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Transplantation in Diabetics with End-Stage Renal Disease

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1. Introduction

Pancreas transplantation is well recognised and established treatment for selected patients with type-1 diabetes. Furthermore, this treatment remains the only therapeutic modality to offer excellent and reliable glycemia control, without the administration of insulin in type-1 diabetics.

It is well documented that combination of pancreas and kidney transplant (i.e. Simultaneous Pancreas and Kidney Transplantation or Pancreas After Kidney Transplantation) gives to patients who suffer from type-1 diabetes and End-Stage Renal Failure superior outcomes, improved patients' survival and better quality of life compared to other therapeutic modalities.

In this chapter will be reviewed current status of pancreas transplantation with focus on recipient selection, management and outcomes.

2. Diabetic Nephropathy

2.1 Definition

Diabetic nephropathy (DN) has been acknowledged as the most common disorder leading to End-Stage Renal Failure (ESRF) in adults (Fig. 1). Renal disease is associated with higher morbidity and mortality in diabetics compared to patients who do not suffer from diabetes. Approximately 0.5% of the population in developed countries (United States and Europe, i.e. Western societies) is thought to have diabetes (ADA, 1999). It is well known that DN is the most common diabetic complication. Patients with type-1 diabetes have the highest risk of developing nephropathy, but those with type-2 have significant risk, too. This condition develops in 50% of type-1 diabetics progressively over a period of 10 to 15 years. In contrast, people suffering from type-2 diabetes can undergo a more variable course and approximately 30% of them will develop DN at some point.

2.2 Etiology

The patho-physiologic mechanisms of diabetic nephropathy are not completely understood yet, but they include hyperglycemia (causing hyperfiltration and renal injury), glycosylation of circulating and intrarenal proteins, hypertension, and abnormal intrarenal hemodynamics.

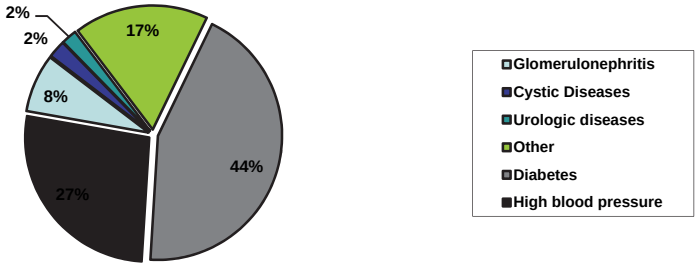


Fig. 1. Primary Causes of Kidney failure (Collins et al., 2008).

For DN are typically three major histological changes that seem to have a similar prognostic impact. Mesangial expansion is induced by hyperglycaemia, causing matrix production or glycosylation of matrix proteins. Another common feature is glomerular sclerosis caused by intraglomerular hypertension; induced by renal vasodilatation or from ischemic injury induced by the hyaline narrowing of the vessels supplying glomeruli. Glomerular basement membran thickening is another common feature, too.

2.3 Secondary complication of diabetes

Among patients with DN we see an increased prevalence of other secondary diabetic complications. Hypertension significantly increases diabetes-related morbidity and is the second most common cause of morbidity in diabetics. It has been documented that hypertension increases mortality in diabetics with renal failure by 37 folders (MacLeod & McLay, 1998). Hypertension also contributes to the developing of DN, microvascular and macrovascular complications.

Diabetic micro and macroangiopatic complications develop simultaneously and have a widespread effect on many organs as well as participating on the development of various diseases (diabetic nephropathy, retinopathy, coronary artery disease, peripheral vascular disease, cerebrovascular disease, etc).

Diabetic retinopathy is the leading cause of visual loss in diabetics due to retinal damage. This condition affects up to 80% of patients who have suffered from diabetes for more than 10 years (Kertes & Johnson, 2007). The main mechanism of diabetes induced retinal damage is a combination of cytotoxic effect of high blood glucose levels and hypertension. Characteristic retinal lesions include the formation of retinal capillary microaneurysms, extensive vascular permeability, vascular occlusion, angio proliferation and basement membrane thickening (Matthew et al., 1997). Some studies have demonstrated (Wong et al., 2008) that the prevalence of retinopathy rises with the increasing duration and severity of the diabetes. However, good glycaemia control reduces retinopathy development by more than 40% (TDCCTG, 1993).

In some diabetics, mainly in patients with long standing or poorly controlled diabetes, symptoms of hypoglycaemia (e.g. palpitation, sweating, tremor, headache, etc.) do not

occur. The absence of these symptoms during hypoglycaemia is called hypoglycaemic unawareness. Patients suffering from this condition have a lack of warning signals and cannot actively correct their hypoglycaemia before plasma glucose falls to extremely low levels. The main factor responsible for the development of hypoglycaemic unawareness is autonomic diabetic neuropathy and brain desensitization to hypoglycaemia.
Absence of glucose homeostasis in diabetes also causes pathological damage and functional disturbance of the peripheral (motor and sensor) and autonomic nerves. Frequently, patients suffer from motor neuropathy: pain, paresthesia and anesthesia. Autonomic neuropathy (arrhythmia, postural hypotension, diabetic diarrhoea, gastroparesis, neurogenic bladder, impotence, etc) is less common than peripheral neuropathy, but is a more symptomatic and has limited therapeutic effect (Watkins & Edmonds, 1997).
The development of complications is related to the severity and length of diabetes, and its management involves glucose control and symptomatic treatment which seems to have a positive effect (Ward, 1997).

2.4 Management

In recent years, there has been significant progress in the management and treatment of diabetics. We have seen not only a reduced morbidity but also increased patients' survival and improved patients' quality of life. Median patient survival in recent years amongst this population has increased from 6 to 15 years (Wiesbauer et al., 2010).
It is well known that poor diabetic control is responsible for developing various diabetic complications; mainly DN. The risk of developing nephropathy is significantly reduced if HbA1c stays below 7.5-8.0% (Deferrari et al., 1998; Di Landro et al, 1998). For that reason the American Diabetes Association highlights in their "Guidelines for Glycemic Control" to target HBA1c level below 7% to achieve a normal or near normal glycemia (ADA, 2005).
It was documented in two large studies on a cohort of 1349 patients, the DCCT (Diabetes Controlled and Complication Trial) and EDIC (Epidemiology of Diabetes Intervention and Complications) that tight glycemic control decreases the risk of development of microvascular disease (retinopathy, nephropathy, and neuropathy) and even slows down established DN (TDCCTRG, 1993), (DCCT, 2003).
In brittle type-1 diabetes serum glucose levels can rapidly swing between extremely low and high levels. This can lead to the development of acute and life threatening conditions: keto-acidosis, coma or even death. Often patients have absent warning symptoms. In some diabetics it is difficult, and even impossible, to achieve a good glycemic control with conventional management.
Nowadays, varieties of insulin preparations are available. The type, the dose and the frequency of insulin doses depends on patient's individual factors. For type-1 diabetics "Basal-bolus insulin regiment" (a combination of high frequency boluses of short-acting insulin with long-acting insulin) is often used. Some people benefit from "Mixed insulin regiment". This includes a mixture of short and long-acting insulin delivered two to three times a day. Regardless of meticulous blood glucose monitoring and accurate insulin dosage, some patients may still have problems achieving an appropriate blood glucose level. These patients may be considered for an insulin pump. The disadvantage of this method is increased frequency of hypo/hyper glycemia episodes and also the fact that it requires a cannula implantation (Collins et al., 2007).
The innovations in insulin formulation and delivery have had a significant impact on the management of type-1 diabetes and they have improved glycaemic control. Despite this

progress, many patients cannot achieve a good degree of serum glucose control and keep suffering from frequent sudden hypoglycaemia episodes. These circumstances have a negative impact on patients' quality of life and can even be life threatening.
In addition, sufficient management of DN also includes rigorous treatment of hypertension in combination with conventional management of renal failure, hyperlipidemia, anaemia, etc.

3. Pancreas transplantation

The first pancreas transplant was performed at the University of Minnesota, in Minneapolis, on 17 December 1966 by the team led by Dr William Kelly and Dr Richard Lillehei (Kelly et all., 1967). A pancreas, together with a kidney, was implanted to a 28-year old woman. Immediately after the transplantation the patient became euglycemic, but unfortunately she died three months later from a pulmonary embolism with functioning grafts. The same team in Minneapolis, on 3 June 1969, performed the first successful pancreas transplant and the pancreas graft functioned for more than one year (Lillehei & et al., 1970). Early experiences with pancreas transplantation were disappointing, as they were associated with a high incidence of rejection, infectious complications and early graft failure. Progressively in the late 70's and early 80's the results of pancreas transplantation improved. First of all, the original Lillehei surgical technique was modified and refined. In 1988 Starz published a technique of anastomozing graft duodenum to the recipient jejunum for draining a pancreas graft exocrine secretion (Fig 2) (Starzl et al., 1988). Subsequently, his technique was adopted by other big pancreas transplant institutions; by Dr Hans Sollinger at the University of

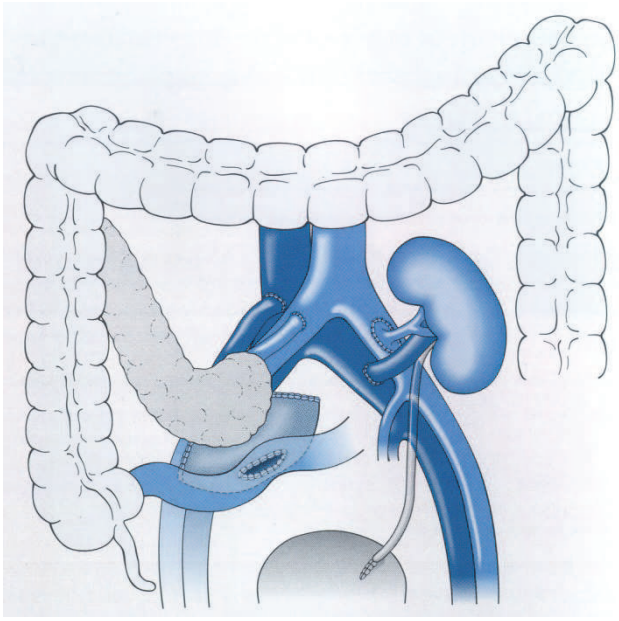


Fig. 2. The Enteric drainage technique in simultaneous pancreas and kidney transplantation. Pancreas graft duodenum is anastomosed side-to-side to the jejunum of a recipient.

Wisconsin and Dr Robert Corry at the University of Iowa. Later, all three centres employed to their routine practice the technique of draining graft duodenum to the bladder (Fig 3) (Sutherland et al., 1988; Sollinger & Belzer, 1988; Corry, 1988). Both techniques, with minimal modifications are still used these days. A number of studies compared the outcomes between bladder and enteric drained pancreas transplants. Most of them showed similar complication rates (Lo et al., 2001; Stratta et al., 2000), graft and patient survival (Sugitani et al., 1998).

