Current indications for pancreas or islet transplant

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Pancreas or islet transplantation can provide good glycaemic control and insulin independence. Pancreas transplantation has been associated with improvement in diabetic retinopathy, nephropathy, neuropathy and vasculopathy, but has the associated morbidity of major surgery. Both forms of therapy require long-term immunosuppression and its attendant risks and both achieve insulin independence rates of about 80% at 1 year. Pancreas transplantation at the same time as a renal transplant is a worthwhile option to employ, especially if the diabetes has been difficult to control. Diabetes associated with frequent severe hypoglycaemia or extreme lability, despite optimization of diabetes management, may benefit from either pancreas or islet transplant alone with the latter being the lower-risk procedure. More quantitative measures of hypoglycaemia and lability are now available to facilitate the assessment of the severity of these problems with glucose control. Diabetic patients with renal involvement (macroproteinuria, but no major elevation of creatinine) and unstable diabetes may be helped with an islet or pancreas transplant, but this approach should still be considered experimental and such a transplant may hasten the need for renal replacement therapy. In the setting of well-controlled diabetes and intact renal function, it is difficult to justify pancreas or islet transplant alone given the risks of immunosuppression.

Introduction

The American Diabetes Association's Clinical Practice Recommendations state that a pancreas transplant is an acceptable procedure in type 1 diabetic patients undergoing renal transplantation [1]. Furthermore, they suggest that a pancreas transplant alone can be considered in the setting of frequent, acute metabolic complications, incapacitating clinical or emotional problems with exogenous insulin or failure of insulin to handle acute complications [1]. Islet transplantation has recently entered the clinical arena [2] and is available in a few specialized centres. Establishing the indications for a pancreas or islet transplant requires an analysis of the benefit and risks associated with each and only then can

an appropriate balance be found. By virtue of the fact that pancreas transplantation has been performed for over 20 years, much more information is available for this field. It should be said at the outset that this is an area bereft of randomized, controlled, clinical trials – few patients who come seeking a transplant would consent to be randomized into a transplant vs. non-transplant programme, so most of the reports are case series. Common terminology used in the field includes simultaneous pancreas–kidney transplant (SPK), kidney transplant alone (KTA), pancreas after kidney transplant (PAK) and pancreas transplant alone (PTA). In this study, we consider the outcomes and risks of pancreas and islet transplantation, the evidence for benefit in terms

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of diabetic complications, and then in this light, evaluate the indications for pancreas or islet transplantation.

Patient Survival and Graft Function

The developments in immunosuppressive therapy over the years have allowed huge strides to be made in terms of transplantation success [3]. With the use of modern immunosuppression involving powerful induction and maintenance therapy, solitary pancreas or islet transplantation has become viable [2,4]. Venstrom *et al.* have provided a careful comparison of people on the waiting list for SPK, PAK or PTA vs. those who were transplanted [5]. In the first 3 months, an SPK increases the relative mortality risk (1.52 (CI = 1.28–1.8, p < 0.001), but by 1 and 4 years, the SPK has a clear advantage vs. remaining on the waitlist with an overall relative risk of death of 0.43 (CI = 0.39–0.48, p < 0.001). PTA or PAK people fare less well with the overall relative risk of death for PTA being 1.57 (CI = 0.98–2.53, p = 0.06) and for PAK 1.42 (CI = 1.03–1.94, p = 0.03) vs. those remaining on the waiting list [5]. Others have also shown that adding a pancreas transplant to a kidney transplant increased the relative mortality risk to 2.2 at 18 months for SPK vs. KTA (living related donor) [6]. On longer-term follow-up at 8 years, the patient survival rate was the same at 72% in the SPK and KTA (living related donor) people and better than the 55% for cadaver donor KTA [6]. Thus, there are demonstrable added risks associated with a pancreas transplant in the short term for SPK, but the long-term outcome is clearly better. Non-uremic patients may actually have a higher mortality, if they have a pancreas transplant. An islet transplant, as a safer procedure, may fill the niche for the patient with intact renal function in need of β-cell replacement therapy.

