kidney disease (CKD).

The transplant options for the treatment of diabetic nephropathy will include

(1) Simultaneous pancreatic and kidney transplantation (SPK)
(2) Pancreatic transplantation after kidney transplantation (PAK)
(3) Islet cell transplantation
(4) Living donor kidney transplantation
(5) Pancreas transplant alone (PTA)

1. *Simultaneous pancreas and kidney transplantation (SPK)*

The option of transplanting the pancreas at the same time as the kidney has the advantage of treating both the type I diabetes and the end stage chronic kidney disease. There has been a significant improvement regarding the safety of whole organ pancreas transplant over the years with better surgical techniques and patient evaluation and management.[6]
The pancreatic allograft is usually sourced from a deceased donor. The surgery usually entails implanting the kidney in the left iliac fossa and the pancreas in the abdominal cavity.[1] There are different options for the exocrine and endocrine pancreatic drainage and these include enteric exocrine drainage and portal venous endocrine drainage, duodenal exocrine drainage and systemic venous endocrine drainage, bladder exocrine drainage and systemic venous endocrine drainage and enteric exocrine drainage and systemic venous endocrine drainage.[7] There are different pros and cons to be considered for each of these approaches. Re-laparotomy rates of up to 40% have been documented following pancreas organ transplantation and re-laparatomy may be for varying reasons such as graft thrombosis, bleeding and enteric and enzyme leaks.[8, 9]

While the survival benefit of a simultaneous pancreas and kidney transplant has been shown to be better than that following deceased donor kidney transplant alone, the patient survival in simultaneous pancreas and kidney transplant when compared to living donor kidney transplant have been found to be similar.[10, 11, 12] In addition, in terms of quality of life measures, improvement in physical health and diabetes specific areas have been reported to be greater in patients who had a simultaneous pancreas kidney transplantation compared to those who had a living donor kidney transplant alone.[13] For patients undergoing a simultaneous pancreas and kidney transplant, the NHSBT Annual Report on Pancreas and Islet Transplantation has documented the 1 year and 5 years post-transplant patient survival as 98% and 88% respectively.[14] Barlow et al have reported the all cause kidney graft survival at 1 year, 5 years and 10 years post SPK transplant as 96%, 89% and 80% respectively. The all cause pancreas graft survival at 1 year, 5 years and 10 years post-transplant were also reported as 86%, 76% and 68% respectively.[12]

Compared with the other options of treating diabetic nephropathy, doing a simultaneous pancreatic and kidney transplant is generally associated with an increased mortality in the short term. This is generally attributable to the increased surgically related complications. However, in the long term, a simultaneous pancreas and kidney transplant has the best outcome for the treatment of type I diabetes with end stage renal disease.[1]

2. *Pancreas transplantation after kidney transplantation (PAK)*.

In a patient with type I diabetes and chronic renal failure, a pancreas after kidney transplantation is an option. This pancreas transplantation can follow either a deceased donor kidney transplantation or a living donor kidney transplantation. Some earlier studies from the US suggested that pancreas transplant wait listed kidney transplant recipients fared better than

those patients who had a pancreas after kidney transplantation.[15, 16] More recent studies have however shown that when the pancreas after kidney transplantation is carried out within a year of a living donor kidney transplant, there has been a trend towards a much better outcome in terms of patient survival.[17] The level of insulin independence following a pancreas after kidney transplant has been found to be higher than that in islet after kidney transplantation, though pancreas after kidney transplantation has a comparatively higher early post-op risks.[18] Carrying out a pancreas transplant after a kidney transplant will have the potential advantage of less surgically related morbidities compared to a SPK at least in the short term.

3. *Islet Cell Transplantation*

Islet cell transplantation involves the isolation of islet cells from the pancreas and the infusion of the isolated islet cells into the recipient's portal venous system usually via a percutaneous technique. To achieve an adequate number of islet cells for satisfactory results, the cells may have to be isolated from multiple donors.[19, 20] The sourcing of the islet cells from multiple donors comes with a higher risk of possible sensitization for the recipients with the attendant negative implication for any future re-transplantation. A major advantage however is the avoidance of the morbidity of open surgery with the other types of pancreas transplant. Islet cell transplantation can be done as an islet cell transplantation alone or as a simultaneous islet – kidney transplantation (SIK).