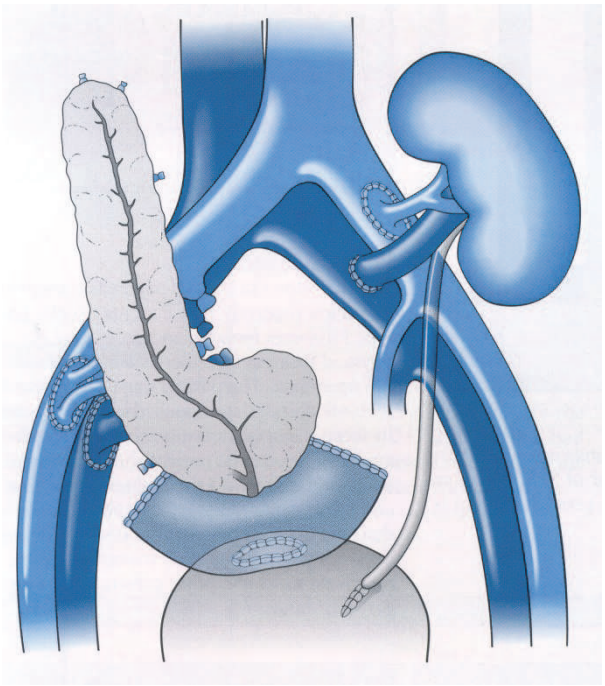


Fig. 3. The Bladder drainage technique in simultaneous pancreas and kidney transplantation. Pancreas graft duodenum is anastomosed side-to-side to the bladder of a recipient.

The Enteric Drainage pancreas technique compared (ED) to the Bladder Drainage pancreas technique (BD) is a more physiological option because it drains pancreatic enzymes into intestinal track. However, this technique is associated with a higher rate of surgical complications (anastomotic leak, chemical and infectious peritonitis, ileus, intra-abdominal abscess formation, etc.). A typical complication of bladder drainage technique is the recurrence of urinary track infections, haematuria, urethral strictures, prostatitis, pyeloneophritis, reflux pancreatitis, etc. Additionally to these complications, the urinary diversion of exocrine pancreas graft secretion potentiates excessive loss of bicarbonates, sodium and fluid. This results in acid-base and electrolytes disturbance (metabolic acidosis) and fluid depletion. Metabolic acidosis is even more exacerbated by renal dysfunction. For those reasons, serum electrolytes must be closely monitored in patients with bladder drained pancreas, patients must be well hydrated and receive bicarbonate supplements.

Enteric conversion is a surgical alternative to manage sever complications related to the bladder drainage of pancreas graft (Stephanian et al., 1992). The United Network for Organ Sharing (UNOS) and the International Pancreas Transplant Registry (IPTR) data from 2005 reports the overall conversion rate from BD to ED of 9% at 1 year and 17% at 3 years after transplant (Gruessner & Sutherland, 2005). The major indications for conversion were recurrent episodes of haematuria, graft pancreatitis, chronic urinary track infections, dehydration and bladder calculi (Jimenez-Romero, et al., 2009).

In terms of pancreas venous drainage there are two available variations: portal venous and systemic venous drainage. Portal drainage is a more physiological alternative, but with regards to the complication rate; graft and patient survival there are not any significant differences. Some data suggests that portal venous drainage is an important factor to determine peripheral insulin sensitivity (Radziuk et al., 1993). In portal venous drainage, serum glucose and insulin concentration recover to normal in contrast with systemic venous drainage, where plasma insulin levels are increased, as a result of bypassing liver circulation (Gu et al., 2002). Hyperinsulinemia contributes to hyperlipidemia, hypercholesterolemia and accelerate the development of atherosclerosis.

A milestone in the history of transplantation occurred in 1976, when Calne published the first clinical experiences with Cyclosporin-A. He reported improved graft and patients' survival in a cohort of 34 transplant recipients (32 kidneys, 2 pancreases and 2 livers) who received only Cyclosporin-A maintenance immunosuppressive regiment (Lillehei et al., 1979). A Cyclosporin-A helped to achieve a better control of rejection and minimise steroid dependence. Although, the introduction of new immunosuppressive drugs (tacrolimus,

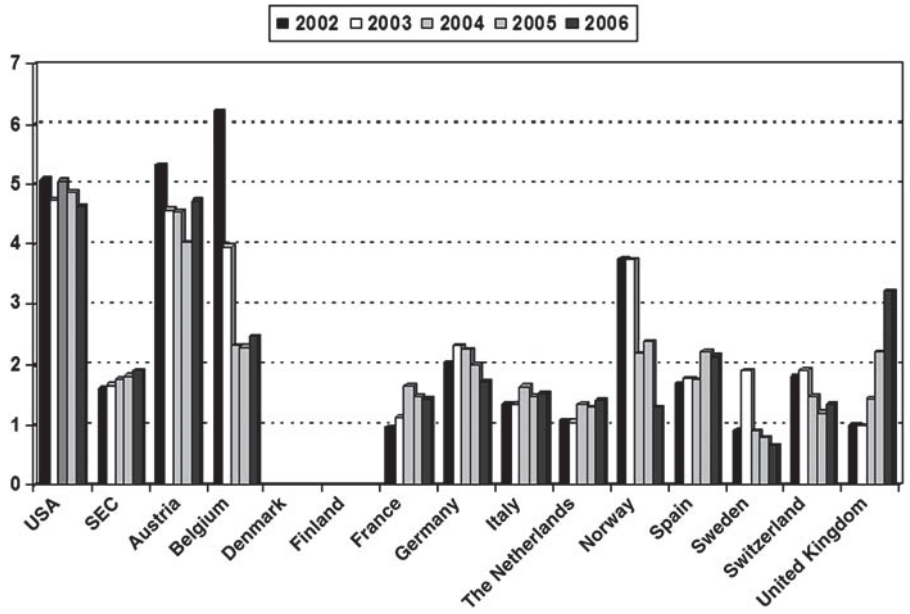


Fig. 4. Pancreas transplant activity rate (incidence per million population) in USA and 13 European countries considered together (SEC) and individually during the period 2002–06 (Gonzales-Posada et al. 2010).

	USA	Europe[a]	Austria	Belgium	Denmark	Finland	France	Germany	Italy	Netherlands	Norway	Spain	Sweden	Switzerland	UK
Population[b]															
2002	287.67	366.73	8.07	10.31	5.37	5.19	61.40	82.44	56.99	16.10	4.52	40.96	8.91	7.25	59.22
2003	290.34	368.82	8.10	10.36	5.38	5.21	61.83	82.54	57.32	16.19	4.55	41.66	8.94	7.31	59.44
2004	293.03	371.05	8.14	10.40	5.40	5.22	62.25	82.53	57.89	16.26	4.58	42.34	8.98	7.36	59.70
2005	295.73	373.34	8.21	10.45	5.41	5.24	62.64	82.50	58.46	16.30	4.61	43.04	9.01	7.41	60.06
2006	298.44	375.29	8.27	10.51	5.43	5.26	63.00	82.44	58.75	16.33	4.64	43.76	9.05	7.46	60.39
							Pancreas Tx[c]								
2002	1460	591	43	64	0	0	59	161	77	17	17	69	8	13	59
2003	1373	614	37	41	0	0	70	191	77	17	17	74	17	14	59
2004	1483	657	37	24	0	0	103	187	95	22	10	74	8	11	86
2005	1444	678	33	24	0	0	92	165	87	21	11	96	7	9	133
2006	1386	718	39	26	0	0	90	141	90	23	6	94	6	10	193
							Pancreas WL[d]								
2002	2835	897	38	56	0	0	189	180	245	15	11	47	20	6	90
2003	2747	877	42	56	0	0	199	145	213	14	11	75	19	5	98
2004	2388	918	36	53	0	0	178	158	216	34	13	79	14	8	132
2005	2071	920	38	34	0	0	169	169	197	40	10	87	15	16	145
2006	1984	1009	32	30	0	0	169	190	222	40	10	73	15	21	207
DD[e]															
2002	6190	6422	195	223	73	89	1198	1001	1020	202	62	1409	98	75	777
2003	6457	6598	187	248	75	85	1119	1110	1042	223	87	1443	114	95	770
2004	7150	6898	181	220	64	109	1291	1052	1203	228	90	1495	123	91	751
2005	7593	7159	200	237	63	85	1371	1185	1197	217	76	1546	128	90	764
2006	8024	7340	201	273	62	109	1442	1227	1231	200	76	1509	137	80	793

[a] All 13 countries.
[b] Million inhabitants.
[c] Tx = transplants.
[d] WL = waiting list.
[e] DD = deceased donors.

Table 1. Population, total number of pancreas transplants, pancreas waiting list and DD in USA and 13 European countries (Gonzales-Posada et al. 2010).

MMF, sirolimus, antibody based agents) contributed to further improved graft survival, reduction of rejection rate and the overall expansion of transplantation.

These days, pancreas transplantation has become a worldwide popular therapeutic alternative for type-1 diabetics. According to data from the United Network for Organ Sharing (UNOS) and the International Pancreas Transplant Registry (IPTR), more than 30,000 pancreas transplants have been performed worldwide (>22,000 reported from the United States and >8,000 from rest of the world) between December 1966 and 31 December 2008 (UNOS & IPTR, 2008). The majority pancreas transplants have been performed in North America and Western Europe (Fig 4), (Tab. 1) (Gonzales-Posada et al. 2010).

4. Indication of pancreas transplantation

At the present, Pancreas Transplantation is the only therapeutic modality that can achieve full insulin independence and euglycemic state in type-1 diabetic patients. It is well known that normoglycemia has a positive impact on preventing secondary diabetic complications. Therefore, this modality does not only improve patients' quality of life but also it has a

positive impact on patients' medical conditions. Nevertheless, this therapeutic alternative is recommended only to a selected group of diabetics.
For a pancreas transplantation should be considered patients with brittle type-1 diabetes who suffer from secondary diabetic complications (diabetic nephropathy, diabetic retinopathy, diabetic neuropathy, diabetic gastro-enetopathy, etc); frequent hypoglycaemic episodes or hypoglycaemic unawareness and failure to achieve eu-glycemia even on intensive insulin treatment (insulin pump, etc.).
A detailed assessment of potential candidates for pancreas transplantation is mandatory because many of these patients have pre-existing cardiac diseases or other medical problems related to diabetes, and these may significantly increase per-operative morbidity, mortality and early graft failure.

