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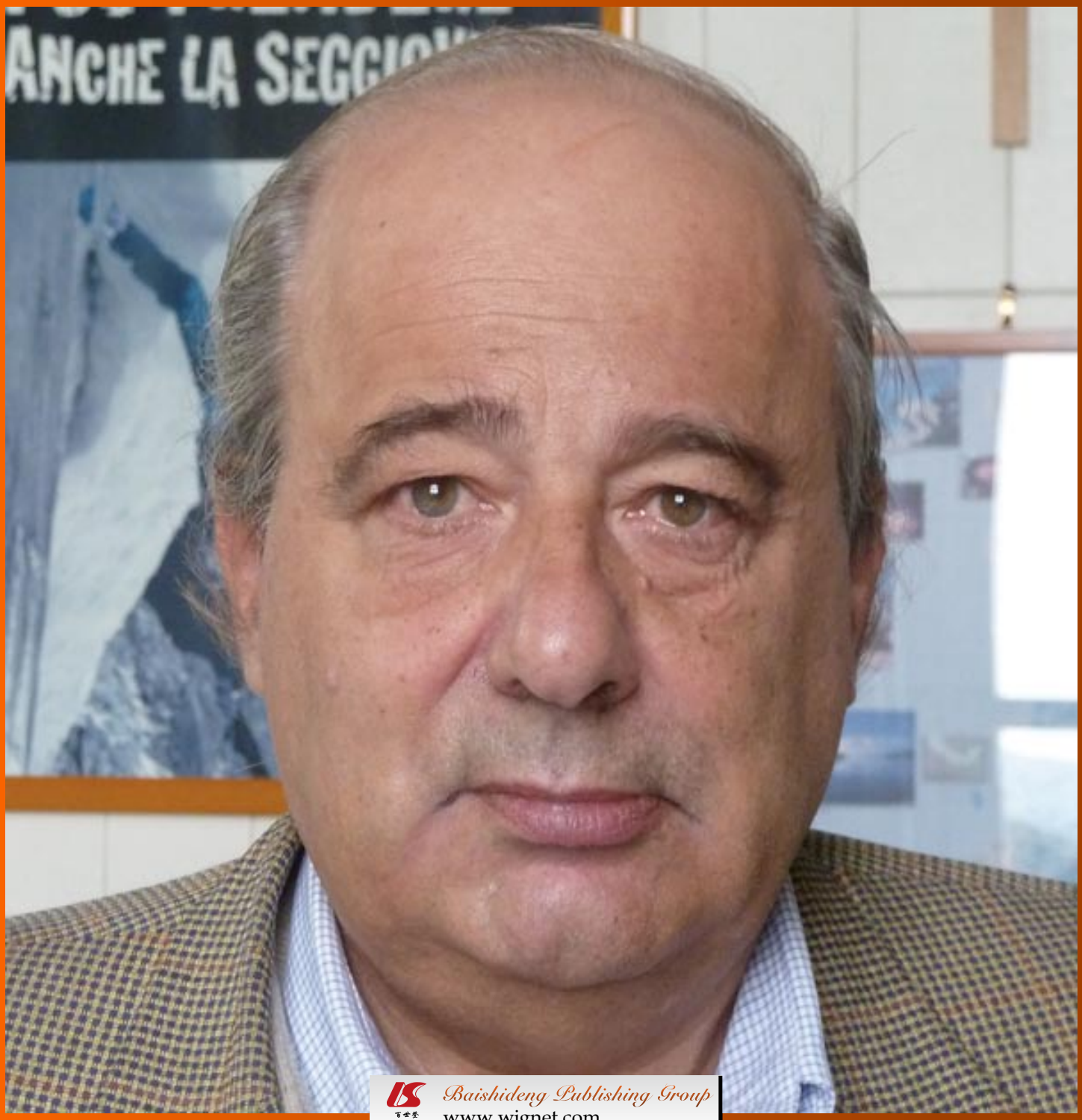

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2011-2015

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EDITORIAL

What is the purpose of launching the *World Journal of Transplantation*?

Maurizio Salvadori

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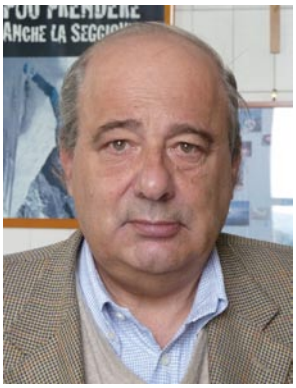

Figure 1 Editor-in-Chief of the *World Journal of Transplantation*. Maurizio Salvadori, MD, Professor of Nephrology, Department of Renal Transplantation, Careggi University Hospital, viale Pieraccini 18, 50139 Florence, Italy.

Abstract

Congratulations to the publisher, members of the editorial board of the journal, all the authors and readers for launching the *World Journal of Transplantation* (*WJT*) as a new member of the World series journal family. Transplantations are rapidly evolving and share knowledge with a number of basic and clinical sciences: molecular biology, stem cell investigators, immune system, pharmacology, biotechnology, surgery and physicians of different organs such as the kidneys, liver, heart, lung, bone marrow and so on. The *WJT* is a peer reviewed open access journal centered on the different fields involved in transplant activity. If you want to share your experiences and new findings in the field of transplantation with your peers you will find the *WJT* a good media to publish your papers.

Key words: Transplantation; Peer reviewed; Open access journal; Transplant related sciences

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Salvadori M. What is the purpose of launching the *World Journal of Transplantation*? *World J Transplant* 2011; 1(1): 1-3 Available from: URL: http://www.wjgnet.com/2220-3230/full/v1/i1/1.htm DOI: http://dx.doi.org/10.5500/wjt.v1.i1.1

INTRODUCTION

I am Maurizio Salvadori, Professor of Nephrology at the Careggi University Hospital of Florence, Italy (Figure 1) and the Editor-in-Chief of the *World Journal of Transplantation* (*World J Transplant*, *WJT*, online ISSN 2220-3230, DOI: 10.5500). It is a great privilege to introduce the *WJT* as a new forum for exchanging thoughts and experiences about the rapidly evolving field of transplantation both of solid organs and tissues. Congratulations to the publisher, members of editorial board of the journal, all the authors and readers.

I am very pleased to announce that the first issue of the *WJT*, whose preparatory work was initiated on Jaunary 16, 2011, will be officially published on December 24, 2011. The *WJT* Editorial board has now been established and consists of 100 distinguished experts from 29 countries. What is the purpose of launching the *WJT*?

Figure 2 Graveyard of recent immunosuppressive agents.

What is the scope and how are the columns designed?

Solid organ transplantation has made incredible breakthroughs in the last decades. After initial success in kidneys, liver, heart, lung and small intestine, more recently new complex grafts of hands and faces have been made successfully. Now outstanding papers and works are distributed over a wide range of topics that allow translating findings from the bench to affect patient care. From this point of view, an open access journal has the privilege to rapidly allow new findings to spread among investigators, improving knowledge sharing in a rapidly evolving field.