Pancreas graft survival at 1 year for SPK and PAK is 80% and for PTA is 88% [4]. Islet survival post-transplant as measured by the presence of detectable C-peptide was 40% at 1 year before 2000 [7] and is now 96% at 1 year and 80% at 2 and 3 years. Although both forms of transplant give stable glucose control, whole pancreas transplant may be more robust in terms of insulin secretion. Islet transplantation usually takes two procedures and has a 1-year 80% insulin independence rate and is associated with good glycaemic control. A further consideration for a pancreas transplant combined with kidney transplant is the fate of the transplanted kidney. For the PAK, the 1-year kidney graft survival was 100 vs. 82% for KTA, with the 4-year kidney survival rates being 93 and 69%, respectively [4].

Acute Risks

The increased mortality risk associated with pancreas transplantation, when added to a kidney transplant [6], reflects the complexity of the surgery and its attendant risks. The risks involved with pancreatic surgery include rejection, graft pancreatitis, peripancreatic abscess or intraabdominal infection, duodenal stump leak, CMV disease, venous or arterial thrombosis requiring graft pancreatectomy and conversion from bladder to enteric drainage [8,9]. An islet transplant is a much simpler procedure that involves percutaneous cannulation of the portal vein. However, there was an associated risk of bleeding (9%), peripheral portal vein thrombosis (4%), puncture of the gallbladder (3%), or increased liver function tests (50%) and abdominal pain [10].

Diabetic Complications

Retinopathy

As mentioned above, in the absence of randomized, controlled trials in the area, outcomes have usually been expressed in terms of a successful pancreas transplant vs. failed pancreas transplant. Thus, Königsrainer *et al.* reported that in patients with a successful SPK (HbA1c 6.2%), 82% had stabilization or improvement in their retinopathy vs. 54% of patients with a failed pancreas transplant (HbA1c 7.5%) [11]. Likewise, Koznarova *et al.* reported that 45% of patients with an unsuccessful pancreas transplant had worsening of their retinopathy vs. 17% if the transplant was successful [12]. Giannarelli *et al.* have reported some improvement in microaneurysms and haemorrhages at 6 months post-PTA [13]. In islet transplantation, four patients of 62 who had an islet transplant have had an acute retinal bleed similar to the 6.1% rate of vitreous haemorrhage reported by Chow *et al.* after a pancreas transplant [14]. Long-term outcomes after islet transplantations are not available.

Renal

The dramatic improvement in diabetic changes on renal biopsy as reported by Fioretto *et al.* [15] is a testimony to the benefits of euglycaemia on renal function. It is of note that it took 10 years for the resolution of the glomerulosclerosis. The euglycaemia attained after a pancreas transplant is clearly beneficial to renal function, as is evidenced by the better survival of the kidney graft in the presence of a pancreas transplant [4]. However, it is recognized that in non-renal transplants, the

immunosuppressive therapy can be nephrotoxic with 16.5% having chronic renal impairment [16]. Islet transplant recipients in our programme have reasonably preserved renal function, but in two patients with an elevated creatinine at the time of transplantation, there was substantial deterioration of the renal function [10]. Proteinuria has increased in 5 of 30 patients post-islet transplantation.

Vascular

Jukema *et al.* reported that there was regression of coronary artery atherosclerosis in 38% of successful pancreas transplants, but in none of the patients in whom the pancreas transplant had failed [17] with similar results reported by Larsen *et al.* [18]. With islet transplantation, the Milan group demonstrated a decrease of carotid intimal thickness ($-73 \pm 30\,\mu m$) over a 1- to 3-year period vs. progression ($+245 \pm 20\,\mu m$), if the islet transplant was not successful [19]. In the majority of islet transplant patients (64%), there was an increased need for either commencing or increasing statin therapy; in half of the patients, anti-hypertensive medications were either started or increased [10].

Neuropathy

The best documented changes in neuropathy post-transplant are from the studies of Navarro *et al.* where the motor nerve conduction index increased with patients who had a PTA, a pancreas–kidney transplant or a KTA [20]. However, in the long term, only the patients, who had a successful pancreas transplant, had the improvements in the neuropathy hold. Changes in autonomic function were favourable, but insignificant [20]. Symptoms have been reported to significantly improve after successful pancreas transplant [21]. No information is available for long-term neuropathy outcomes post-islet transplant.