4.1 Diabetes assessment

The first part of the evaluation is to determine the type of diabetes. It is generally accepted that pancreas transplantation should be reserved for type-1 diabetics. However, there are published data reporting successes of pancreas transplantation also in type-2 diabetic patients. Nevertheless, a more strict patients' selection is required (Orlando et al., 2010). For diagnosis type-1 diabetes it is satisfactory to detect an absence or very low levels of C-peptide together with raised HbA1c (>7.5%). However, the patient's considered for pancreas transplantation cannot exceed insulin requirements beyond 1.5mg/kg/day; as this is the marker of peripheral insulin resistance. These patients do not achieve full insulin independence even with successful pancreas transplantation. Patients who are failing to achieve a reasonable serum-glucose control with conventional insulin treatment should be also considered for pancreas transplantation. Usually, they suffer from frequent hypo and hyper-glycemic episodes. Sever hypoglycaemia is the most common casualty in diabetics on insulin treatment. These complications are potentially life-threatening, associated with high morbidity and mortality rate.

4.2 Cardiac evaluation

Diabetes doubles the risk of developing cardio-vascular disease; coronary-artery disease, cerebro-vascular disease and peripheral vascular disease (Grundy et al., 1999). Over 50% of diabetics have some degree of coronary artery disease. Also, it is well known that diabetics suffer from accelerated atherosclerosis and a high incident of silent ischemia and cardio-myopathy compared to the non-diabetic population. Furthermore, cardio-vascular disease is the leading cause of death in the general population (35%) but diabetic patients are two times (67%) more likely to die due to this cause (Watkins, 2003).
The key purpose of the pre-transplant cardiac assessment is to identify risk factors (reversible ischemia, impaired left ventricular function, coronary artery disease, etc.) that may increase per-operative morbidity and mortality; and minimize them with the appropriate management and treatment. For cardiac evaluation standard echocardiography, Dobutamine stress echocardiography (DSE), exercise tolerance testing, nuclear (thalium) myocardial perfusion scan and formal coronary angiogram are routinely used. Because each of these tests has some limitations, there is not a consensus yet regarding which method has the highest predicting value.
Dobutamine stress echocardiography (DSE) is a non-invasive imaging modality which combines two-dimensional echocardiography with cardiovascular stress induced by

dobutamine infusion. This test is sensitive to detect coronary artery disease in asymptomatic, high risk (diabetic, patients with peripheral vascular disease, etc.) patients.
The nuclear myocardial perfusion study (MPI) is a sensitive, non-invasive test for the assessment of myocardial perfusion, ejection fraction, wall motion and wall thickness. Stress radionuclide myocardial perfusion imaging, on the other hand, displays the downstream functional consequences of epicardial coronary artery disease in the myocardium. It also may visualize the regional effects of micro vascular endothelial dysfunction and impairment of regional coronary flow reserve.
DSE and MPI methods are generally accepted as standard and non-invasive screening studies useful to identify patients (diabetics with ESRF) with significantly increased risk of myocardial infarction or cardiac death (Rabbat et al., 2003; Cai et al., 2010). Nevertheless, they have low sensitivity and specificity to define coronary artery disease in patients with ESRD (Letine et al., 2010).
On the other hand, the coronary-angiogram (CA) offers high sensitivity to detect coronary-artery disease but it is limited in regards to predicting survival. This is mainly because myocardial infarction is more likely to be caused by plague instability rather than angiographic stenosis. Additionally, the contrast used for this test is nephro-toxic and it can have a catastrophic impact on impaired kidney function (Letine et al., 2010).
There is only one published study which directly compares doputamine stress echocardiography to coronary angiogram in renal transplant candidates (Herzog et al., 1999). Fifty potential transplant candidates underwent DSE followed by CA. Twenty of fifty DSE were positive for inducible ischemia. Sensitivity and specificity of DSE were 52% and 74%, respectively, for stenosis ≥50%; 75% and 71% for stenosis greater than 70%; 75% and 57% for stenosis greater than 75%. At the end the authors concluded that DSE is a good screening method, in spite of low sensitivity to detect coronary artery disease. For that reason, CA is reserved for high risk groups of patient with a previous history of cardiac problems (cardiac event, ishemic heart desease etc) or for patients with positive stress echocardiography or MPI scan.

4.3 Dietitian management

4.3.1 Pre-transplant assessment

A well balanced nutrition in transplant recipients plays a vital role in a pre and pos-transplant period to ensure the best possible outcomes. The role of a dietician is to evaluate the patient's nutrition status and design a nutrition plan for a pos-transplant period. For that reason it is important we ensure pre-operatively the following parameters:

a. *Good glucose control:* It is well documented (Kuo et al., 2010) that diabetes mellitus is a major predictor of cardiovascular morbidity and mortality in kidney transplant recipients. A recent study (Sato et al., 2010) analysed the outcomes of patients undergoing cardiac surgery and revealed that increased of HbA1c levels (>6.5%) predicts insulin sensitivity and increases the incidence of major complications. In addition, a well controlled diabetes improves gastroparesis and delays gastric empting (Reddy, 2010) as well as preventing other gastro intestinal symptoms including nausea, vomiting, bloating, early satiety and abdominal pain (Kashyap & Farrugia, 2010).
b. *Weight maintenance:* A Body Mass Index (BMI) ≥25kgs/m^2 is a strong predictive factor with significantly negative impact on long term renal graft outcomes (Cheung et al., 2010). So, in these patients weight loss is strongly recommended.

c. *Balanced nutrition status*: Prior to transplantation it is also crucial to optimize good nutrition status in patients with low BMI. According to some data (Meier-Kriesche et al, 2002) poor nutrition is associated with significantly worse patient and graft survival.
d. *Adequate electrolyte balance:* Patients with chronic renal failure may be on a low potassium, phosphate and low salt diets and fluid restrictions. Raised levels of potassium and phosphate are associated with increased mortality in these patients (Noori et al 2010; Ganesh et al., 2001).

4.3.2 Immediate pos-transplant management

The transplant recipient must receive adequate nutrition support (25-30 kcal/kg ideal body weight per day) during the first seven pos-operative days to avoid starvation and to enhance postoperative recovery (Braga et al., 2009). We should aim to identify the patient's post-transplant nutrition requirements prior to a surgery and in advance to design an individual sufficient nutrition plan.

The European Society for Clinical Nutrition and Metabolism (ESPEN) developed guidelines on enteral nutrition management after surgery (Weiman et al., 2006). These guidelines suggest that oral diet and supplements should be initiated early after surgery, where possible. Furthermore, enteral nutrition should be considered in patients with obvious under-nutrition and those whose oral intake will be inadequate (<60% of requirements) for 10 days after surgery. These patients should ideally have a naso-jejunal tube placed during surgery and feeding commenced on the first pos-operative day. According to these guidelines, parenteral nutrition is reserved for those patients who are unable to tolerate enteral feeding; due to complication including interstinal obstruction, ileus and sever shock (Braga et al., 2009).

4.3.3 Pos-transplant surveillance

In the long term, it is important to maintain a healthy weight and maintain good nutrition status. A team from the Netherlands (Hoogeveen et al., 2011) reports that 1-year post-transplant BMI is more strongly related to death and graft failure than pre-transplant BMI. According these data, patients who reached pos-transplant BMI>30 kg/m^2 have a 20-40% higher risk of death and graft failure compared to patients with lower BMI.

4.4 Other tests

A routine part of the pre-transplant assessment includes blood tests:

a. *Haematology Blood Tests:* Blood group identifying, antibody screen, full blood count, Thrombophilia screen, APTT, PT, and INR.
b. *Biochemistry Test:* Urea & electrolytes, creatinine, uric acid, calcium, phosphate, 24-hour urine collection (tested for protein/micro albuminuria and creatinine clearance), eGFR (radioisotope glomerular filtration rate if needed), liver function tests, amylase, thyroid function, fasting blood glucose, fasting and stimulated C-peptide levels if needed, fasting blood lipids.
   Additional studies may include oral or intravenous glucose challenge, anti-insulin and islet cell antibodies, proinsulin level and lipoprotein.
c. *Viral screen:* Hepatitis B and C, HIV, HTLV, BK virus, Polioma virus, Syphilis, Rubella, Epstein Barr Virus, Toxoplasma, Varicella-Zoster, Herpes , simplex, Cytomegalovirus.
d. *Immunology Blood Tests:* HLA typing and antibody screening.

5. Contraindications

Overall, contraindications to pancreas transplantation are the same as for kidney transplantation, and they are often determined by patient co-morbidity.

5.1 Absolute contraindications

a. Insufficient cardiovascular reserve:
   - Ejection fraction below 50%
   - Myocardial infarction within 6 months
   - Non-correctable coronary artery disease or refractory congestive heart failure
b. Non curable malignancy (excluding localised skin malignancy)
c. Active sepsis
d. Active peptic ulcer
e. Major psychiatric history likely to result in non-compliance
f. Inability to withstand surgery and immunosuppression

(UKT, 2003)

Some contraindications are relative and must be individually assessed and discussed with the responsible specialist on multidisciplinary bases and with the patient, too.

5.2 Relative contraindications

a. Cerebrovascular accident with long term impairment.
b. HIV (subject to discussion).
c. Chronic liver disease: Candidates with Hepatitis B/C need recent viral screen, LFT and assessment by hepatologist prior activating on a WL. The aim is to exclude active viral disease as well as advanced irreversible liver disease.
d. Body Mass Index greater than 30.
e. Malignancy: In patients with a history of cancer a cancer free interval from three to five years according the type of cancer, stage and cancer therapy are required. This issue must be discussed in detail with an oncologist. A valuable source of information is "Israel Penn International Transplant Tumor Registry" (www.ipittr.org).
f. Type-2 diabetes was originally an absolute contraindication to pancreas transplantation. However, a recently published review reports that selected group type-2 diabetics benefit from whole organ pancreas transplantation, too. Transplant outcomes (after SPK) are comparable between type 1 and 2 diabetics. But a strict patient selection is required; BMI less than 30 kg/m^2, insulin requirements <1.0 units/kg/day, C-peptide level less than 10 ng/ml, etc. (Orlando et al., 2010).
g. Extensive aorta/iliac and/or peripheral vascular disease.
h. Continued abuse of alcohol, smoking or other drugs.

(UKT, 2003)

6. Transplant alternatives for diabetic patients

For diabetic patients with ESRF three transplant alternatives are currently available: kidney transplantation (including cadaver and living donor kidney transplantation); Simultaneous Pancreas-Kidney Transplantation (SPK) and Pancreas After Kidney Transplantation (PAK). Each of them has some recognised advantages and disadvantages (Tab. 2).