The main topics emerging in the more recent international meetings are (1) the relevance of donor-specific antibodies as cause of late allograft failure[1]; growing evidence of (2) novel mediators for late allograft failures as monocytes and natural killer cells[2,3]; (3) Novel pathways of allograft injury have been identified as LFA1/ICAM, an adhesion pathway in T cell activation[4,5]. As available organs are not enough with respect to the need, expanding the donor pool became essential; In this context (4) tissue engineering seems to be essential for the evolution of transplantation[6,7]; These strategies include (5) the recellurization of a decellularized organ to realize bioartificial organs; (6) Organ preservation is also improving and there is a general move towards new technologies in donation after cardiac death. A recent study suggests that the normothermic *ex vivo* lung perfusion can salvage lungs which would otherwise not be transplanted[8]; and (7) Discovery of new immunosuppressive agents is more and more difficult and expensive, also because many of these drugs fail before entering the market (Figure 2). At present, Belatacept, a CTLA4-Ig protein engineered with high affinity for CD86 and CD80 on antigen presenting cells, is one of the more promising molecules[9] with CP-690,550, an oral Janus associated kinase 3 inhibitor suppressing signaling from a number of cytokines[10].

SCOPE

The aim of the *WJT* is to rapidly report new theories, methods and techniques for prevention, diagnosis, treatment, rehabilitation and nursing in the field of transplantation. The *WJT* covers topics concerning organ and tissue donation and preservation; tissue injury, repair, inflammation and aging; immune recognition, regulation, effector mechanisms, and opportunities for induction of tolerance, thoracic transplantation (heart, lung), abdominal transplantation (kidney, liver, pancreas, islets), transplantation of tissues, cell therapy and islet transplantation, clinical transplantation, experimental transplantation, immunobiology and genomics, xenotransplantation, and transplantation-related traditional medicine, and integrated Chinese and Western medicine. The journal also publishes original articles and reviews that report the results of transplantation-related applied and basic research in fields such as immunology, physiopathology, cell biology, pharmacology, medical genetics, and pharmacology of Chinese herbs.

CONTENTS OF PEER REVIEW

In order to guarantee the quality of articles published in the journal, *WJT* usually invites three experts to comment on the submitted papers. The contents of peer review include: (1) whether the contents of the manuscript are of great importance and novelty; (2) whether the experiment is complete and described clearly; (3) whether the discussion and conclusion are justified; (4) whether the citations of references are necessary and reasonable; and (5) whether the presentation and use of tables and figures are correct and complete.

COLUMNS

The columns in the issues of *WJT* will include: (1) Editorial: to introduce and comment on the substantial advance and its importance in the fast-developing areas; (2) Frontier: to review the most representative achievements and comment on the current research status in the important fields and propose directions for the future research; (3) Topic Highlight: this column consists of three formats, including (A) 10 invited review articles on a hot topic, (B) a commentary on common issues of this hot topic, and (C) a commentary on the 10 individual articles; (4) Observation: to update the development of old and new questions, highlight unsolved problems, and provide strategies on how to solve the questions; (5) Guidelines for Clinical Practice: to provide guidelines for clinical diagnosis and treatment; (6) Review: to systematically review the most representative progress and unsolved problems in the major scientific disciplines, comment on the current research status and make suggestions on future work; (7) Original Articles: to originally report the innovative and valuable findings in transplantation; (8) Brief Articles: to briefly report novel and innovative findings in transplantation; (9) Case Report: to report a rare or typical case; (10) Letters to the Editor: to discuss and reply to the contributions published in the *WJT*, or to introduce and comment on a controversial issue of general interest; (11) Book Reviews: to introduce and comment on quality monographs of transplantation; and

(12) Guidelines: to introduce consensuses and guidelines reached by international and national academic authorities worldwide on the research in transplantation.

In conclusion, if you want to share your studies and findings rapidly with the aid of the format of an open access journal, you now have the possibility of using the *WJT*.

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GUIDELINES FOR CLINICAL PRACTICE

Transplant nephrectomy

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Abstract

About 10% of all renal allografts fail during the first year of transplantation and thereafter approximately 3%-5% yearly. Given that approximately 69400 renal transplants are performed worldwide annually, the number of patients returning to dialysis following allograft failure is increasing. A failed transplant kidney, whether maintained by low dose immunosuppression or not, elicits an inflammatory response and is associated with increased morbidity and mortality. The risk for transplant nephrectomy (TN) is increased in patients who experienced multiple acute rejections prior to graft failure, develop chronic graft intolerance, sepsis, vascular complications and early graft failure. TN for late graft failure is associated with greater morbidity and mortality, bleeding being the leading cause of morbidity and infection the main cause of mortality. TN appears to be beneficial for survival on dialysis but detrimental to the outcome of subsequent transplantation by virtue of increased level of antibodies to mismatched antigens, increased rate of primary non function and delayed graft function. Many of the studies are characterized by a retrospective and univariate analysis of small numbers of patients. The lack of randomization in many studies introduced a selection bias and conclusions drawn from such studies should be applied with caution. Pending a randomised controlled trial on the role of TN in the management of transplant failure patients, it is prudent to remove failed symptomatic allografts and all grafts failing within 3 mo of transplantation, monitor inflammatory markers in patients with retained failed allografts and remove the allograft in the event of a significant increase in levels.

Key words: Allograft intolerance syndrome; Hemorrhage; Immunosuppression; Infection; Panel reactive antibody; Patient survival; Subsequent graft survival

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INTRODUCTION

It is estimated that 7%-10% of all renal allografts fail during the first year of transplantation. Thereafter, approximately 3%-5% allografts fail yearly[1,2]. If the 69400 renal transplants performed worldwide in 2008[3] is an indication of annual transplant activity, then the number of patients returning to dialysis following failure of their renal allograft is increasing in absolute numbers year after year. A failed transplant kidney, whether maintained by low dose immunosuppression or not, elicits an inflammatory process characterized by hypoalbuminemia, erythropoietin (EPO) resistance, anemia, high ferritin and elevated C-reactive protein (CRP); and is associated with an increased incidence of infectious and cardiac complications, failure to thrive and increased morbidity and mortality[4-6]. The United States Renal Data System data suggest that overall annual adjusted death rates were > 3-fold higher

after graft loss as compared to before graft loss (9.42% *vs* 2.81%). Death after graft loss is strongly associated with infection, acute rejection or thrombosis related graft failure[7]. Low-dose immunosuppressive medication is often continued in patients returning to dialysis with a failed renal allograft *in situ* in order to reduce the risk of rejection but this is associated with increased mortality both from infectious and cardiovascular diseases[8]. However, continuation of immunosuppressive medication does not result in fewer rejections[8] and in another series that did not continue immunosuppressive therapy, increased rejection rates were not reported[9].

Following allograft failure, patients may be classified into the following categories: permanent dialysis/unsuitable for re-transplantation; bridge dialysis/waiting list for re-transplantation; and unsuitable for dialysis or re-transplantation. Current controversies relate to what to do with a failed allograft in patients on dialysis awaiting re-transplantation and the role of transplant nephrectomy (TN) in asymptomatic patients or dialysis patients unsuitable for renal transplantation[10]. In asymptomatic patients, the risk of surgical morbidity and mortality and a rising number of circulating antibodies associated with TN are among the arguments to support non intervention. On the other hand, chronic inflammation, the potential for malignancy, infection and the need for low-dose immunosuppression are concerns often addressed by performing a pre-emptive nephrectomy[11]. Other authors argue that TN should not be routinely performed but be reserved for those patients who develop symptoms related to the allograft or those who require space for re-transplantation[1,12]. About 20% of patients with established renal failure on the waiting list for renal transplantation in the US have had a TN[13]. The effect of TN on outcome of subsequent transplantation has been investigated by several authors[14-16] but it remains unclear whether removal of the failed allograft is beneficial or not. It is not well understood whether removal of the failed renal allograft affects patient survival while receiving long-term dialysis[13]. The aim of this review is to provide an update on current practice regarding TN with a view to proffering recommendations.