Hypoglycaemia

The response to hypoglycaemia is frequently blunted in longstanding type 1 diabetes giving rise to the problem of hypoglycaemic unawareness. After pancreas transplantation, the glucagon response was restored [22,23]. Interestingly, the glucagon response after islet transplantation was not restored to normal [24], although the frequency of hypoglycaemia was greatly reduced [25], a testimony to the predominant role of insulin in glucose homeostasis. Once insulin supply is under physiological control and can be turned off in response to a low glucose level, the occurrence of hypoglycaemia is greatly diminished. With less hypoglycaemia, most patients after an islet transplant lose weight (pre-islet transplant 70.3 ± 2.3 vs. post-islet transplant $65.4 \pm 2.3\,kg$, $p \leq 0.001$), although the side effects of the immunosuppressive medications likely also contribute to the loss [10].

Infection

Immunosuppression carries with it an increased risk of infection that is evidenced by the 42-fold increased risk of infection post-renal transplant [26]. Fungal infections (often candidiasis and aspergillosis) are a particular risk and most typically present as esophagitis or pneumonia [27]. The risk of infection is far greater in solid organ transplant recipients where there is the risk of surgical site abscess, prolonged intensive care and hospital stays and central line use as typically required in pancreas–kidney transplantation. The typical 1- to 2-day hospital stay for an islet transplant mitigates these risks. The mean white cell count in the Edmonton patients post-islet transplant fell from 6.2 ± 0.3 to $4.9 \pm 0.3 \times 10^9$/l ($p = 0.002$) and some patients required granulocyte colony-stimulating factor [10]. Other complications that were seen were mouth ulcer (96%), diarrhoea (67%) and acne (36%). Mouth ulcer was usually treated with local hygiene; if persisting or more severe, triamcinolone acetonide ointment was used once it was felt that the ulcer was not herpetic. Diarrhoea was treated with diphenoxylate HCL, codeine or cholystramine for symptomatic relief, but both these problems usually abated with a decrease in sirolimus. Of note is the finding that the risk of CMV infection appears low after islet transplants, compared to other solid organs presumably related to the lack of passenger lymphocytes in the islet preparations [28].

Malignancy

The risk of malignancy is also increased with immunosuppression post-transplantation. There is a 10–15% risk of cancer over a 10-year period post-kidney transplantation [29]. The risk of skin cancer may be as high as 50% [30], especially if there is an increased sun exposure. Specific rates post-pancreas or islet transplant alone are not available, but there is no reason to expect them to differ markedly given the potent immunosuppression therapy used, although the use of sirolimus with possible anti-proliferative effects may mitigate this risk [31].

Quality of Life

The quality of life post-pancreas transplantation is improved [32]. In the setting of concomitant renal transplantation, it may be difficult to separate the benefit of correcting uraemia from improvement in glycaemic lability or problems with hypoglycaemia. Post-islet transplantation, the fear of hypoglycaemia, is eliminated [33]. For many patients with difficulties of glycaemic lability or frequent severe hypoglycaemia, the stabilization of glucose levels and the virtual elimination of hypoglycaemia after a successful islet transplant is a major boon [25].

We can, thus, summarize the situation as follows: a patient with type 1 diabetes in need of a kidney transplant who undergoes an SPK has an increased risk of death in the short term, but gains a clear long-term advantage. Thus, the American Diabetes Association arrived at the recommendation that a pancreas transplant is an acceptable alternative to standard insulin therapy for patients undergoing renal transplant [1]. The benefits of islet/pancreas transplant alone are stable glucose control and improved quality of life with pancreas transplant giving confirmed improvement in secondary diabetic complications. The risks are acute morbidity and the long-term risks of immunosuppression with the evidence showing a possible overall increased relative risk of death for PTA. Thus, a PTA should be considered, only if there are major concerns with glycaemic control not amenable to current therapy, while accepting that there are problems in quantifying such difficulties in glycaemic control. A final issue is the imbalance between supply and demand. In the US, there were 902 kidney–pancreas transplants performed in 2002 with a current waitlist of 2427. There were 141 PTA performed with a waitlist of 1569 (UNOS web site, accessed April 2004). Thus, it becomes evident that criteria are needed to judge the degree of difficulty in glucose control in order to assist the decision of who should have these scarce resources.