	Advantages	Disadvantages
CKT	Provides better survival than dialysis options	Inferior to other transplant options with respect to kidney graft survival and patient survival
LRD	Minimizes waiting time, time spent on dialysis Very low early morbidity and mortality	Absence to normalize of blood glucose Inferior patient survival over time when compared with SPK recipients with functioning grafts
SPK	Glycemic control, with recent median pancreas graft survival of >10 years High-quality, deceased donor kidney graft	Higher morbidity and mortality due to larger operation If pancreas fails within the first year, outcomes are worse than LRD
PAK	Glycemic control If living donor kidney transplant, comparable/better patient and kidney graft survival than LRD	Two separate surgical procedures, increased mortality early postoperatively following pancreas transplant Historically inferior pancreas graft survival (35% at 10 years) than SPK

Table 2. Summary of advantages and disadvantages of transplant options for diabetic kidney disease (Wiseman, 2010).

6.1 Kidney transplantation

Kidney transplantation is a widely used and well accepted transplant option for patient with ESRF secondary to DN. It is indisputable that this alternative gives survival advantages to these patients over chronic dialysis. The estimated survival of a diabetic on dialysis is only 30-40% at five years, while kidney transplantation increases their 5 year survival to up to 70% for Cadaver Kidney Transplantation (CKT), and to up to 80% for Living Donor Kidney Transplantation (LRD) (Reddy et al., 2003; USRDS 1998; Cecka et al. 1997). As we know, LRD is associated with better outcomes due to a superior quality of kidney graft and reduced cold ischemia time. This type of transplantation has relatively low risk of post-transplant complications (10-12%) and compared to pancreas transplantation it is less traumatic, too. For that reason, a greater population of diabetic patients with ESRF is eligible for renal transplantation rather pancreas transplantation. A successfully treated ESRF with renal transplantation does not only improve overall patients' medical conditions (anaemia, hypertension, etc) but in many cases it also stabilises brittle diabetes.

6.2 Simultaneous pancreas and kidney transplantation

During recent years, Simultaneous Pancreas and Kidney Transplantation (SPK) has become the most popular transplant alternative and golden standard for type-1 diabetic with ESRF. Additionally to renal transplantation in these patients pancreas transplantation helps to achieve euglycemia, insulin independence and enhances patients' quality of life (Sureshkumar et al., 2006). Also, the tight glycaemic control prevents the recurrence of diabetic nephropathy and improves secondary diabetic complications; mainly diabetic retinopathy, cardiovascular disease, diabetic neuropathy, etc.

Overall, it has been proven that SPK gives some survival benefits to these patients. In one of the largest studies (Ojo et al., 2001) SPK was associated with a 10-year patient survival of 67% compared to 46% in a CKT recipient group. However, in comparison with the LRD benefit of SPK, in terms of patient and graft survival, it does diminish. Wisconsin experiences (Tab. 3) (Rayhill et al., 2000) have shown that patient and renal graft survival was not different between the LRD and the SPK groups, but it was significantly lower in the CKT group (Fig 5,6) (Young et al., 2009).

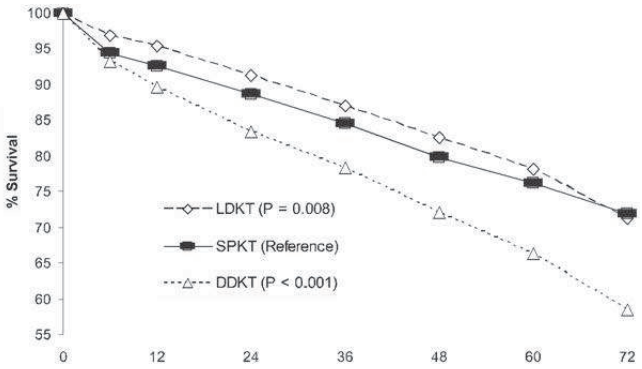
The main advantage of LRD is the low immunological risk and good quality kidney graft that participates on excellent kidney function and prolongs graft survival. However, only an additional pancreas transplant gives a protective role to prevent the recurrence of DN, maintain a good kidney function, improve the quality of life and eliminate secondary diabetic complications. On the other hand, we cannot forget that SPK is associated with a double level of morbidity (20-40%) and mortality (2-5%) compared to kidney transplantion. For that reason, younger patients with better medical conditions (Rayhill et al., 2000) should be considered for SPK.

	1y patient survival	5-y patient survival
LRDi	100%	94%
LRDh	99%	85%
SPK	96%	88%
CKT	94%	72%

	1y graft survival	5-y graft survival
LRDi	96%	85%
LRDh	94%	72%
SPK	87%	78%
CKT	86%	64%

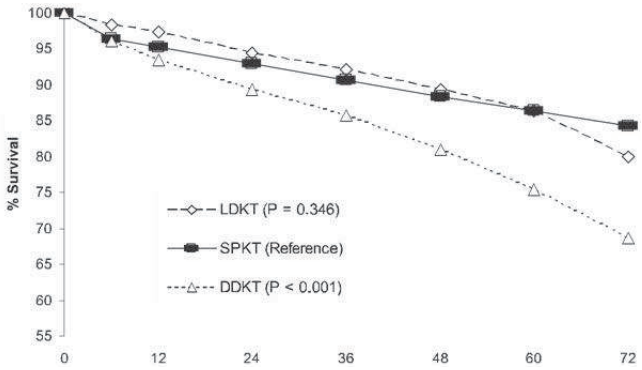
LRDi – HLA-identical living related donor, LRDh – haplotype-identical living related donor

Table 3. The 1-year and 5-year pos-transplant outcomes (Rayhill et al., 2000).



(LDKT - living donor kidney transplant; SPKT - simultaneous pancreas kidney transplant; DDKT - deceased donor kidney transplant).

Fig. 5. Unadjusted kidney graft survival by transplant type (Young et al., 2009).



(LDKT - living donor kidney transplant; SPKT - simultaneous pancreas kidney transplant; DDKT - deceased donor kidney transplant).

Fig. 6. Unadjusted patient survival by transplant type (Young et al., 2009).

6.3 Pancreas after kidney transplantation

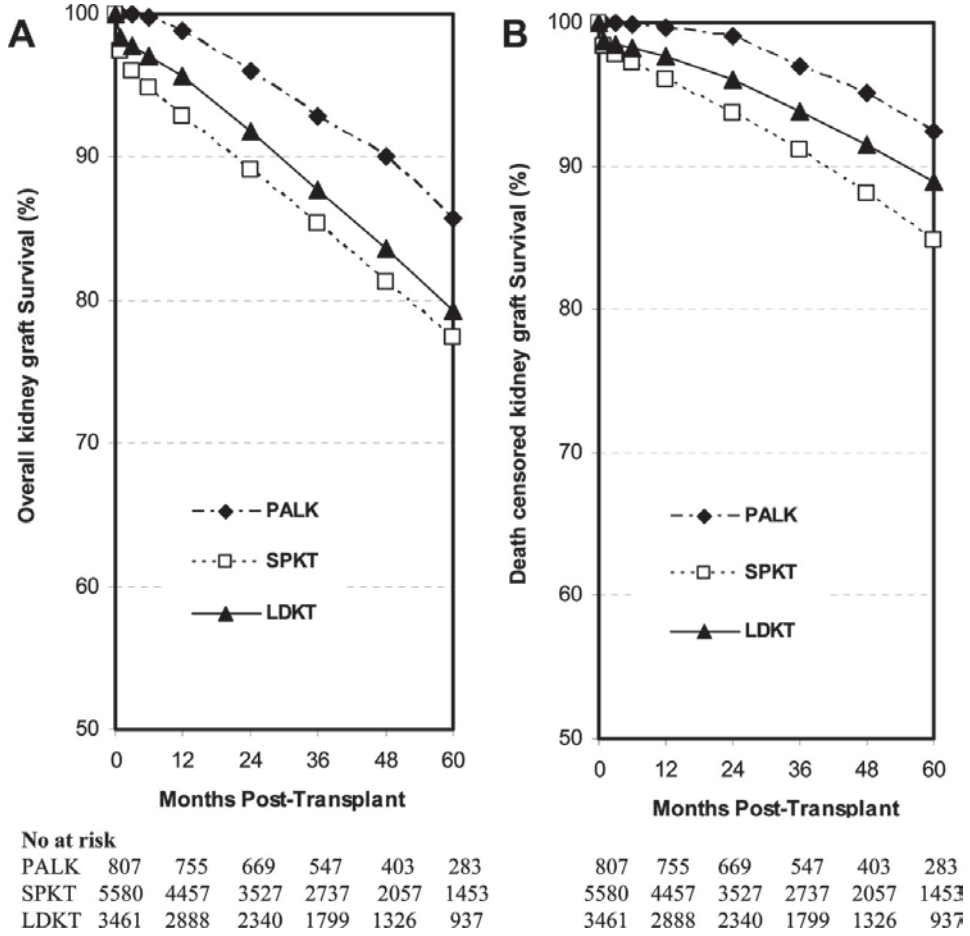
Historically, Pancreas After Kidney Transplantation (PAK) was not a very popular pancreas transplant alternative due to the inferior pancreas graft survival compared to SPK. The impact of pancreas graft on patients with kidney graft from two different donors was associated with high immunological graft failure. However, the development of new immunosuppressive regiments based on depleting antibody induction and Tacrolimus and MMF maintenance reduced the risk of immunological graft loss and improved graft survival outcomes. For those reasons, this alternative has become more popular (Larson et al., 2004).

Diabetic patients who have undergone kidney transplant or who underwent SPK and have lost pancreas graft might be today considered for PAK. With increased frequency, this two-stage procedure involves a living donor kidney transplantation followed by a cadaver pancreas transplant (PALK). This alternative has the advantage of a short waiting time and of a superior quality kidney graft (Kleinclauss et al., 2009). The second great advantage of PAK is performing major pancreas transplant surgery on a non-uremic patient. This minimizes the risk of per-operative morbidity and mortality related to renal failure.

Pominipanin analysed data of the Organ Procurement Transplant Network/United Network of Organ Sharing (OPTN/UNOS) database and compared outcomes of SPK with CKT and PALK. He reports that renal graft outcomes were superior in PALK compared to SPK. The 1-year pancreas graft survival was marginally higher for the SPK cohort (86%) vs. 80% for PALK. The overall patient survival was better in PALK compared to SPK (Fig 7 a,b). Even this study showed that PAK is an alternative with competitive results to SPK.