NEED FOR TRANSPLANT NEPHRECTOMY

Reasons for transplant nephrectomy

Urgent and non urgent reasons for TN may occur during the early or late phase of transplantation or transplant failure. Indications vary according to the time course after transplantation. The common indications for TN are shown in Table 1.

With the increasing use of kidneys derived from elderly donors, it is likely that there is a higher risk of developing neoplasms[20,21]. Malignant degeneration of a chronically rejected kidney allograft has been reported several years after the transplant[22]. Treatment options for renal cell carcinoma (RCC) in a renal allograft include radical nephrectomy and nephron-sparing surgery (NSS). The risk of local recurrence of an RCC in kidney allograft raises the need for continued surveillance after NSS[23]. With respect to post transplant lymphoproliferative disease involving the allograft, TN alone has superior patient survival over other measures without allograft removal[24].

Renal allograft rupture is a rare but potentially serious complication and may be associated with acute rejection[25], renal vein thrombosis or severe acute tubular necrosis in the absence of acute rejection. Frequently, nephrectomy is necessary but conservative surgical treatment could be attempted to preserve the allograft in selected cases[26]. In cases of later graft failure, the main indication for TN is graft related complications associated with chronic rejection in 58.2% of cases[18].

Risk factors for transplant nephrectomy

Prior rejection: In a study of 41 patients, Madore *et al*[27] used univariate analysis to show that allograft nephrectomy was significantly more frequent in patients with a history of two or more episodes of acute rejection than in patients with no rejection episode (83% *vs* 30%, $P = 0.03$) or if the immunosuppressive regimen included cyclosporine (62% *vs* 27.3%, $P = 0.04$). Following multivariate analysis of the same data, the number of previous episodes of rejection was found to be the only significant predictor for allograft nephrectomy. Patients with a history of numerous rejection episodes may either suffer continuing subclinical rejection or have an increased propensity to develop acute rejection when immunosuppression is reduced or stopped. They should thus be considered more likely to require allograft nephrectomy once immunosuppression is withdrawn. The introduction of an effective immunosuppressive agent in the early 1980s led to a reduction in the need for TN. Of the 280 recipients undergoing transplantation before 1984 (pre-cyclosporin era), 70 (25%) underwent TN, whereas only 61 (12.5%) of the 486 recipients in the cyclosporine period had TN ($P < 0.01$)[28].

Chronic graft intolerance: It is currently standard practice to leave failed kidney transplants in place upon return to HD and to treat symptomatic graft intolerance syndrome with immunosuppression. While this approach may reduce clinical symptoms in the short term, treatment failure necessitating TN occurs in the majority of cases. Medical treatment of graft intolerance syndrome has not been shown to reduce chronic inflammation or decrease mortality. Similarly, embolization of failed kidney transplants is associated with a high rate of treatment failure and has not been shown to reduce chronic inflammation[29]. Therefore, biochemical evidence of chronic inflammation increases the risk of TN prior to the development of clinical symptoms[30].

Sepsis: Dialysis patients are at risk for sepsis and the risk may be even higher among transplant failure patients because of previous or ongoing immunosuppression. Analysis of the incidence of sepsis among 5117 patients initiating dialysis after transplant failure between 1995 and 2004

Table 1 Indications for transplant nephrectomy

Type	Reason	Comments
Cause of failure	Renal vein thrombosis	Transplant pyonephrosis
	Renal artery occlusion	
	Acute rejection refractory to treatment[17]	
	Sepsis	
Allograft associated complications	Primary non function	Apart from tumors, these occur in the early phase after transplantation
	Bleeding post biopsy[17]	
	Transplant rupture[18]	
	Rupture of pseudoaneurysm	
	Malignant tumors[18]	
Following failure	Pain due to uncontrolled rejection[5]	
	Graft tenderness[14]	
	Anemia resistant to treatment	
	Recurrent urinary tract infection	
	Persistent hematuria	
	Sepsis	
Miscellaneous	Preliminary measure prior to re-transplantation[19]	For example, failed kidney-pancreas transplant awaiting combined re-transplantation
	Recurrence of primary disease	
	Polyoma virus nephropathy	

in the US showed the highest rates in the first 6 mo - 35.6 per 100 patient years (95% CI: 29.4-43.0) during 0-3 mo and 19.7 per 100 patient years (95% CI: 17.2-22.5) during 3-6 mo[31]. In comparison, the sepsis rate among incident dialysis patients between 3 and 6 mo after dialysis initiation was 7.8 per 100 patient years (95% CI: 7.3-8.3). Smak Gregoor *et al*[4] compared the morbidity and mortality due to infections between patients with retained failed allograft and those undergoing TN and reported more serious and life-threatening infections associated with those who have retained failed allografts on low-dose immunosuppression.

Vascular complications: Anastomotic pseudoaneurysm following renal transplantation is uncommon but may result in graft loss. TN was required in five of six patients who underwent surgical excision of a ruptured anastomotic pseudoaneurysm[32,33]. Dorffner *at al*[34] evaluated the outcome in seven patients in whom iatrogenic vascular complications of renal transplants were treated with catheter embolization using coils. Angiographic success with total occlusion of the vascular injury was achieved in five of the seven patients but in two cases nephrectomy was necessary because of renal artery occlusion or acute hemorrhage at the renal artery anastomosis, respectively.

Percutaneous embolization: Gonzalez-Satue *et al*[29] successfully managed 28 (85%) of 33 patients by percutaneous embolization without complications but the remaining five (15%) required TN. If it can be proved that percutaneous embolization does not make subsequent TN more hazardous, then it may become an attractive option in managing symptomatic failed allografts with the possibility of reducing the necessity for TN.

Probability of transplant nephrectomy

Allograft nephrectomy is not routinely performed at the time of graft failure when loss of graft function occurs more than 6 mo after transplantation. However, little is known about the characteristics that make patients more likely to require allograft nephrectomy. The probability of TN is highly dependent on the duration of allograft function prior to failure. There is no agreement on the definition of early allograft failure with various time points being used - < 2 mo[35], < 6 mo[36] and < 12 mo[10,17]. Early graft failures are far more likely to result in TN. The National Health Service Blood and Transplant (UK) statistics show that 41% of allografts failing during the first 3 mo after transplantation are removed compared to 23% during 3 to < 12 mo, 9% during 12 to < 24 mo and 4% after 2 years[37]. Zerouali *et al*[38] studied the outcome of 182 renal transplants who were managed according to a conservative treatment policy for allografts failing after 1 mo of transplantation. Of 63 failed allografts, 53 grafts (84%) were removed: 100% of the group failing during 0-1 mo, 86% 1-12 mo and 68% > 1 year. Further evidence is provided by a large observational study of the likelihood of TN among 19107 transplant failure patients between 1995 and 2003 in the US. Johnston *et al*[10] showed that among 3707 patients with early transplant failure (graft survival < 12 mo), nephrectomy was performed in 56% compared to 27% among 15400 patients with late transplant failure (graft survival ≥ 12 mo). Secin *et al*[18] found that the steepest rise in the Kaplan-Meier cumulative incidence curve was within the first 2 years after transplantation, reaching 11% (95% CI: 9-15). About half of all TN in their series were performed within 1 year of patients returning to dialysis.