Indications

Lability

The major indications for an islet transplant alone are labile diabetes or severe recurrent hypoglycaemia. Brittle diabetes has been defined as erratic glucose values that follow no pattern and interfere with patient lifestyle. Previous definitions of lability used the mean amplitude of glycaemic excursion (MAGE), but the MAGE can give a high value, if there is a gradual decline

of glucose over the day even if the glucose values are not extremely erratic [34]. A more recent scoring system has been developed – the Lability Index (LI) – based on changes in glucose values over time that encompasses all glucose readings over a week-long period [25]. The score has been validated in a group of patients attending a general diabetes clinic and the median value in this group was $223 \, mM^2/h/week$, 25–75th interquartile range (130–329) and with a value of ≥ 433 (the 90th centile) indicative of severe lability. Thus, the typical patient in the diabetes clinic with glucose values ranging between 5 and 15 mmol/l will have an LI score of under $300 \, mM^2/h/week$, but the patient with daily chaotic glucose values, 2–25 mmol/l, will have a score over $500 \, mM^2/h/week$. The LI score showed a good correlation with the subjective measures of lability by two experienced diabetologists and confirmed the excellent response to correction of the problem with islet transplantation [25]. Other ways of looking at lability are with the continuous glucose monitoring (GCSM) [35] and evaluating the number of times that the standard deviation is exceeded, but this had the limitation that it is only for a limited 3-day period and concerns for accuracy at lower glucose values [36].

Hypoglycaemia

Severe hypoglycaemia is defined as episodes of hypoglycaemic reactions that require outside assistance for treatment. With the greater emphasis on achieving good glycaemic control, it has become more problematic with 4% of patients having a severe reaction in a year or a typical occurrence rate of about 1.4 per year [37–39]. For some patients, the frequent occurrence of unheralded episodes of hypoglycaemia, especially if asymptomatic, is very disruptive, making driving unsafe, working difficult and interfering with day-to-day quality of life. However, quantifying the severity of hypoglycaemia has been problematic with no measure describing it until recently. The HYPO score is a composite measure of the severity of the problem based on 4 weeks of records (frequency, lack of warning, autonomic symptoms) and a year-long historical review of the number of episodes of severe hypoglycaemia [25]. It provides a measure of the problem that allows a comparison between patients. The HYPO score in the general diabetes population median was 143, 25th to 75th interquartile range: 46–423 and the 90th centile was 1047. Thus, those diabetic patients with awful problems with hypoglycaemia, no warning and frequently needing outside assistance will have HYPO scores over 1000 and frequently over 2000, but the more usual patient with the occasional mild hypoglycaemic

episode will have a HYPO score under 150. Patients of post-islet transplant show a clear improvement in the HYPO score [25].

Other Issues

In addition to deciding on the lability of the diabetes or the severity of the problem with hypoglycaemia, there are other important issues that should be addressed. The presence of diabetic complications can have a negative impact on transplant outcomes. As mentioned above, there can be a temporary worsening of retinopathy that may be critical, if there is severe retinopathy to begin with and little leeway for change [14]. Cardiovascular disease is a common complication of anyone with long-standing type 1 diabetes and with pancreatic surgery being an invasive, perioperative cardiac ischaemia is a significant risk [40,41]. Specific cardiac work up for an islet transplant includes an MIBI scan and for patients over 30 years old or with one other significant risk factor in addition to the diabetes a coronary angiogram. Once any correctable lesion is dealt with and medical therapy is optimized, an islet transplant can still be performed even in the presence of known coronary disease given its less invasive nature. Aspirin therapy is discontinued before the islet transplant in order to lessen the risk of post-operative bleeding. Renal disease can be problematic in which the immunosuppressive therapy may be nephrotoxic [42]. Neuropathy can cause difficulties, particularly if there is GI autonomic involvement with gastroparesis present. Such a situation can lead to problems in maintaining adequate immunosuppressive drug levels, if persistent vomiting occurs.