6.4 Simultaneous cadaver pancreas and living donor kidney transplantation

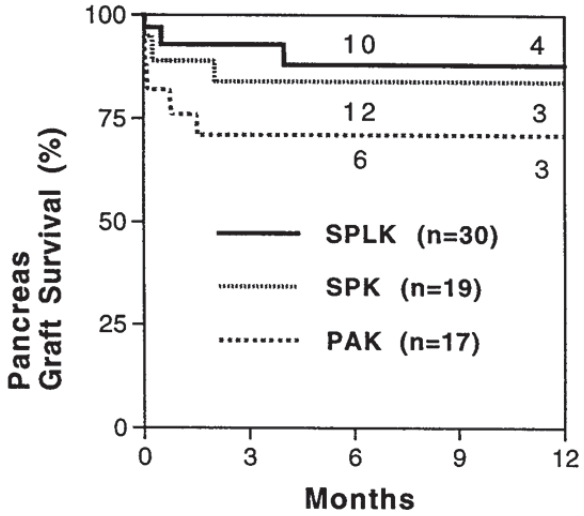
At present, SPK and PAK are the most common options for uremic type-1 diabetics. SPK is a one-stage procedure and this is its main advantage over PAK. On the other hand, PAK has the advantage of involving living donor with superior quality of kidney graft function and subsequently of performing pancreas transplantation on a non-uremic patient. Simultaneous Cadaver Pancreas and Living Donor Kidney Transplantation (SPLK) is an innovative approach that merges some benefits of both alternatives; superior quality of living donor kidney and s single procedure with shorter waiting time for cadaver pancreas graft.



a/ Overall kidney graft survival (%)
b/ Death censored kidney graft Survival (%)
PALK - pancreas after living kidney transplant,
SPKT - simultaneous pancreas kidney transplant,
LDKT - living donor kidney transplant.

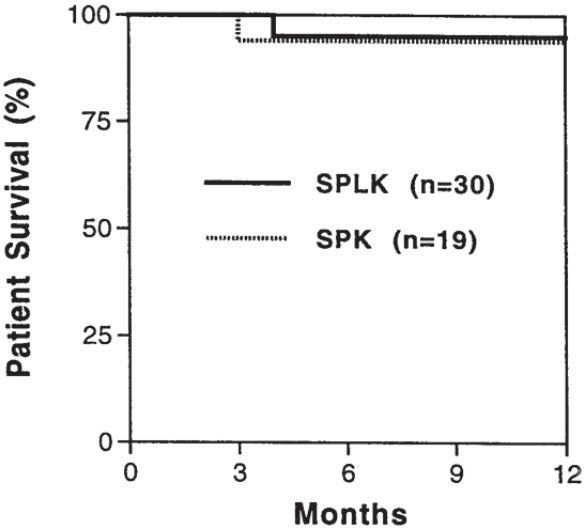
Fig. 7. Kidney graft survival (Poommipanit et al., 2010).

Despite increased immunological risk, SPLK showed comparable results with SPK and PAK (Boggi et al., 2004). In a study from Maryland (Farney et al., 2000), it was reported that 1-year pancreas graft survival in the SPLK group was not significantly higher than in SPK and PAK (88% vs. 84% vs. 71%) Fig. 8,9,10 (Farney et al., 2000). The 1-year patient survivals were 95% (SPLK), 94% (SPK) and 100% (PAK). The SPLK group showed lower incidence of delay graft function and better kidney function.



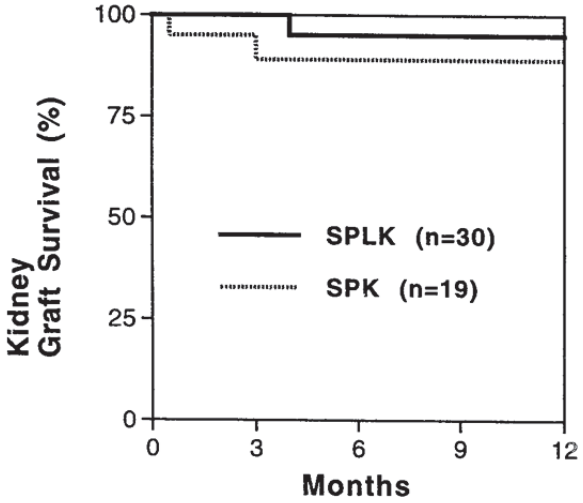
One-year pancreas graft survival rates were 88%, 84%, and 71%, respectively, for simultaneous cadaver-donor pancreas and living-donor kidney transplantation (SPLK), simultaneous cadaver kidney and pancreas transplantation (SPK) and living-donor kidney transplantation alone followed by a solitary cadaver-donor pancreas transplant (PAK)

Fig. 8. Pancreas graft survival rates (Farney et al., 2000).



One-year patient survival rates were 95% and 94% for simultaneous cadaver-donor pancreas and living-donor kidney transplant (SPLK) and simultaneous cadaver kidney and pancreas transplant (SPK) recipients. The patient survival rate was 100% in living-donor kidney transplantation alone followed by a solitary cadaver-donor pancreas transplant (PAK) recipients (not shown).

Fig. 9. Patient survival rates (Farney et al., 2000).



One-year kidney graft survival rates were 95% and 89% for simultaneous cadaver-donor pancreas and living-donor kidney transplant (SPLK) and simultaneous cadaver kidney and pancreas transplant (SPK) recipients. The only SPLK loss was death with function. No living-donor kidney transplantation alone followed by a solitary cadaver-donor pancreas transplant (PAK) kidney grafts were lost (not shown).

Fig. 10. Kidney graft survival rates (Farney et al., 2000).

7. Surgical complications

Despite worldwide growing experience with pancreas transplantation, this procedure is still associated with high incidence of pos-transplant complications; and compared with other solid organ transplants; it has the highest incidence of serious intrabdominal complications and reoperations. We know that up to 50% of pancreas recipients develop pos-transplant complication and around 32% of patients require further surgery to deal with these problems (Troppmann et al., 1998). According the United Network for Organ Sharing report, from 11% to 21% of all pancreas grafts are lost because of surgical complication (Gruessner & Sutherland, 2005).

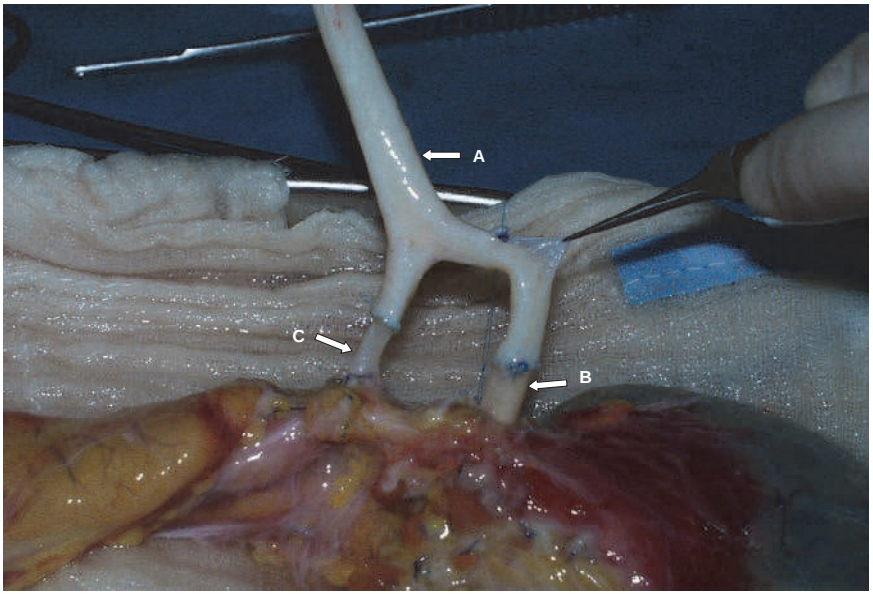
There are recognised several factors that participate in development of postransplan complications. Diabetes was found to be the strongest independent risk factor. It is well documented that diabetics have significantly higher complication rate compared with non-diabetic population. Also, these patients receive strong immunosuppressive regiment, compared to other solid organ recipients. This makes patients more immunocompromised and vulnerable to infection. Open bowel or bladder, during pancreas implantation is other possible source of abdominal contamination and infection. Furthermore, SPK recipients are compromised by uraemia and PAK recipients are chronically immunosuppressed at the time of transplant. Additional risk factors include: older donors and recipients, long cold ischemia time and high BMI (UNOS & IPTR, 2008).

The most common surgical complication after pancreas transplantation is abdominal infection and graft pancreatitis (38%), followed by pancreas graft thrombosis (27%) and anastomotic leak (9%) (Troppmann et al., 1998).

7.1 Thrombosis

Vascular thrombosis is the second leading cause of pancreas graft failure after rejection. Incidence is reported between 2-20% and it can be either arterial or venous (Gruessner & Sutherland, 2000).

It is well known that pancreas is more susceptible to thrombosis than other organs. Pancreas has naturally low microvascular flow. Removing the spleen from pancreatic graft as a part of the pancreas bench-work, venous flow does reduce even more. The pancreas also requires vascular reconstruction because blood supply to the pancreas is divided during explantation. The donor iliac artery extension ″Y″ graft is joined to the superior mesenteric artery and the splenic artery to create a single arterial conduit (Fig. 11). The venous extension graft is an additional risk factor causing venous thrombosis. Furthermore, hyper-coagulable status in renal failure patients and endothelial damage are recognised as other negative factors in developing venous thrombosis (Muthusamy et al., 2010).



An end-to-end anastomosis between limb of internal iliac artery of the "Y" graft and stump of the splenic artery of the pancreas graft; and limb of external iliac artery and stump of the superior mesenteric artery.
A - "Y" graft, B- superior mesenteric artery, C – splenic artery

Fig. 11. Vascular reconstruction

If venous thrombosis occurs, often a patient develops abdominal pain due to organ swelling with an acute drop of haemoglobin levels. Raising levels of serum glucose are usually late sings of thrombosis. Arterial thrombosis is much less common with a less dramatic clinical picture. In the majority of cases, the pancreas graft is non-salvageable and requires urgent graftectomy. Some data report that in an early stage urgent radiological intervention with thrombectomy or thrombolysis can salvage a pancreas allograft (Stockland et al., 2009) (Fig. 12).