An islet cell transplantation alone will suffice for the treatment of type I diabetes in a patient if the eGFR is at least 40ml/min. However, if the eGFR is 20ml/min, for a patient to have an islet cell transplantation done, the preferred option will be a simultaneous islet – kidney transplantation. A simultaneous islet - kidney transplantation will take care of both type I diabetes and end stage CKD. Simultaneous islet – kidney transplantation is usually carried out for those patients who ordinarily should have a simultaneous pancreas and kidney transplantation but are considered too high risk for the kind of anaesthesia that a SPK will require.[3] This is because a much less level of cardiovascular fitness is all that is required for the cannulation of the portal vein for islet cell infusion which can be carried out with local anaesthesia and conscious sedation when compared to the major anaesthesia in pancreas organ transplant.[3]

Islet cell transplantation is generally a safe procedure with minimal mortality. While Hering et al. in an American study reported no mortality in their series,[21] the Collaborative Islet Transplant Registry reported a crude mortality rate of 3% in patients followed up for an average of 4.4 years.[22] Though there are various ways of assessing islet graft survival, a UK report has documented the 5 year islet graft survival to be 48%.[23] In addition though the data on SIK is limited for now, there are suggestions of similar kidney graft survival but with a lower insulin independence in the SIK transplantation group compared to the SPK group. The SPK however has a greater risk of early post-op complications.[24, 25] Since islet cell transplantation is generally a percutaneous procedure, the complications tend to be less than those associated with open procedures like SPK. The documented complications following islet cell transplantation include perihepatic and portal venous bleeding,[21] portal venous thrombosis,[26] and post-operative hepatic dysfunction.[27]

4. *Living Donor Kidney Transplant*

A living donor kidney transplant will solve the problem of the chronic kidney disease that a patient with end stage diabetic nephropathy has but will not treat the type I diabetes. However it is important to note that the patient survival after living donor kidney transplant has been found to be approximately equivalent to that following a simultaneous pancreas kidney transplantation.[11, 12] When such a patient has a potential live donor available, a living donor kidney transplant alone remains a valid option.

5. *Pancreas Transplant Alone (PTA)*

Having a patient with diabetic nephropathy undergo a pancreas transplant alone will take care of the patient's type I diabetes and could be adequate for a patient with an eGFR of > 40ml/min. But in a patient with an eGFR of 20ml/min, a pancreas transplant alone will be inadequate treatment.

Immunosuppression

Adequate attention has to be paid to immunosuppression in pancreas transplantation. The use of induction regimen involving depleting antibodies agents such as alemtuzumab and antithymocyte

globulin (ATG) is common in pancreas transplantation.[6] The supporting evidence is however conflicting. While Niederhaus et al in a review found no benefit in the use of depleting antibodies regimens such as ATG and alemtuzumab over the use of the non-depleting antibodies like basiliximab,[28] other workers have suggested that the use of an induction regimen with non-depleting antibodies is an independent risk factor for the loss of the pancreas graft in pancreas transplant alone.[29] The use of depleting antibodies however has the potential benefit of allowing for an early steroid withdrawal or complete avoidance of steroid and thus can help reduce the risk of steroid induced hyperglycaemia.[3] It is advisable that with the use of depleting antibodies during induction, the dose of mycophenolate mofetil should be reduced in order to reduce the risk of possible lymphopenia.[3] Though the pancreas transplant maintenance regimens are poorly defined, there is a general trend towards allowing higher trough levels of tacrolimus in pancreas transplant patients compared to those recipients who receive kidney transplant only.[3]

Consideration in Diabetic Nephropathy in Children

A rising incidence of both type 1 and type 2 diabetes mellitus in children and adolescents means there has been a rise in the incidence of diabetic nephropathy. Both types of diabetes can lead to diabetic nephropathy after several years of diagnosis. Strict glycaemic control reduces microvascular and macrovascular complications.[30] The prevention of end stage renal disease forms the focus of the management of diabetic nephropathy in children. When macroalbuminuria (clinical nephropathy) sets in, there is inevitable progression, regardless of treatment, to a decline in GFR and end stage renal disease which is usually observed by adulthood.[31, 32] Spontaneous remission with resolution of the albuminuria however sometimes occurs in a few cases.[33] ESRD is rarely caused by diabetic nephropathy and hypertension in children as the disease progresses over decades until the patient becomes an adult and requires renal transplant. Disease recurrence may occur in the transplanted kidney except when accompanied by the pancreas transplant.

Pancreas transplant is rarely indicated in children with diabetes as renal complications are rarely seen[34] however, a case of simultaneous living donor renal transplant and deceased donor islet cell transplant for a patient with bilateral renal hypoplasia and type 1 DM has been reported.[35] In addition, pancreas transplantation alone has also been done which significantly improved the patient's insulin dependence and quality of life. Paediatric donors have been successfully used for SPK transplant into adult recipients.[36]

The Work up of the Recipient

The evaluation of a patient being considered for any of the options of pancreatic transplantation with a possible kidney transplant will follow the line of a clinical history, physical examination and relevant investigations.

Basic Laboratory Investigations

The basic laboratory investigations to do will include a full blood count, electrolytes and urea and lipid profiles.