The cumulative incidence of TN is 4.5%-84.4%[10,17,18,35,39-41]. Following a policy of removing early and late failed grafts only in symptomatic patients, 70 of 762 (9.2%) failed allografts were removed by Mazzucchi *et al*[35]. In a review of 631 renal transplants performed in 598 patients and 91 transplant nephrectomies in 85 patients in one institution from 1970 to 2000, Secin *et al*[18] reported the

Table 2 Techniques of transplant nephrectomy

	Extracapsular	Intracapsular
Description of technique[43]	Dissection outside kidney capsule to remove kidney including capsule, ureter and most of the transplant vessels	Dissection within kidney capsule which is densely ardent to surrounding tissues by the time of late graft removal
Mean procedure time[35]	125.3 min	109.4 min
Blood loss[35]	385 (60-1500) mL	638 (70-2200) mL
Blood transfusion[35]	6/17 (35.3%)	16/30 (53.3%)
Complication rate[35]	3/17 (17.6%)	6/30 (20%)
Comments	Suitable for early graft failures	Generally used for late graft failures

cumulative incidence of TN of 74% (95% CI: 49-90) at 10 years after return to dialysis[18]. The advent of cyclosporine significantly decreased the TN rate at the expense of fewer graft failures but not at the expense of a lower amount of graft related symptoms after patients returned to dialysis[18].

Hansen *et al*[42] retrospectively examined the courses of 34 graft failures leading to TN in 19 patients. Having diagnosed graft failure, the immunosuppressive treatment was continued for about 2-3 mo and then tapered slowly. They reported no deaths related to graft failure but in three cases, a delay in TN caused complications such as sepsis and coagulopathy. They concluded that continuing immunosuppression a few months after having diagnosed graft failure may postpone or avoid TN.

TECHNICAL CONSIDERATIONS

TN is performed using the extracapsular or intracapsular technique (Table 2)[35,43] *via* the same oblique incision in the iliac fossa as the original transplantation. In order to reduce the complication rates, Zomorrodi *et al*[44] described a debulking technique, leaving an intact ureter with intracapsular instillation of betadine. In their technique, the capsule of the allograft was exposed and incised from pole to pole for the renal parenchyma to be bluntly dissected free with an index finger. After TN, small doses of immunosuppressive drugs were continued for at least 2 mo. This surgical approach to allograft nephrectomy was applied in 25 patients between 1991 and 2006 with no significant complications. To avoid bleeding during and following TN, some have adopted a slight modification of the technique of renal extracapsular nephrectomy, performing three running sutures between the two sides of the renal capsule. Ghinolfi *et al*[45] used this technique in nine patients without any complications.

Among patients developing a renal tumor in the kidney allograft, TN reduced the quality of life due to the loss of renal function, prompting the search for alternate treatment options such as NSS, and local ablative procedures (like radiofrequency ablation or cryoablation) have been described[23]. An important issue is to find the balance between the preservation of transplant function on the one hand, which is dependent on the maintenance of an immunosuppressive regimen, and a sufficiently radical tumor therapy on the other hand[21,46].

In the case of TN due to anastomotic pseudoaneurysms, positioning a stent in the external iliac artery prior to the procedure avoids ligature of the iliac artery in the majority of cases[33]. In an attempt to decrease blood loss, Neschis *et al*[47] performed intraoperative pre-nephrectomy coil embolization of the transplant renal artery during 13 consecutive transplant nephrectomies and compared them with the 13 most recently performed consecutive transplant nephrectomies without coil embolization. They demonstrated a reduction in the estimated blood loss (465 mL *vs* 198 mL, $P = 0.035$) and shorter operating time in the embolization group.

Table 3 Complications of transplant nephrectomy

Complication	Comments
Hemorrhage	Commonest problem
Hematoma	
Infection: superficial deep	Extremely high in earlier series[39]
Lymphocele	
Pseudoaneurysm of iliac vessels	Treat by endovascular techniques
Urinary fistula	
Bowel injury	
Injury to obturator nerve or lateral cutaneous nerve of the thigh	Uncommon
Miscellaneous	

COMPLICATIONS

TN is considered to be a procedure with high morbidity (17%-60%) and mortality (1.5%-14%) rates due to immunosuppression, co-morbid conditions of patients and the technical difficulty of the procedure[11,18,35,38-40,44,48-50]. In the pre-cyclosporin era, TN was considered a risky intervention with a mortality ranging from 7.3%-38.7%[11,49,50]. Death was mainly due to septic complications. Since the more widespread use of cyclosporin and the lower doses of steroids, TN has become a safer procedure with almost no mortality and a low incidence of major morbidity[42,51].

Infection is the most frequent complication of TN followed by hemorrhage (Table 3). Early reports of TN after failed transplantation revealed a high incidence of wound infection and sepsis due to the effects of immunosuppression[52]. TN site sepsis or generalised sepsis was encountered in 56% of cases in an earlier report, where it was observed that sepsis often remained occult until subsequent transplantation and immunosuppression[53]. Without prophylactic antibiotics, wound infections after TN were common (20% with 81% due to staphylococcal or-

ganisms) such that wounds containing a pre-existing focus of infection or at a high risk for infection were left open for secondary healing[54]. The use of modern techniques of wound closure/management and more powerful antibiotics have improved the outlook for these patients.

Mazzucchi *et al*[35] reviewed the surgical complications of 70 consecutive patients who underwent TN between May 1994 and April 2002, noting that the mean blood loss, likelihood of blood transfusion and severity of complications were higher in patients undergoing TN for late allograft failure. The technique of TN also influenced the complication rates (Table 2).

The incidence of vascular complications following TN ranges from 0.9%-14%[17,55] and are associated with a significantly poor outcome. The presence of sepsis is a significant risk factor for vascular complications[56]. Nine patients (5.6%) sustained significant vascular complications with three deaths - two from overwhelming sepsis and one from an intra-cerebral hemorrhage. Immediate attempts to reconstruct the vascular supply to the lower limb are associated with a high morbidity rate. Where possible, vascular reconstruction should be deferred and the external iliac artery ligation can be performed safely with a low risk of limb ischemia[17]. Iliac pseudoaneurysm may also develop following TN[57-59]. Endovascular treatment with a covered stent is a safe and effective alternative to open surgery in the treatment of a symptomatic pseudoaneurysm arising from a TN site[60].

OUTCOME

One series reported the need for blood transfusion in 58.6% during TN but found a significant improvement in the hematological, biochemical and clinical parameters - EPO resistance index, serum albumin, prealbumin, ferritin, fibrinogen, CRP and erythrocyte sedimentation rate. Six months after allograft failure, those with TN had higher Hb and serum albumin levels, and lower CRP and EPO resistance index in comparison to incident hemodialysis patients. Parameters in those without TN showed no change during follow-up[5]. Another series demonstrated complete resolution of pain, fever and macroscopic hematuria in all patients and hypertension in 8 (36%) of 22 patients[38]. Wan *et al*[61] described an unusual case of refractory inflammatory ascites, along with cachexia, hypoalbuminemia and EPO resistance, associated with the chronic inflammatory state induced by a failed kidney transplant with no other identifiable cause of the ascites. The inflammatory ascites did not respond to antibiotic therapy but promptly resolved, along with the other manifestations of the chronic inflammatory state, after TN.