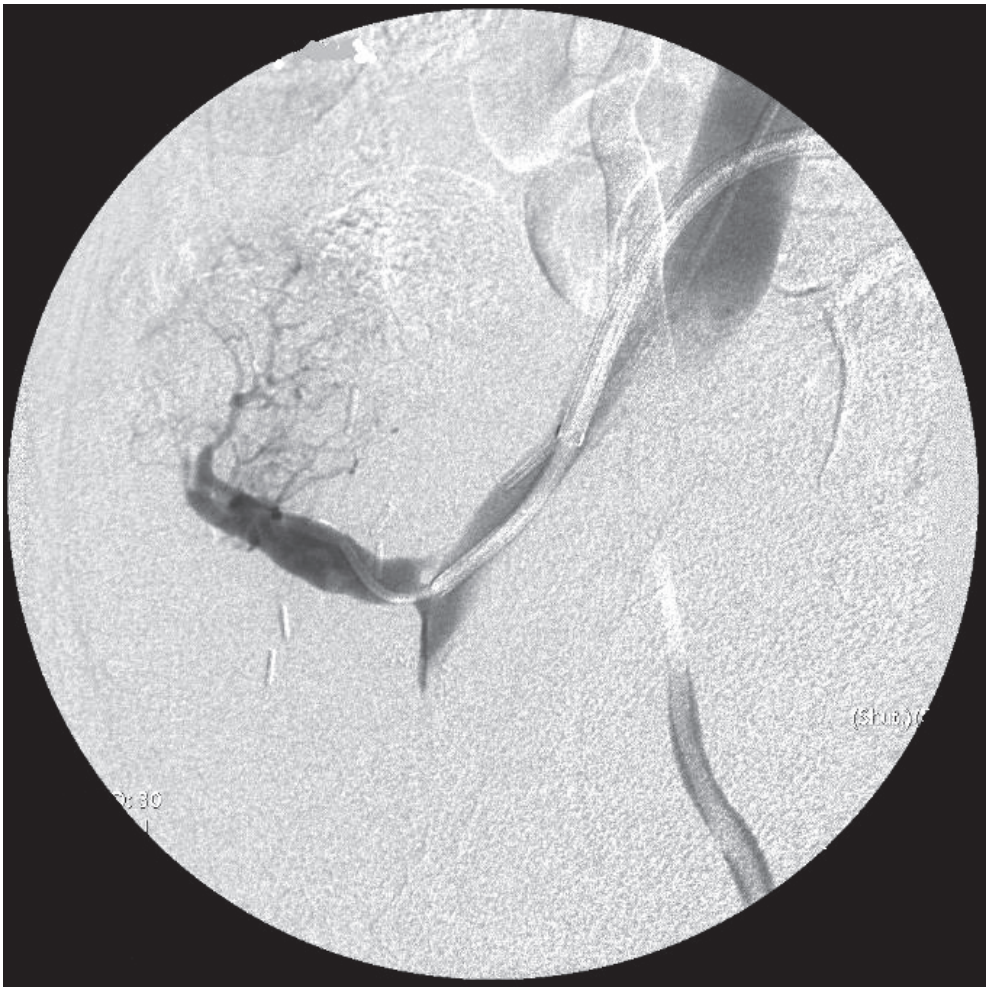


Fig. 12a

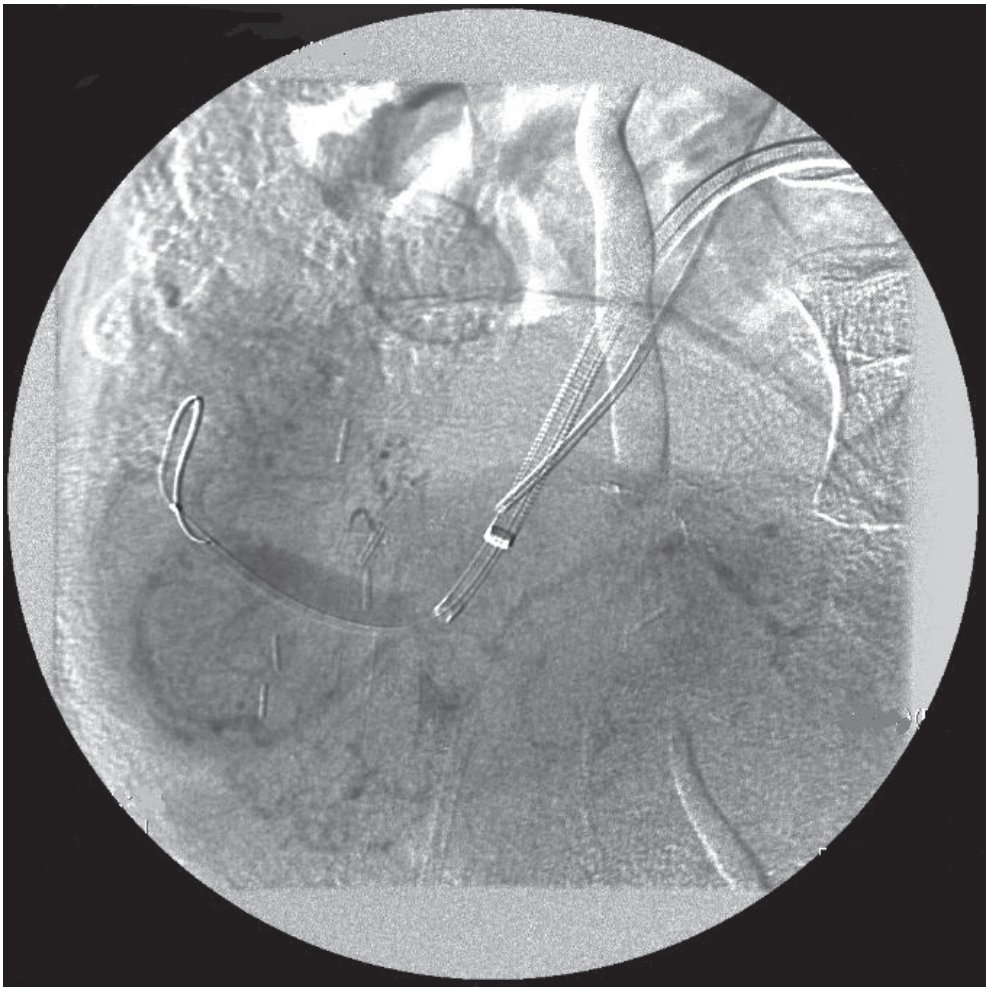


Fig. 12 b

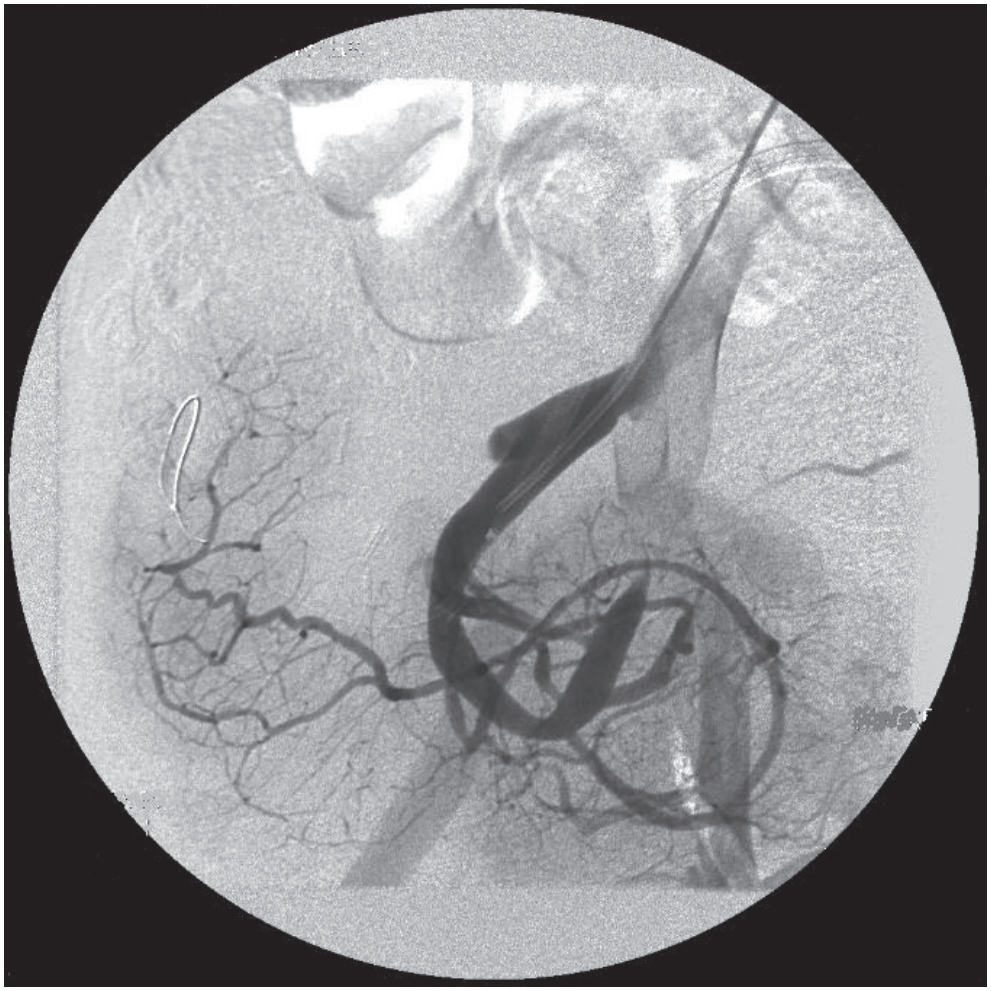


Fig. 12 c

a/ Thrombus in the portal vein of pancreas graft (black arrow points on filling defect, thrombus, in portal vein). A thrombectomy catheter is in the graft's portal vein via right external iliac vein by cannulation right femoral vein.
b/ Status after thrombectomy. Improvement in venous flow and full patency of portal vein without a thrombus.
c/ Normal angiogram of pancreas graft.

Fig. 12. Conventional angiography of pancreas graft.

A key part of the post-operative thrombosis management is prevention, close monitoring, early diagnosis and early intervention, but mainly meticulous vascular reconstruction, bench-work and refine implantation technique. Patients after transplantation receive a high dose of fractionated/continued infusion heparin to develop hypo-coagulable status to reduce clot formation. Sensitive markers for careful coagulation monitoring are APTT ratio (INR) and Thromboelastogram (TEG) (Burke et al., 2004). Several diagnostic methods are recommended for graft monitoring and diagnosis vascular complications: duplex ultrasound, CT-angiography or MR-angiography and formal angiography.

7.2 Bleeding

This vascular complication does mainly occur in combination with intra-abdominal infection or during sever hypo-coagulable status secondary to heparin treatment. Heparin induced bleeding usually has a slow progress and it is often managed conservatively; with antibiotics and blood transfusions. Bleeding secondary to infection is a serious event and it can be life-threatening. Clinical presentation is rapid, sudden hypotension, significant fall of haemoglobin levels and pulsative intra-abdominal mass. In that case urgent laparotomy is vital to control bleeding and abdominal sepsis. At presence of advanced abdominal sepsis or infection involving pancreas graft it is recommended to perform graftectomy to prevent fatal bleeding.