Financial issues are also important. Transplantation involves expensive immunosuppressive drugs and frequent monitoring visits that place a burden in terms of finances and time on the patient. Psychosocial issues are also critical to address. Difficult diabetes can lead to psychological problems and psychological problems can lead to difficulties with diabetes. Resolving these issues is challenging and involves detailed assessments by nurse, dietician, social worker and physician and it needs a referral to psychologist or psychiatrist. If the patient is having a renal transplant, then the additional islet or pancreas transplant is seen as an add-on. However, in the setting of an islet or pancreas transplant alone, the patient is exchanging insulin therapy for immunosuppressive drugs. Given the potential toxic effect of these drugs, it is essential that the patient fully understand what is involved before the procedure is embarked upon and it reinforces the need for careful assessment pre-transplant that the problems are truly

severe enough to require a transplant. A further concern for both islet and pancreas transplants alone is that sensitization to donor antigens may occur creating difficulties for subsequent transplants.

Type-1 diabetes is associated with other autoimmune diseases that may exacerbate diabetes control and those, which may have an impact on glycaemic control, should be excluded pre-transplant, such as Addison's, thyroid or celiac disease. The other issue specific to islet transplantation is that the chance of insulin independence is increased with the increased number of islets per kilogram provided. Thus, recipients of $> 90\,kg$ or using $> 1.2\,U/kg$ (presumed insulin resistance) are generally excluded from routine islet transplant programmes. Such obesity, however, would increase the perioperative risks of a whole pancreas transplant and likely contribute to insulin resistance in the long term. Finally, if the indication for a transplant is lability or hypoglycaemia, it is a prerequisite that all reasonable avenues of good diabetes management have been exhausted, e.g. multiple daily insulin, insulin pump, nutrition counselling, carbohydrate counting and frequent monitoring. Optimization of these aspects of care should be confirmed before proceeding with an islet or pancreas transplant alone.

Given the scarcity of organs described above, some may feel a natural competition between whole pancreas and islet transplant programmes. Both programmes can co-exist, particularly because organs from donors under the age of 45 are best suited for whole organ transplant and pancreases from donors over 45 are best for islet isolation.

Conclusion

Given this information, who should have β-cell replacement therapy? If the glucose values are stable and renal function is normal, then an islet or pancreas transplant is not indicated. If there is an unrelenting progression of complications of diabetes, e.g. painful neuropathy, a transplant could be considered, but there is little evidence to support that it will clearly benefit the patient and it should be considered experimental.

If the patient has advanced renal disease and is undergoing a renal transplant, an SPK or PAK is reasonable especially if there are problems with lability or hypoglycaemia. If the centre has local expertise in preparing islets, then simultaneous islet kidney or islet after kidney transplants could be considered. If the patient has a kidney transplant and has stable diabetes, performing a pancreas transplant, in addition, increases the risk

of surgery and requires full discussion with the patient in regard to short- and long-term risks/benefits.

If the patient has labile diabetes ($LI \geq 433 \, mM^2/h/week$) or has major problems with hypoglycaemia (HYPO score ≥ 1047) and no renal disease, then an islet transplant is a reasonable option given its lower morbidity vs. a pancreas transplant alone. If the centre involved has more experience with a pancreas transplant, then a PTA can be considered.

The most challenging patients are those with unstable diabetes (lability or hypoglycaemia problems) and some renal dysfunction. If the renal dysfunction is limited to the presence of microalbuminuria, then islet transplantation is reasonable. If there is macroproteinuria present, the outcomes are less certain and a pancreas or islet transplant alone can be considered in the light of the possibility that the immunosuppressive drugs may hasten the decline of renal function. Further studies will help us elucidate the answers to these questions and allow appropriate therapy to be identified.

Acknowledgements

References

1 American Diabetes Association Pancreas Transplantation for patients with Type 1 diabetes. Diabetes Care 2004; **27** (Suppl. 1): S105.

2 Shapiro AMJ, Lakey JRT, Ryan EA *et al.* Islet transplantation in seven patients with Type 1 diabetes mellitus using a glucocorticoid-free immunosuppressive regimen. N Engl J Med 2000; **343**: 230–238.