Whether the timing of TN after allograft failure has any significant effect on outcome is not fully known. Toledo-Pereyra *et al*[11] compared the morbidity, mortality and hospitalisation costs of 37 patients undergoing TN within 14 d after graft failure and return to dialysis, with 31 patients undergoing delayed TN (more than 14 d after graft failure and return to dialysis). Although there were no significant differences in patient morbidity and mortality between these groups, there was, however, a substantial increase ($P < 0.05$) in the cost of hospitalization in the delayed nephrectomy group[11]. It can be argued that a 14 d cut off is probably too short a period to make any meaningful difference.

TN reduces the risk of sepsis in patients returning to dialysis after transplant failure[31]. TN was not associated with septicemia but patients who were hospitalized for sepsis had an increased risk for death with a hazard ratio (HR) of 2.93 (95% CI: 2.64-3.24, $P < 0.001$). The risk of death following TN was dependent on whether it was performed for early (associated with an increased risk of death) or late (decreased risk of death) graft failure - HR were 1.13 (95% CI: 1.01-1.26) and 0.89 (95% CI: 0.83-0.95) respectively. Strategies to prevent sepsis during the transition from transplantation to dialysis may improve the survival of patients with allograft failure.

TN improves survival on dialysis. Ayus *et al*[40] identified all adults who received a kidney transplant and returned to long-term dialysis after renal allograft failure between January 1994 and December 2004 from the US Renal Data System. Among 10,951 transplant recipients who returned to long-term dialysis, 3451 (31.5%) received an allograft nephrectomy during follow-up. Overall, 34.6% of these patients died during follow-up. TN was associated with a 32% lower adjusted relative risk for all-cause mortality (adjusted HR 0.68, 95% CI: 0.63-0.74) after adjustment for sociodemographical characteristics, comorbidity burden, donor characteristics, interim clinical conditions associated with TN and propensity to receive TN. Study of this large, nationally representative sample of high-risk patients returning to long-term dialysis after failed kidney transplant revealed that TN was independently associated with improved survival[40]. However, the group that underwent TN was composed of younger individuals who were less likely to have diabetes and/or cardiovascular disease, more likely to be black, to have required the use of T cell-depleting antibodies and to have experienced anemia, sepsis and urinary tract infections. Despite these complications, the rate of death within 30 d of the TN was only 1.5% (53 deaths of 3451 patients). In their series, those undergoing TN were more likely (10% *vs* 4.1%, $P < 0.001$) to receive a second transplant when compared with those who did not undergo a nephrectomy[40]. However, Perl *et al*[13] were unable to demonstrate whether immunosuppression reduction or TN affected survival.

EFFECT OF TN ON SUBSEQUENT TRANSPLANTATION

TN increases the likelihood of developing antibodies to mismatched human leukocyte antigens (HLA), partly due to the absence of immunosuppression and the removal of the organ that adsorbs the antibodies. Rosenberg *et al*[62] found that 30% (10/34) of their patients had antibodies to all of the mismatched HLA, 43% had antibodies to

Table 4 Effect of transplant nephrectomy on subsequent transplant function

Study	TN	No	PRA (%) > 30%	HLA (mm)	Delayed graft function (%)	Acute rejection (%)	Graft survival (%)		Comments
							1 yr	5 yr	
Sumrani	Yes	35	57		63				AR rates similar between groups
et al[14], 1992	No	52	33		30				
Yagmurdur	Yes	21		1.9 ± 1.1		43	83	45	Retrospective
et al[16], 2005	No	32		1.0 ± 0.6		38	69	68	TN has no advantage
Johnston	Yes	6213	14.7	64.8%[1]	33.6				USRDS 1995-2003
et al[10], 2007	No	12894	12.6	53.4%[1]	24.4				Early TN associated with lower risk of transplant failure
Ahmad	Yes	68	37[2]			49.1	83.8	66.2	PRA level significantly influences graft
et al[15], 2009	No	21	29[2]			31.2	94.7	69.5	survival independent of TN
Schleicher	Yes	121	16	2.2 ± 1.5	29.3	29.7			Retrospective study
et al[19], 2011	No	45	2	2.0 ± 1.7	20	13.3			Graft survival worse in TN group

[1]4-6 mismatches; [2]Proportion of positive patients.

some and 27% did not develop antibodies to any of the mismatched antigens. Sixty percent of the patients who developed antibodies to all of the mismatched HLA had had a TN. In an earlier study by Adeyi *et al*[63], sera from 27 patients with HLA-mismatched kidney transplants that had been removed following rejection were screened for HLA-specific antibodies by direct complement-dependent lymphocytotoxicity with HLA-typed cell panels. Circulating donor-specific antibodies were detected in 3 cases (11%) before and in 26 cases (97%) after allograft nephrectomy. These findings demonstrate the production of donor-specific antibodies in patients with rejected transplants but, in most cases, they were undetectable before nephrectomy because the graft had adsorbed them. This has important implications with respect to utilising "unacceptable antigens" in an allocation system for patients awaiting a second transplant who have had a TN[62].

Sumrani *et al*[14] studied 95 consecutive cyclosporin treated re-transplant patients - 52 without primary allograft nephrectomy, 35 with TN prior to re-transplantation due to symptoms and 8 had TN at the time of re-transplantation. Nephrectomy of the primary allograft prior to re-transplantation was associated with a significant subsequent rise in preformed cytotoxic antibody levels, a significantly higher incidence of delayed graft function among re-transplants and a trend toward decreased allograft survival in the subgroup who lost their primary allografts in the first year post transplant. The incidence of acute rejection and 3-year post transplant renal function in re-transplants were not, however, influenced by nephrectomy of the primary allograft. The effect of TN on subsequent renal transplant function is shown in Table 4[10,14-16,19].

Abouljoud *et al*[36] studied 192 patients receiving a primary and a subsequent kidney transplant between 1980 and 1992, reporting that patients having primary TN had a worse second allograft outcome than patients who kept their failed grafts ($P = 0.0003$). They demonstrated a significant relationship between primary allograft survival and re-transplant outcome which persisted even after excluding patients whose first graft failed within 6 mo of transplantation. Multivariate analysis identified primary allograft nephrectomy, older donor age, longer interval from nephrectomy to re-transplant and lack of antibody induction as negative risk factors[36]. In another retrospective comparison of outcomes in 121 patients who underwent TN prior to re-transplantation with 45 who did not, Schleicher *et al*[19] showed TN led to increased panel reactive antibody (PRA) levels prior to re-transplantation, increased rates of primary non function (PNF, $P = 0.05$) and acute rejection ($P = 0.04$). Overall graft survival after re-transplantation was significantly worse in those who had preliminary TN compared with those who had not ($P = 0.03$). On the multivariate analysis, pre transplant graft nephrectomy and PRA > 70% were independent and significant risk factors associated with graft loss after kidney re-transplantation[19]. However, Ahmad *et al*[15] undertook a retrospective analytical study of 89 patients with kidney re-transplants to determine the effect of removal of a failed kidney allograft on the outcome of subsequent transplant and came to a different conclusion. They reported no significant difference in the two groups (68 had a TN while 21 had retained failed grafts) in the PRA level at the time of re-transplantation. Multivariate analysis showed that PRA level significantly influenced graft survival independent of nephrectomy ($P = 0.04$) and concluded that nephrectomy of a failed allograft does not seem to significantly influence the survival of a subsequent graft.