7.3 Pancreatitis

Graft pancreatitis usually occurs instantly after transplant as a result of excessive handling of an organ during retrieval, storage, bench-work and transplantation, as well as a consequence of ischemic-reperfusion injury. Most episodes of pancreatitis resolve uneventfully, however some may lead to secondary complications (fistula, pseudocyst, etc.). Also, Octreotide (synthetic somatostatin analog that inhibits exocrine pancreatic secretion) has been used to prevent and treat some pos-transplant complications (i.e. graft pancreatitis, pancreatic fistula). But data from published studies are controversial with no statistical difference in complication rate between recipients who received octreotide and patient treated by placebo (Stratta et al., 1993).

7.4 Miscellaneous

Other common early surgical complications involve anastomotic leak, pancreatic fistula, intra-abdominal sepsis, ileus, wound infection, etc. They may cause graft lost and recipients' mortality so it is important to actively search for them, to detect them early and to treat them.

8. Immunosuppression

The key role of immunosuppression in transplantation is to minimize graft lost due to rejection. Despite this major benefit, all immunosuppressive medication has some side effects. For that reason, a good immunosuppressive regiment should balance both aspects to deliver the best possible outcomes. The pancreas is a more immunogenic organ than the kidney, and precisely for that reason the majority of immunosuppressive regiments for pancreas transplantation are mainly based on quadruple drug therapy; including antibody agents for induction in combination with calcineurin inhibitors (CNI) and mycophenolate mofetil (MMF) or sirolimus and steroids (Singh & Stratta, 2008).

Initially, the IL-2 receptor antagonists (basiliximab, daclizumab) have been used as induction agents in pancreas transplantation for long period. In the PIVOT Study daclizumab induction was compared to no antibody induction in pancreas transplantation. The results showed that daclizumab significantly reduced the incidence of acute rejection. The 1-year rejection free interval in the daclizumab group was 68% compared to 51% in the non antibody induction group (Stratta et al., 2003). T-cells depleting antibody agents, such as antithymocyte globulin (ATG) and alemtuzumab (Campath), have gained great popularity these days. According to the United Network of Organ Sharing data, this type of induction significantly decreases incidence of immunologically related pancreas graft failure (Gruessner & Sutherland, 2003).

According to a review published in 1999 (Stratta, 1999), a combination of MMF and tacrolimus in primary immunosuppressive regiment resulted in an improved 2-years patient, kidney and pancreas survivals; 97.7%, 93.3% and 90%, respectively.

Lymphocyte-depleting antibody agents in combination with tacrolimus, and MMF or sirolimus, are effective in preventing acute rejection and allow corticosteroids elimination or even full avoidance (Heilman et al., 2010). The principle of the steroid sparing regiment is to avoid steroids related side effects (increased risk of hypertension, glucose intolerance, cholesterol, infection, cardiovascular events, anaemia, osteoporosis, etc.) in pancreas transplant recipients. There is strong evidence that steroid sparing/avoidance regiments are safe and effective with a positive impact on patient and graft survival. Also, we have seen significantly improved the short-term outcomes whereas the long-term outcomes are still insufficient (Mineo et al., 2009).

9. Monitoring pancreas function

The development of surgical techniques and immunosuppressive drugs has significantly improved short-term outcomes of pancreas transplantation (Fig. 13). So these days the main target is to improve long-term results and minimize late graft dysfunction.

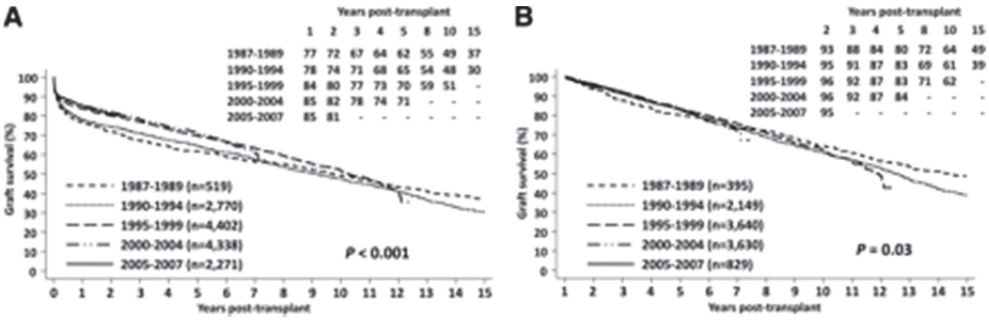


Fig. 13. Pancreas graft survival by era for all transplants, 1987–2007: UNOS registry analysis. *B*: Pancreas graft survival by era for transplants surviving more than 1 year, 1987–2007: UNOS registry analysis (UNOS, 2010).

Immunological graft loss still remains the main cause of graft failure; its rate in 1-year is significantly lower in SPK groups (2%) compared to solitary pancreas transplants (6% for PAK and PTA) (Fig 14) (Gruessner et al., 2008).

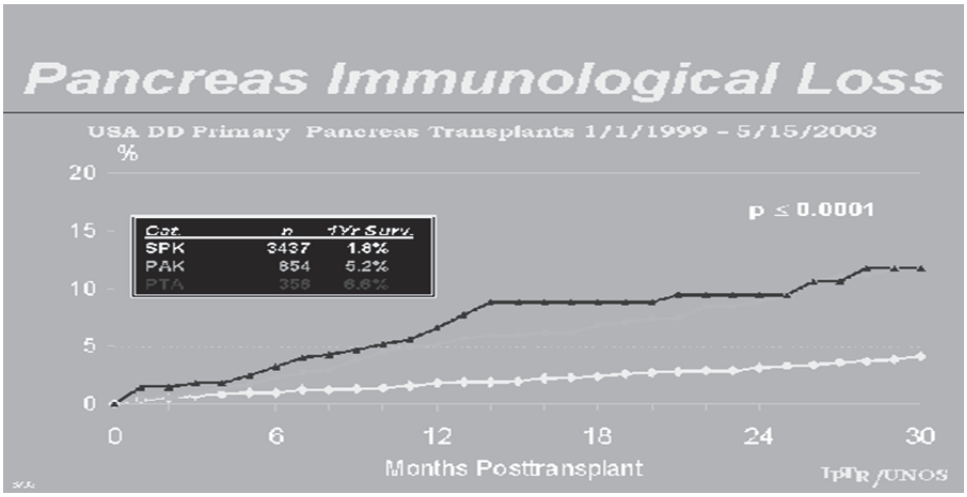


Fig. 14. Pancreas Immunological loss (Waiki et al., 2010).

The incidence of acute rejection is at its highest early after the transplantation. Induction regiments based on antibody depleting agents (i.e. ATG, Campath) delay the repopulation of lymphocytes; so the peak of rejection rate is around six to nine months after transplantation instead of three months as we see in regiments based on IL-2 receptor antagonists induction. A clinical picture of acute rejection is non-characteristic (fever, abdominal pain, ileus, tenderness, diarrhea, haematuria in bladder drained pancreas) or in the majority of cases absent.

Close monitoring of the pancreatic graft is a crucial part of pos-transplant surveillance. Unfortunately, there are not any biomarkers that can sensitively predict rejection yet. For that reason routinely are monitored the levels of fasting blood glucose, fasting C-peptide, HbA1c, serum amylase, serum lipase, oGTT and CRP; but with limited sensitivity and specificity. In SPK patients we do monitor serum creatinine as an indirect marker, too. Also, we know that islet function is resistant to pancreas damage so serum glucose elevation is a late manifestation of pancreas graft dysfunction and predicts poor prognosis; i.e. acute or chronic rejection, pancreatitis, thrombosis, etc.

The bladder-drained pancreas technique gives easy and convenient access to monitor pancreas graft function by measuring urine amylase. A low amylase level is a marker of graft dysfunction (rejection, pancreatitis, etc). Also, cystoscopy enables to perform repeated pancreas graft biopsies with a relatively low risk of complication rate.

The only objective way to diagnose rejection is a histological evaluation of the pancreas graft. Precise diagnoses help to tailor management and subsequently improve graft function. Despite a higher incidence of biopsy related complications pancreas graft biopsy is now widely employed (Gaber, 2007). SPK cases have a high incidence of synchronous pancreas and kidney rejection rate, around 62.5%. Kidney graft biopsy has lower risks of complications compared to pancreas biopsy. Also for that reason, kidney biopsy is routinely employed to diagnose pancreas graft rejection. On the other hand, there is a 25% occurrence of kidney only rejection; that usually correlates with elevation of serum creatinine. In 12.5% cases rejection involves only pancreas without involvement of renal graft (Kitada et al., 2009).

A successful Banff scheme of grading rejection in kidney (Solez et al., 2007) and liver (ICD, 1997) transplantation was subsequently applied in pancreas transplantation, too. On the 9th Banff conference on Allograft Pathology in 2007 (La Coruña, Spain) a final version (Tab. 4,5) of Banff Schema for Grading Pancreas Allograft Rejection was agreed (Drachenberg et al., 2008).

10. Benefits of pancreas transplantation

The main purpose of pancreas transplantation is to achieve eu-glycemia, insulin independence and improve the quality of life in diabetics. A number of studies examined the impact of successful pancreas transplantation also on secondary diabetic complications (nephropathy, retinopathy, neuropathy, etc).

Nephropathy: Diabetic nephropathy has a high recurrence rate, effects almost all kidney grafts and can lead to graft failure. Development of histological sings of diabetic nephropathy is seen within two years after transplantation (Bohman et al., 1984). It has been well documented that functioning pancreatic grafts have a protective role on kidney graft function. Achieving permanent normo-glycemia not only prevents the development of DN but it can also reverse histological lesions characteristic for DN (Fioretto et al., 1998).

Retinopathy: There is good evidence that pancreas transplantation and subsequent normoglycemia stabilizes and even improves retinopathy. However, patients with a high grade of retinal damage before a transplant may get a progression of retinopathy (Königsrainer et al., 1991).