Cardiovascular Assessment

It is vital to carry out a thorough cardiovascular assessment in these potentially high risk patients who are about to undergo extensive surgeries. An ECG is usually mandatory in the patient work up. It is also advisable to carry out an echocardiogram in this group of patients to assess the left and right ventricular functions, the ejection fraction and rule out any valvular disease. The extent of the additional cardiovascular testing a recipient should undergo will vary with different practices and guidelines and is best decided upon in conjunction with a cardiologist. There might be need for non-invasive myocardial functional tests such as myocardial perfusion scintigraphy or a dobutamine stress echocardiography in order to rule out possible myocardial ischaemia.[3]

A plain pelvic XR of the patient may show some suggestion of phleboliths in the pelvis. This may be indicative of calcification in the iliac vessels and underlying peripheral vascular disease. It may then be necessary to do a Doppler ultrasound and a Duplex scan to assess the blow flow through the iliac vessels in such patients before the transplant. Other means of assessing the iliac vessel blood flow will include computerized tomogram angiography and a magnetic

resonance angiography.[3] Whether a coronary angiography is needed in light of the presence of peripheral vascular disease in any particular patient will be discussed with the cardiologist.

Though guidelines vary, the use of algorithms such as those from the American Society of Transplantation and the American College of Cardiology/American Heart Association can be helpful in stratifying the patient's risk and carrying out appropriate investigations.[1]

Screening for Infections/Viruses

It is important to screen the recipient for viruses such as cytomegalovirus (CMV), Epstein Barr virus (EBV), HIV, hepatitis B, hepatitis C and Herpes simplex virus. There might be need to screen for additional viruses such as HLTV 1, HLTV 2 and the varicella zoster virus.

A Chest XR will help rule out an occult infection like tuberculosis or pulmonary mass.

Screening for Malignancy

Besides taking a good history and having a thorough physical examination done, an abdominal ultrasound +/- CT may also help to rule any occult abdominal masses. Older female recipients should have a mammogram done whilst a serum prostate specific antigen assay is important for older males.

Psychological Assessment

This is important in order to identify any potentially non-concordant behavior that may affect patient's compliance with treatment in the short and long term.

Counselling and work up of a potential donor

Counselling

Adequate counselling of the potential donor is important. If a female donor is still planning on getting pregnant in the future, she should be counselled on the documented increased risk of developing pregnancy induced hypertension in female kidney donors.[37] A hypertensive donor is still qualified to donate a kidney if the BP is controlled on one medication.[38]

Work up

The work up of the donor will follow the line of clinical history, physical examination and relevant investigations.

Clinical History

This aims amongst other things to detect unknown disease, infection, haematuria, cardiovascular risk factors or use of medications.

Clinical Examination

This may detect previously unknown conditions such as undetected breast lumps or skin lesions, evidence of obesity amongst others.

Medical assessment/Investigations

It is important to assess the general health and fitness of the donor for kidney donation by carrying out the following tests:

- *Urinalysis:* Look out for haematuria, proteinuria, glycosuria, pyuria.

- *Blood Tests:* Full Blood Count, Serum Electrolytes, Urea and Creatinine, Fasting Blood Sugar, Lipid Profile, Liver Function Tests, Coagulation Profile.

- *Infection Screening and Virology:* The donor should be screened for Hepatitis B and C, HIV, EBV, CMV, Toxoplasma and Syphillis.

- *Cardiorespiratory Evaluation:* A Chest XR and ECG remain the baseline investigations to assess the cardiorespiratory status of the donor.

- *Abdominal Ultrasound:* This will pick any abnormality with the kidneys eg cysts, masses.

- *Renal CT Angiography* will help to delineate the anatomy of the renal vasculature of the donor with possible implication for the side of the intended donor nephrectomy.

Assessment of Renal Function

It is vital to measure the donor's estimated glomerular filtration rate (eGFR) initially and a reference measured method glomerular filtration rate (mGFR) later.[38] A differential renal function test will be done if the size disparity between the donor's kidneys is >10%.

Psychological Assessment

The potential donor will also have a full psychological assessment to assess her fitness to consent.

Follow up plan for the recipient

A suggested follow-up plan for a patient after pancreatic and kidney transplantation will be as per the recommendation of the British Transplant Society.[39]

In the first one month, the patient is seen two to three times a week.

In the following two months, the patient is seen once a week.

Thereafter, the patient is seen every month for three months.

The subsequent follow-up visits will then be every two to three months.

It is important that the patient has a multi-disciplinary input in his care during each visit.

Hormonal and biochemical measures of graft function should be assessed periodically.

CONCLUSION

The optimal treatment of patients with diabetic nephropathy should not only concentrate on kidney transplantation alone. Strong consideration should be given to the various available pancreatic transplantation options which can offer adequate long term glycaemic control in these patients.

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