LIMITATIONS OF STUDIES

No randomised controlled trials of the role of TN were encountered during the literature search for this article. The series reported by Ayus *et al*[40], one of the largest nationally representative sample in recent times, is also subject to important limitations. As pointed out by Rubin *et al*[64], if the need for TN was triggered by an immune event (for example, humoral rejection), then the procedure may just be a marker of high immune responsiveness and an indication of an adverse outcome with repeated transplantation (selection bias). The study design (obser-

vational analysis of administrative data) did not permit a random selection of allograft nephrectomy and represented a potential source of bias, not completely removed by the adjustments such as sensitivity analyses and propensity scores applied by the authors.

Many of the studies were characterized by a retrospective and univariate analysis of small numbers of patients[36,65]. Given the patient population undergoing TN, it is arguable that the reason for the decreased mortality in the group of patients undergoing nephrectomy was that they were a younger, healthier population as compared with those with retained transplants, who may have been considered too high risk to undergo a surgical procedure[40]. The lack of randomization in many studies introduces a selection bias and conclusions drawn from such articles must be applied with caution.

In a retrospective review of 345 patients with failed kidney transplants, 79% of patients ultimately required nephrectomy primarily for clinical symptoms. The finding of significant inflammation on histological examination of the TN specimens in the vast majority of cases does not mean that asymptomatic patients with failed allografts would have similar histopathological features[12].

Studies of the effect of pre-transplant allograft nephrectomy may be comparing patients of different backgrounds. The interval between transplant failure, or TN where applicable, and re-transplantation was not stated in many of the reports. Most patients undergoing TN lost their grafts during the earlier phase post transplantation (< 2 years) and may be predisposed to higher immunogenicity and may also have spent a longer period on dialysis prior to re-transplantation[16,19].

CONCLUSION

A growing number of patients are returning to dialysis after a failed transplant and it is vital to optimize their treatment and to consider the potential role of TN in this subset that have a high risk of morbidity and mortality. TN appears to be beneficial for survival on dialysis but detrimental to the outcome of subsequent transplantation. In case of early graft failure, early nephrectomy and complete interruption of immunosuppressive therapy is recommended. When graft failure occurs later, the graft can be left in place, while immunosuppressive therapy is tapered and eventually stopped. Patients must be followed carefully as, in at least one third of the patients, side-effects will occur necessitating subsequent TN.

The role of nephrectomy in the management of dialysis treated transplant failure patients and the implications of nephrectomy for repeat transplantation should be further studied in prospective studies. Such a study is likely to clarify the indications for TN. In addition to testing various immunosuppression attrition rates, it may be possible to discern a protocol that minimizes drug exposure while leading to reduced nephrectomy rates after returning to dialysis. Pending such a randomised controlled trial, it is prudent to remove failed symptomatic allografts and all grafts failing within 3 mo of transplantation, monitor inflammatory markers in patients with retained failed allografts and remove in the event of a significant change in levels. It is important to select an appropriate technique of TN to minimise blood loss and other complications.

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REVIEW

Recent progress in pancreatic islet transplantation

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Abstract

Diabetes mellitus remains a major burden. More than 200 million people are affected worldwide, which represents 6% of the world's population. Type 1 diabetes mellitus is an autoimmune disease, which induces the permanent destruction of the β-cells of the pancreatic islets of Langerhans. Although intensive insulin therapy has proven effective to delay and sometimes prevent the progression of complications such as nephropathy, neuropathy or retinopathy, it is difficult to achieve and maintain long term in most subjects. The successes achieved over the last few decades by the transplantation of whole pancreas and isolated islets suggest that diabetes can be cured by the replenishment of deficient β cells. However, islet transplantation efforts have various limitations, including the limited supply of donor pancreata, the paucity of experienced islet isolation teams, side effects of immunosuppressants and poor long term results. The purpose of this article is to review the recent progress in clinical islet transplantation for the treatment of diabetes and to describe the recent progress on pancreatic stem/progenitor cell research, which has opened up several possibilities for the development of new treatments for diabetes.

Key words: Type 1 diabetes; Pancreatic islet transplantation; Islet isolation; Pancreatic β-cells; Islet regeneration

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INTRODUCTION

Type 1 diabetes results from a cell-mediated autoimmune attack against insulin-producing β cells in the islets of Langerhans of the pancreas. At the time of clinical diagnosis, over 70% of the β cell mass has typically been destroyed. For patients with type 1 diabetes, exogenous insulin injection to control blood glucose is a lifesaving treatment, but it also has a negative impact on personal and social functioning, not least because of the daily risk of hypoglycemic episodes. In addition, normoglycemia cannot be achieved by exogenous insulin and secondary complications such as retinopathy, neuropathy, nephropathy and cardiovascular disease occur despite good glycemic control. Intensive insulin therapy can help prevent long term diabetic complications and the introduction of insulin pumps into clinical practice has raised the possibility of mimicking the basic endogenous insulin secretion pattern, which directly relates to better glycemic control[1-3]. For insulin-dependent diabetes, controlling the blood glucose level is sometimes difficult, even with intensive insulin therapy. Pancreatic islet transplantation has recently emerged as one of the most promising therapeutic approaches for improving glycometabolic control in type 1 diabetic patients. Although the first human islet allograft transplant was performed in 1974[4], clinical success rates were low until 2000[5]. At that time, dramatic improvement was achieved with the Edmonton

Protocol[6] (Table 1).

The "Edmonton Protocol" introduced several modifications to the transplantation procedure, such as the use of a steroid-free immunosuppression regimen and transplantation of a mean islet mass of 11 000 islet equivalents per kilogram of the patient's weight[6]. The Edmonton breakthrough produced sudden changes: approximately 35 centers began to perform islet isolations and the annual numbers of procedures increased to more than 100 transplants a year, the insulin-free status changed to about 85%, or approximately 60%-70% if all centers were counted[7]. However, islet transplantation efforts have limitations, including the limited supply of donor pancreata, the paucity of experienced islet isolation teams, the side effects of immunosuppressants and poor long term results[8]. Further improvements are necessary to make islet transplantation a routine and effective clinical treatment. This review describes the recent progress in clinical islet transplantation for the treatment of diabetes.

PANCREAS PROCUREMENT AND PRESERVATION

The procedure used for pancreas procurement has remained relatively unchanged since the first transplant and is often performed as part of a multi-organ procurement of the pancreas, liver and kidney[9]. Pancreata are procured using a standardized technique for whole pancreas transplantation to minimize warm ischemia. University of Wisconsin (UW) solution is used for *in situ* perfusion of the donor[10,11].

We recently reported the ductal injection of 1 mL/g pancreas weight of preservation solution before pancreas storage to improve islet yields[12,13]. Since UW solution has several disadvantages for islet isolation, including the inhibition of Liberase activity, we used a new preservation solution [modified Kyoto (MK) solution][14,15]. Compared with the UW solution, the MK solution exerted lower inhibition of collagenase digestion. Moreover, the MK solution significantly inhibited trypsin activity in the digestion step because the solution contains ulinastatin[16]. Ductal injection of the MK solution increased the ATP level in the pancreas tissue, reduced trypsin activity during the digestion step and prevented islet apoptosis[12]. This suggests that the ductal injection of the MK solution leads to improved outcomes for pancreatic islet transplantation.