3 Carpenter CB. Improving the success of organ transplantation. N Engl J Med 2000; **342**: 647–648.

4 Sutherland DER, Gruessner RW, Dunn DL *et al.* Lessons learned from more than 1,000 pancreas transplants at a single institution. Ann Surg 2001; **233**: 463–501.

5 Venstrom JM, McBride MA, Rother KI, Hirshberg B, Orchard TJ, Harlan DM. Survival after pancreas transplantation in patients with diabetes and preserved kidney function. JAMA 2003; **290**: 2817–2823.

6 Reddy KS, Stablein D, Taranto S *et al.* Long-term survival following simultaneous kidney-pancreas transplantation versus kidney transplantation alone in patients with type 1 diabetes mellitus and renal failure. Am J Kidney Dis 2003; **41**: 464–470.

7 Brendel MD, Hering BJ, Schulz AO, Bretzel RG. International islet transplant registry report 1999. 1–20. Justus-Liebig-University of Giessen.

8 Humar A, Kandaswamy R, Granger D, Gruessner RW, Gruessner AC, Sutherland DER. Decreased surgical risks of pancreas transplantation in the modern era. Ann Surg 2000; **231**: 269–275.

9 Becker BN, Odorico JS, Becker YT *et al.* Simultaneous pancreas-kidney and pancreas transplantation. J Am Soc Nephrol 2001; **12**: 2517–2527.

10 Ryan EA, Lakey JRT, Paty BW *et al.* Successful islet transplantation. Continued insulin reserve provides long-term glycemic control. Diabetes 2002; **51**: 2148–2157.

11 Königsrainer A, Miller K, Steurer W *et al.* Does pancreas transplantation influence the course of diabetic retinopathy? Diabetologia 1991; **34** (Suppl. 1): S86–S88.

12 Koznarova R, Saudek F, Sosna T *et al.* Beneficial effects of pancreas and kidney transplantation on advanced diabetic retinopathy. Cell Transplant 2000; **9**: 903–908.

13 Giannarelli R, Coppelli A, Sartini MS *et al.* Early improvement of unstable diabetic retinopathy after solitary pancreas transplantation. Diabetes Care 2002; **25**: 2358–2359.

14 Chow VCC, Pai RP, Chapman JR *et al.* Diabetic retinopathy after combined kidney-pancreas transplantation. Clin Transplant 2003; **13**: 356–362.

15 Fioretto P, Steffes MW, Sutherland DER, Goetz FC, Mauer M. Reversal of lesions of diabetic nephropathy after pancreas transplantation. N Engl J Med 1998; **339**: 69–75.

16 Ojo AO, Held PJ, Port FK *et al.* Chronic renal failure after transplantation of a nonrenal organ. N Engl J Med 2003; **349**: 931–940.

17 Jukema JW, Smets YFC, van der Pijl JW *et al.* Impact of simultaneous pancreas and kidney transplantation on progression of coronary atherosclerosis in patients with end-stage renal failure due to Type 1 diabetes. Diabetes Care 2002; **25**: 906–911.

18 Larsen JL, Ratanasuwan T, Burkman T *et al.* Carotid intima media thickness decreases after pancreas transplantation. Transplantation 2003; **73**: 936–940.

19 Fiorina P, Folli F, Bertuzzi F *et al.* Long-term beneficial effect of islet transplantation on diabetic macro-/microangiopathy in type 1 diabetic kidney-transplanted patients. Diabetes Care 2003; **26**: 1129–1136.

20 Navarro X, Sutherland DER, Kennedy WR. Long-term effects of pancreatic transplantation on diabetic neuropathy. Ann Neurol 2003; **42**: 727–736.

21 Müller-Felber W, Landgraf R, Scheuer R *et al.* Diabetic neuropathy 3 years after successful pancreas and kidney transplantation. Diabetes 1993; **42**: 1482–1486.

22 Diem P, Redmon JB, Abid M *et al.* Glucagon catecholamine and pancreatic polypeptide secretion in Type 1 diabetic recipients of pancreas allografts. J Clin Invest 1990; **86**: 2008–2013.

23 Paty BW, Lanz K, Kendall DM, Sutherland DE, Robertson RP. Restored hypoglycemic counterregulation is stable in successful pancreas transplant recipients for up to 19 years after transplantation. Transplantation 2001; **72**: 1103–1107.