1. Normal. Absent inflammation **or** inactive septal, mononuclear inflammation not involving ducts, veins, arteries or acini. There is no
graft sclerosis. The fibrous component is limited to normal septa and its amount is proportional to the size of the enclosed structures
(ducts and vessels). The acinar parenchyma shows no signs of atrophy or injury.
2. Indeterminate. Septal inflammation that appears active but the overall features do not fulfill the criteria for mild cell-mediated acute
rejection.
3. Cell-mediated rejection
Acute cell-mediated rejection
- Grade I/Mild acute cell-mediated rejection
Active septal inflammation (activated, blastic lymphocytes, ± eosinophils) involving septal structures: venulitis (sub-endothelial
accumulation of inflammatory cells and endothelial damage in septal veins, ductitis (epithelial inflammation and damage of ducts).
Neural/peri-neural inflammation.
and/or
Focal acinar inflammation. No more than two inflammatory foci^per lobule with absent or minimal acinar cell injury.
- Grade II/Moderate acute cell-mediated rejection
Multi-focal (but not confluent or diffuse) acinar inflammation (≥3 foci^per lobule) with spotty (individual) acinar cell injury and drop-out.
and/or
Minimal intimal arteritis

- Grade III/Severe acute cell-mediated rejection
Diffuse, (widespread, extensive) acinar inflammation with focal or diffuse multi-cellular /confluent acinar cell necrosis.
and/or
Moderate- or severe-intimal arteritis
and/or
Transmural inflammation-Necrotizing arteritis
Chronic active cell-mediated rejection. Chronic allograft arteriopathy (arterial intimal fibrosis with mononuclear cell infiltration in fibrosis,
formation of neo-intima)

4. Antibody-mediated rejection = C4d positivity[oo] + confirmed donor specific antibodies + graft dysfunction
Hyperacute rejection. Immediate graft necrosis (≤1 h) due to preformed antibodies in recipient's blood
Accelerated antibody-mediated rejection. Severe, fulminant form of antibody-mediated rejection with morphological similarities to
hyperacute rejection but occurring later (within hours or days of transplantation).
Acute antibody-mediated rejection. Specify percentage of biopsy surface (focal or diffuse). Associated histological findings: ranging
from none to neutrophilic or mononuclear cell margination (capillaritis), thrombosis, vasculitis, parenchymal necrosis.
Chronic active antibody-mediated rejection. Features of categories 4 and 5.

5. Chronic allograft rejection/graft sclerosis
- Stage I (mild graft sclerosis)
Expansion of fibrous septa; the fibrosis occupies less than 30% of the core surface but the acinar lobules have eroded, irregular
contours. The central lobular areas are normal.
- Stage II (moderate graft sclerosis)
The fibrosis occupies 30–60% of the core surface. The exocrine atrophy affects the majority of the lobules in their periphery (irregular
contours) and in their central areas (thin fibrous strands criss-cross between individual acin).
- Stage III (severe graft sclerosis**)**
The fibrotic areas predominate and occupy more than 60% of the core surface with only isolated areas of residual acinar tissue and/or
islets present.

6. Other histological diagnosis. Pathological changes not considered to be due acute and/or chronic rejection. e.g. CMV pancreatitis,
PTLD, etc.

[a] Categories from 2 to 6 may be diagnosed concurrently and should be listed in the diagnosis in the order of their clinico-pathological significance.
[o] See Table 2 for morphological definition of lesions.
[oo] If there are no donor-specific antibodies or these data are unknown, identification of histological features of antibody-mediated rejection may be diagnosed as 'suspicious for acute antibody- mediated rejection', particularly if there is graft dysfunction

Table 4. Diagnostic categories Banff working grading schema[a/o] (Drachenberg et al., 2008).

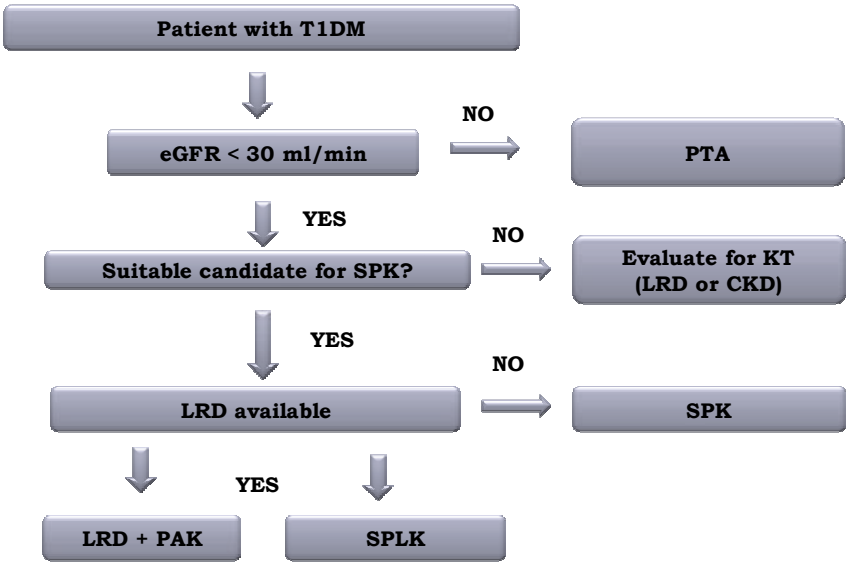
Diagnosis	Main histological findings	Clinical presentation
Posttransplant ischemic pancreatitis	Inflammation: neutrophils, foamy macrophages. Location: septal if mild or diffuse if severe Other features: fat necrosis, edema and interstitial hemorrhage. Patchy coagulation necrosis of clusters of acinar cells may be present. No fibrosis, the septa may be expanded due to edema/fat necrosis.	Increase in amylase and lipase in serum. Decrease in urinary amylase.* Hyperglycemia if there is extensive necrosis.
Peripancreatitis/peri - pancreatic fluid collection	Inflammation: mixed (lymphocytes, plasma cells, eosinophils, neutrophils). Location: septa and periphery of lobules Other features: dissecting bundles of active fibroblastic proliferation with obliteration of septal structures, relative preservation of the center of lobules ('cirrhotic appearance')	Local or systemic infectious symptoms, abdominal pain, peri-tonitis. Peripancreatic fluid accumulation.Increase in amylase and lipase in serum.
Cytomegalovirus pancreatitis	Inflammation: mostly mononuclear. Location: septal and acinar, patchy. Other features: cytomegalovirus cytopathic changes in acinar, endothelial or stromal cells.	Increase in serum amylase and lipase. Decrease in urinary amylase.* Systemic symptoms if generalized disease. Other: Duodenal cuff perforation.
Posttransplant lymphoproliferative disorder	Inflammation: ranging from polymorphic with lymphoblasts, plasma cells, eosinophils in low-grade disease, to monomorphic, predominantly lymphoid in high-grade disease (lymphoma). Other features: lymphoid proliferation is nodular, expansive. Necrosis may be present.	Asymptomatic, or increase in serum amylase and lipase. Lymphadenopathy. Tumor mass. May coexist with acute rejection.
Bacterial or fungal infection	Inflammation: variable; acute, chronic, purulent, necrotizing (abscess), granulomatous. Location: random. Other features: same as bacterial and fungal infections in other organs.	Systemic and/or localized infectious symptoms. Peritonitis, duodenal cuff perforation. Increase in serum amylase and lipase.
Recurrent autoimmune disease/diabetes mellitus	Inflammation: islet-centered lymphocytic inflammation (isletitis). No inflammation in late stages after disappearance of beta cells. Other features: immuno-histochemical stains for insulin and glucagon demonstrate absence of insulin producing beta cells in some or all islets depending if early or late disease.	Acute or chronic deterioration in glucose metabolism with increasing need for insulin. Although not pathognomonic, islet cell auto-antibodies typically present (i.e. GAD 65, IA-2, etc.).
Acute calcineurin inhibitor toxicity	Absence of inflammation. Variable degrees of islet cell injury (cytoplasmic swelling, vacuolization, islet cell drop-out. formation of empty spaces (lacunae), apoptotic fragments). Immuno-peroxidase stains: markedly diminished staining for insulin in comparison to controls and to glucagon stain. Electron microscopy: loss of insulin dense core granules with preservation of glucagon dense core granules.	Acute hyperglycemia. High levels of cyclosporine or tacrolimus with return to normoglycemia with adjustment of drug dose or discontinuation.

* In bladder-drained grafts.

Table 5. Pathological changes "other" than rejection in pancreas needle biopsies (Drachenberg et al., 2008).

Neuropathy: Initially after transplantation (SPK) neuropathy improves with correction of uraemia. Several studies reported improvement in motor and sensory nerve functions; confirmed by improved nerve conduction velocity. Less clear is the impact on autonomic function (arrhythmia, postural hypotension, diabetic diarrhoea, gastroparesis, neurogenic bladder, impotence, etc). Some data suggest that patients improve even with these symptoms but it is difficult to quantify (Nusser et al., 1991).
Cardio-vascular disease: Also, the positive impact of functioning pancreas graft on micro-vascular disease and cardiac function is well documented. This involve improvement in ventricular ejection function, reversal of diastolic function, and improved endothelial function.
Quality of Life: The main benefit of pancreas transplantation is the improved patients' quality of life. Sureshkumar, in his study (Sureshkumar et al., 2006), used three quality of life questionnaires (Diabetes Quality of Life Questionnaire, Medical Outcomes Questionnaire and Quality of Well-being Questionnaire) to compare outcomes of diabetics after SPK with patients on the Waiting List. He reports that SPK groups showed better diabetes-related quality of life.
Patient Survival: Results of SPK suggests that this group of patients do better over diabetics receiving cadaveric kidney transplants but there are no survival benefits compared to LRD recipients. The same study concludes that pancreas transplantation is not only life enhancing but also a life saving procedure (Reddy et al., 2003).

Algorithm of transplant alternatives in diabetics



T1DM – type-1 diabetes mellitus, KT – kidney transplant, LRD - living related donor, CKD – cadaver kidney donor

Fig. 15. Algorithm to choose the best transplant alternatives for diabetics.

11. Summary

The outcomes following pancreas transplantation have significantly improved in the last decade. Careful patient selection, better organ procurement, refinements in surgical technique, new immunosuppressive drug regiments and better graft monitoring have all contributed to excellent outcomes. The available data provides strong evidence that pancreas transplantation not only improves diabetics' quality of life but also improves their medical conditions and prolongs their life expectancy.

Pancreas transplantation has become the option of choice to treat patients with type-1 diabetes. Currently several alternatives for these patients are available. The best option should be selected after careful patient assessment and individually weight pros and cons of each alternative (Fig. 15).

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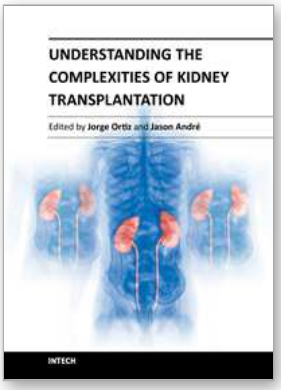

Understanding the Complexities of Kidney Transplantation
Edited by Prof. Jorge Ortiz

ISBN 978-953-307-819-9
Hard cover, 564 pages
Publisher InTech
Published online 06, September, 2011
Published in print edition September, 2011

Kidney transplantation is a complex field that incorporates several different specialties to manage the transplant patient. This book was created because of the importance of kidney transplantation. This volume focuses on the complexities of the transplant patient. In particular, there is a focus on the comorbidities and special considerations for a transplant patient and how they affect kidney transplant outcomes. Contributors to this book are from all over the world and are experts in their individual fields. They were all individually approached to add a chapter to this book and with their efforts this book was formed. Understanding the Complexities of Kidney Transplantation gives the reader an excellent foundation to build upon to truly understand kidney transplantation.

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