The two-layer preservation method (TLM), which uses the concept of normobaric oxygenation comprising a cold organ preservation solution (UW solution) with a perfluorochemical (PFC) oxygen carrier solution, with the pancreas being suspended between the two immiscible layers, has been utilized for many clinical trials of islet transplantation[17-20]. However, two recent large-scale studies showed no beneficial effect of TLM, compared with UW storage, on human islet isolation and transplantation[21,22]. We reevaluated the effect of TLM using three different groups: group 1: UW simple storage; group 2: TLM performed by multiorgan procurement teams (not specialists in islet isolation); and group 3: TLM performed by specialists in islet isolation. There were no significant differences between groups 1 and 2 whereas islet yields were significantly higher for group 3 compared with either group 1 or 2. Our data suggest that performance of TLM by experts could improve the outcome of islet isolation and transplantation[17]. Interestingly, one of the groups which reported the lack of beneficial effects of TLM found that the PFC-based one-layer method improved islet yield[23] and the isolation index (fragmentation rate of islets, which is calculated as the ratio between islet equivalents and islet number), compared with TLM[24]. Their data clearly suggest the beneficial effects of pancreas oxygenation by PFC.

ISLET DIGESTION

Human islet isolation is conducted using the standard Ricordi technique with modifications introduced in the Edmonton protocol. The introduction of the semi-automated method for controlled pancreatic digestion using a dissociation chamber (Ricordi Chamber) has dramatically increased islet yields from human pancreata[25] and the general principles of this method still form the basis of current islet isolation technology[26-29]. The factors that influence the process include digestion time, digestion temperature, collagenase concentration and the route of administration of collagenase, which vary widely among protocols. Tissue dissociation enzymes are critical reagents that affect the yield and quality of human pancreatic islets required for islet transplantation. After the discontinuation of the manufacturing Liberase HI because of a small potential for prion disease transmission, the Serva NB-1 enzyme has been commonly used for human islet isolations. Recently, a new enzyme, Liberase mammalian tissue free (MTF) was developed, which is similar to Liberase HI with the exception that no mammalian tissue is used in the manufacture of the collagenase component. One group reported a comparison of the MTF enzyme with Serva NB-1 in clinical islet isolations[30]. The average islet mass after purification was similar between the two groups and there were no significant differences in the isolation success rates (> 400 000 IE) between the two groups, suggesting that MTF may be successfully used for high-yield human islet isolation and clinical transplantation and provides similar quality islets to those derived using NB-1.

ISLET PURIFICATION

Purification of islets from exocrine tissue is a critical step for maintaining high islet yields. Large-scale continuous purification using the COBE2991 cell processor, with Ficoll solutions, is the current gold standard method[27-32]. Two solutions with fixed density (low density; approximately 1.077 g/cm^3, high density; approximately 1.100 g/cm^3) are commonly used for the purification. However, the density of islets/acinar tissue depends on several condi-

Table 1 Criteria for clinical islet transplantation in Japan

Inclusion criteria
< 75 yr of age
Undetectable C-peptide levels (< 0.1 ng/mL)
Duration of type 1 diabetes mellitus for > 5 yr accompanied by recurrent neuroglycopenia
Reduced awareness of hypoglycemic episodes and/or severe glycemic lability despite intensive insulin therapy and glycemic monitoring
Exclusion criteria
Presence of uncorrectable coronary disease
A body mass index of > 25 kg/m^2
Inadequate renal reserve defined as serum creatinine level of > 1.5 mg/dL, creatinine clearance of < 80 mL/min per 1.73 m^2 of body surface area, or a urinary albumin level of > 300 mg/24 h
Negative serological findings for Epstein-Barr virus at the time of assessment

tions, such as warm ischemic time, cold ischemic time, pre-incubation time before purification and osmolality of both the pre-incubation solution and purification solution. The percentage of islets recovered from a standard Ficoll purification has been reported to range from 55%-65%[33,34]. We recently showed the effectiveness of controlled-density gradients using iodixanol[35]. According to the outcome of the density determination step, the density of the purification solutions was controlled (low density, 1.075 g/cm^3; high density, 1.085-1.110 g/cm^3) by changing the volumetric ratio of iodixanol and the purification solutions. The islet yield after purification and the post-purification recovery rate was significantly higher when the controlled density gradient purification method was used than when using the standard continuous gradient purification by Ficoll solutions. The percentage of islets recovered from the controlled-density solution was approximately 80%[35]. Another group also showed the effectiveness of controlled-density gradients using a continuous gradient for the density determination step[36].

Although a controlled-density gradient improves the islet recovery rate in human islet isolation, 20% of islets were still lost during the purification. Ichii *et al*[37] reported that an additional gradient purification method following regular purification could be of assistance in maximizing the number of islet preparations successfully used for transplantation. We also evaluated a combined continuous density/osmolality gradient for supplemental purification of human islets[38]. Low-density/osmolality (1.075-1.110 g/cm^3/400-410 mOsm/kg) and high-density/osmolality (1.090-1.125 g/cm^3/495-505 mOsm/kg) solutions were produced by changing the volumetric ratio of iodixanol, 10 × HBSS, and RP solutions. The addition of supplemental purification could contribute approximately 8% to islet recovery, with viability and potency comparable to that obtained by regular purification. These supplemental purifications following regular purification could maximize the islet yield and improve clinical islet transplantation.

ISLET CULTURE/PRESERVATION

Recently, many centers have introduced the culturing of human islets prior to transplantation[39-43] because it provides many benefits to clinical islet transplantation. *In vitro* culture may reduce islet immunogenicity by depletion of viable hematogenous and lymphoid cells[44] and reduce exocrine contamination of transplanted tissue. Culturing islets may also help them recover from the insult of collagenase digestion. Other benefits are additional quality control testing of isolated islets, initiating time-dependent immunosuppressive protocols, and culture also preserves the islets during travel time for recipients living far away from transplant centers. However, we and other groups have shown that freshly isolated islets are superior to cultured islets for islet transplantation[45-49]. We also reported that the clinical outcome in patients who received cultured islets was significantly lower than in patients who received fresh islets, although the number of subjects evaluated was not sufficient to draw definitive conclusions[50]. It is well documented that isolated islets deteriorate rapidly in culture[41,42,50,51]. Since barely half of the processed pancreata meet the criteria for clinical transplantation in most centers, islet loss during culture results in an even lower transplant rate.

We evaluated the optimal temperature for the culture/preservation of isolated human islets before transplantation. Isolated islets were cultured or preserved for 48 h in the following culture/preservation conditions: preservation at 4℃ in UW solution, and culture at 22℃ or 37℃ in culture medium. The 4℃ preservation of isolated islets prevents deterioration of islet equivalents (24% loss in 37℃ culture and 19% loss in 22℃ culture, but less than 5% loss in 4℃ preservation) and improves the outcome of islet transplantation, thus suggesting that 4℃ preservation is superior to 22℃ or 37℃ culture before human islet transplantation[52].