24 Paty BW, Ryan EA, Shapiro AMJ, Lakey JRT, Robertson RP. Intrahepatic islet transplantation in type 1 diabetic patients does not restore hypoglycemic hormonal counterregulation or symptom recognition after insulin independence. Diabetes 2002; **51**: 3428–3434.

25 Ryan EA, Shandro T, Green K *et al.* Assessment of the severity of hypoglycemia and glycemic lability in Type 1 diabetic subjects undergoing islet transplantation. Diabetes 2004; **53**: 955–962.

26 Abbott KC, Oliver JD III, Hypolite I *et al.* Hospitalizations for bacterial septicemia after renal transplantation in the United States. Am J Nephrol 2001; **21**: 120–127.

27 Abbott KC, Hypolite I, Poropatich RK *et al.* Hospitalizations for fungal infections after renal transplantation in the United States. Transpl Infect Dis 2001; **3**: 203–211.

28 Eckhard M, Martin I, Eich T *et al.* Incidence of cytomegalovirus infections after immunosuppression induction in clinical islet transplantation and impact on graft function. Transplant Proc 2002; **34**: 1922–1924.

29 Lutz J, Heemann U. Tumours after kidney transplantation. Curr Opin Urol 2003; **13**: 105–109.

30 Euvrard S, Kanitakis J, Claudy A. Skin cancers after organ transplantation. N Engl J Med 2003; **348**: 1681–1691.

31 Mita MM, Mita A, Rowinsky EK. The molecular target of rapamycin (mTOR) as a therapeutic target against cancer. Cancer Biol Ther 2003; **4** (Suppl. 1): S169–S177.

32 Robertson RP, Davis C, Larsen J, Stratta R, Sutherland DER. Pancreas and islet transplantation for patients with diabetes. Diabetes Care 2000; **23**: 112–116.

33 Johnson JA, Kotovych M, Ryan EA, Shapiro AM. Reduced fear of hypoglycemia in successful islet transplantation. Diabetes Care 2004; **27**: 624–625.

34 Service FJ, Molnar GD, Rosevear JW, Ackerman E, Gatewood LC, Taylor WF. Mean amplitude of glycemic excursions, a measure of diabetic instability. Diabetes 1970; **19**: 644–655.

35 Kessler L, Passemard R, Oberholzer J *et al.* Reduction of blood glucose variability in Type 1 diabetic patients treated by pancreatic islet transplantation. Diabetes Care 2002; **25**: 2256–2262.

36 Diabetes Research in Children Network Study Group. Accuracy of the GlucoWatch G2 Biographer and the continuous glucose monitoring system during hypoglycemia: experience of Diabetes Research in Children Network. Diabetes Care 2004; **27**: 722–726.

37 Allen C, LeCaire T, Palta M, Daniels K, Meredith M, D'Alesso DJ. Risk factors for frequent and severe hypoglycemia in Type 1 diabetes. Diabetes Care 2001; **24**: 1878–1881.

38 Pramming S, Thorsteinsson B, Bendtson I, Binder C. Symptomatic hypoglycaemia in 411 Type 1 diabetic patients. Diabet Med 1991; **8**: 217–222.

39 ter Braak EWMT, Stolk RP, Appelman AMMF, van Haeften TW, van de Laak MF, Erkelens DW. Clinical characteristics of Type 1 diabetic patients with and without severe hypoglycemia. Diabetes Care 2000; **23**: 1467–1471.

40 Lin K, Stewart D, Cooper S, Davis CL. Pre-transplant cardiac testing for kidney-pancreas transplant candidates and association with cardiac outcomes. Clin Transplant 2001; **15**: 269–275.

41 Larsen J, Brekke M, Sandvik L, Arnesen H, Hanssen KF, Dahl-Jorgensen K. Silent coronary atheromatosis in type 1 diabetic patients and its relation to long-term glycemic control. Diabetes 2002; **51**: 2637–2641.

42 de Mattos AM, Olyaei AJ, Bennett WM. Nephrotoxicity of immunosuppressive drugs: long-term consequences and challenges for the future. Am J Kidney Dis 2000; **35**: 333–346.