ISLET TRANSPLANTATION

The implantation site for human islet transplantation has not changed over the years. In more than 90% of cases, the portal vein is cannulated either as part of an operation or as an invasive radiology procedure. The Edmonton group has reported complications of bleeding (8%), portal venous thrombosis (3%) and bile leakage (1%) due to the implantation procedure[7]. Heparin has been added to the process in order to reduce clotting, termed the instant blood mediated inflammatory reaction[53,54]. Moreover, the use of heparin or anti-coagulative agents for several days following islet transplantation, together with intensive

insulin treatment for the first few weeks after transplantation, have recently been reported as critically important variables which improve the efficiency of initial islet engraftment.

IMMUNOSUPPRESSION

A steroid-free immunosuppressive protocol with a combination of sirolimus and tacrolimus, which the Edmonton group reported, has been utilized in many clinical islet transplant trials. However, even with this relatively safe immunosuppressive therapy, the islet graft function deteriorates within 5 years in 50%-80% of patients. Some immunosuppressive agents also have significant and harmful side effects for the transplanted islets[55].

It is currently difficult to sensitively monitor islet rejection, and improvements in such monitoring are mandatory. For example, Close *et al*[56] reported that polyclonal antibody induction may offer better results than daclizumab, according to registry data. Bellin *et al*[57] recently showed improved success with a modified immunosuppressive protocol and use of antithymocyte globulin plus etanercept as induction therapy. These results suggest that modifications of the immunosuppressive protocol are key to improving long term graft survival.

NEW SOURCES OF INSULIN-PRODUCING CELLS

The results obtained through human pancreatic islet transplantation have spurred the search for new sources of insulin-producing cells. Regeneration of β cells from stem and progenitor cells is an attractive method to restore the islet cell mass. Pancreatic stem/progenitor cells have been identified and the formation of new β cells from pancreatic duct, acinar and liver cells is an active area of investigation[58-62]. Embryonic stem (ES) cells and induced pluripotent stem (iPS) cells are also alternative sources for the treatment of diabetes[63,64]. D'Amour *et al*[65] recently developed a five-step protocol for differentiation of human ES cells to endocrine cells capable of synthesizing the pancreatic hormones insulin, glucagon, somatostatin, pancreatic polypeptide and ghrelin. Protocols for the *in vitro* differentiation of ES cells based on normal developmental processes have generated β-like cells that produce high levels of insulin, although at low efficiency and without full responsiveness to extracellular levels of glucose.

On the other hand, a significant number of problems remain unsolved in terms of the clinical application of these strategies, such as the ethical issues and need for immunosuppression after transplantation. The technical breakthrough of iPS cells has significant implications for overcoming the ethical issues associated with ES cell derivation from embryos. iPS cells can also yield insulin-producing cells following similar approaches. Although two papers showed the generation of insulin-secreting islet-like clusters from human iPS cells[66,67], the efficiency of the method for generating these insulin-producing cells seems low. However, the method used for ES cells may represent a critical step in the development of insulin-producing cells from iPS cells.

CONCLUSION

Islet transplantation is an alternative method to whole pancreas transplantation in patients with type 1 diabetes because of its low invasiveness and safety for the recipient[68,69]. Significant progress in clinical islet transplantation has occurred during recent years, with a progressive improvement of short and long term outcomes. However, the overall long term function of transplanted islets is not satisfactory enough to merit widespread clinical application; at 5 years after transplantation, only 15% of islet recipients remain insulin independent[70]. Moreover, the risk for sensitization after islet transplantation has been reported recently[71]. The hope remains that 1 d islet transplantation will replace insulin therapy, but there is still much work that needs to be done before this goal can be reached. Improving the efficacy of islet transplantation seems to be the most realistic and prudent method to cure diabetes and further investigations to induce the differentiation of stem/progenitor cells into insulin-producing cells will help to establish cell-based therapies for diabetes.

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Events Calendar 2011

January 29 - 31, 2012
2nd Joint AIDPIT and EPITA Winter Symposium & 31st AIDPIT Workshop
Innsbruck, Austria

February 1 - 5, 2012
2012 BMT Tandem Meetings
American Society for Blood and Marrow Transplantation
Manchester Grand Hyatt,
San Diego, CA, United States

February 22 - 24, 2012
British Transplantation Society 15th Annual Congress
Glasgow, Scotland

February 23 - 25, 2012
2012 Canadian Society of Transplantation Annual Scientific Conference
Fairmont Château Frontenac,
Québec, Canada

March 8 - 10, 2012
3rd International Conference on Transplantomics and Biomarkers in Organ Transplantation
La Jolla/San Diego,
CA, United States

April 18 - 21, 2012
The International Society for Heart and Lung Transplantation (ISHLT), 32nd Annual Meeting and Scientific Sessions
Prague, Czech Republic

April 25 - 27, 2012
United Network for Organ Sharing's 20th Annual Transplant Management Forum
Wyndham Rio Mar Beach Resort,
Puerto Rico

June 2 - 6, 2012
2012 American Transplant Congress
John B. Hynes Convention Center,
Boston, MA, United States

July 15 - 19, 2011
24th International Congress of the Transplantation Society
Berlin, Germany

September 13 - 15, 2012
ELITA - LICAGE LIVER MEETING and 4th ELITA Split-Liver Course
Ghent, Belgium

September 29 - 30, 2012
Advances in nephrology, dialysis, Kidney Transplantation
Odessa, Ukraine

October 5 - 7, 2012
V Congress of Transplantologists
Kharkiv, Ukraine

October 5 - 7, 2012
2012 European Organ Donation Congress, 24th ETCO-EDC
Dubrovnik, Croatia
October 12 - 14, 2012
ESOT and AST Joint Meeting - Transformational therapies and diagnostics in transplantation
Nice, France

November 2 - 4, 2012
5th ELPAT Invitational Working Groups Meeting
Sicily, Italy

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INSTRUCTIONS TO AUTHORS

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Format

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English journal article (list all authors and include the PMID where applicable)

1 **Jung EM**, Clevert DA, Schreyer AG, Schmitt S, Rennert J, Kubale R, Feuerbach S, Jung F. Evaluation of quantitative contrast harmonic imaging to assess malignancy of liver tumors: A prospective controlled two-center study. *World J Gastroenterol* 2007; **13**: 6356-6364 [PMID: 18081224 DOI: 10.3748/wjg.13.6356]

Chinese journal article (list all authors and include the PMID where applicable)

2 **Lin GZ**, Wang XZ, Wang P, Lin J, Yang FD. Immunologic effect of Jianpi Yishen decoction in treatment of Pixu-diarrhoea. *Shijie Huaren Xiaohua Zazhi* 1999; **7**: 285-287

In press

3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

Organization as author

4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

Both personal authors and an organization as author

5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

No author given

6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

Volume with supplement

7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

Issue with no volume

8 **Banit DM**, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop Relat Res* 2002; (**401**): 230-238 [PMID: 12151900 DOI:10.1097/00003086-200208000-00026]

No volume or issue

9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

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Personal author(s)

10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

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11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

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12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

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13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

Conference paper

14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

Electronic journal (list all authors)

15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

Statistical data

Write as mean ± SD or mean ± SE.

Statistical expression

Express *t* test as *t* (in italics), *F* test as *F* (in italics), chi square test as χ^2 (in Greek), related coefficient as *r* (in italics), degree of freedom as υ (in Greek), sample number as *n* (in italics), and probability as *P* (in italics).

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