Transplantation in type 1 diabetes

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Introduction

In the clinical course, type 1 diabetic patients suffer from several micro- and macrovascular complications and usually have progressive renal impairment. For these patients, several transplant strategies are available. These include kidney transplantation, pancreas transplantation and clinical islet transplantation, either alone, in a combined procedure or in a sequential approach [1,2]. Herein we give a short overview on transplantation strategies in type 1 diabetes. We focus on new aspects in simultaneous pancreas–kidney transplantation and the effects of normoglycaemia (achieved by a functioning pancreas allograft) on diabetic complications as well as patient and kidney graft survival.

Transplantation strategies in type 1 diabetic patients

In the USA, 78% of all pancreas transplants are simultaneous pancreas–kidney transplants, 16% are pancreas after kidney transplants and 7% are pancreas transplants alone. Outside the USA, a clear majority of pancreas transplants are performed as combined transplants (91%) as compared to pancreas after kidney transplantation and pancreas transplantation alone (4% each) (International Pancreas Transplant Registry; IPTR; http://www.iptr.umn.edu; [2]).

Simultaneous pancreas–kidney transplantation

In 2004, 1-, 3- and 5-year renal allograft survival rate after simultaneous pancreas–kidney transplantation was 92%, 85% and 77%, respectively. The 1-, 3- and 5-year pancreas allograft survival rate after simultaneous pancreas–kidney transplantation was 86%, 79% and 71%, and patient survival was 95%, 91% and 86%, respectively (IPTR; http://www.iptr.umn.edu; [2]).

Pancreas transplantation

Pancreas after kidney transplantation and pancreas transplantation alone represent <10% of the pancreas transplants performed in Europe (IPTR; http://www.iptr.umn.edu; [2]). Especially in pancreas transplantation alone, one has to consider that the benefit of this procedure (normoglycaemia without exogenous insulin) is outweighed by the need of immunosuppressive medication. In contrast, pancreas after kidney transplantation might be an alternative for the type 1 diabetic patient who has already received a kidney transplant and has good renal allograft function. Allograft survival in pancreas after kidney transplantation, however, is much lower than that in simultaneous pancreas–kidney transplantation (IPTR; http://www.iptr.umn.edu; [2]). This might be the consequence of an increased rate of immunological graft loss in pancreas after kidney transplantation.

Clinical islet transplantation

Clinical islet transplantation was long considered an experimental procedure until the so-called Edmonton protocol was published, showing excellent outcome with all seven patients being free of insulin 1 year after the procedure [3]. Unfortunately, the results were not confirmed by a multicentre study where only 53% of patients were free of insulin for 1 year (another 19% received a reduced insulin dose; www.immunetolerance.org). A recent report showed
Kidney lesions can even be prevented [11]. After kidney transplantation, the development of diabetic lesions could be prevented by the use of normoglycaemia [9]. In patients with diabetes and chronic kidney disease stage 4 or 5, after 10 years, 8 of the initial 13 patients were studied again. They showed a significant improvement of renal pathology with either regression or the complete absence of diabetic lesions [9]. In patients with diabetic nephropathy (of native kidneys), they found no regression of diabetic kidney lesions 5 years after pancreas transplantation [10]. After 10 years, 8 of the initial 13 patients were studied again. They showed a significant improvement of renal pathology with either regression or the complete absence of diabetic lesions [9]. In patients with type 1 diabetes and chronic kidney disease stage 4 or 5, after 10 years, 8 of the initial 13 patients were studied again. They showed a significant improvement of renal pathology with either regression or the complete absence of diabetic lesions [9].

### Impact of glycaemic control on diabetic lesions

Several studies impressively illustrated that intensified glycaemic control in diabetic patients (without a renal allograft) can retard the progression of diabetic lesions of different organ systems [5,6]. It had been shown in the Steno studies that multifactorial intervention, e.g., tight glucose control in combination with the use of renin–angiotensin system blockers, aspirin and lipid-lowering agents, reduces cardiovascular deaths, the progression to end-stage renal disease as well as microvascular lesions in type 2 diabetic patients with microalbuminuria [7,8]. There is also evidence that the transplantation of a vascularized pancreas can halt the progression of diabetic micro- and macrovascular lesions in patients with type 1 diabetes (Table 1). However, it takes a long period of normoglycaemia until positive effects become visible, which is impressively illustrated by the work of Fioretto et al. [9,10]. In 13 patients with diabetic nephropathy (of native kidneys), they found no regression of diabetic kidney lesions 5 years after pancreas transplantation [10]. After 10 years, 8 of the initial 13 patients were studied again. They showed a significant improvement of renal pathology with either regression or the complete absence of diabetic lesions [9]. In patients with simultaneous pancreas–kidney transplantation or pancreas after kidney transplantation, the development of diabetic kidney lesions can even be prevented [11].

### Impact of glycaemic control on renal allograft and patient survival

Simultaneous pancreas–kidney transplantation is considered to be the treatment of choice for patients with type 1 diabetes and chronic kidney disease stage 4 or 5. After successful simultaneous pancreas–kidney transplantation, a majority of patients have normal or near-normal fasting blood glucose and normal glycosylated haemoglobin levels as well as good kidney function. This is accompanied by a substantial improvement in the quality of life. However, there is still a lack of evidence to support the superiority of simultaneous pancreas–kidney transplantation compared to kidney transplantation alone (either from a living or a deceased donor) in type 1 diabetic patients with chronic kidney disease. There is indeed a survival benefit (with regard to graft and patient survival) for patients who received a combined transplant in contrast to those patients who received a single kidney transplant. However, much of this benefit is attributable to the selection of the allograft recipient as well as the donor organ. Patients who underwent a combined procedure were often younger and in better physical shape. They often had a shorter waiting time and also a shorter time on dialysis. Furthermore, donor organs in simultaneous pancreas–kidney transplantation are usually of better quality. The donors are younger and the cold ischaemia time is short (compared to recipients of deceased donor kidneys). Several studies on this issue with varying results have been published in the past (Table 2). In a recent

<table>
<thead>
<tr>
<th>Diabetic lesion/investigated parameter</th>
<th>Type of transplantation</th>
<th>Effect</th>
<th>Observation period</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic nephropathy</td>
<td>PTA</td>
<td>No effect</td>
<td>5 years</td>
<td>[10]</td>
</tr>
<tr>
<td>Diabetic nephropathy</td>
<td>PTA</td>
<td>Improved</td>
<td>10 years</td>
<td>[9]</td>
</tr>
<tr>
<td>Diabetic nephropathy (of the renal allograft)</td>
<td>SPK</td>
<td>Inhibited</td>
<td>2–3 years</td>
<td>[11]</td>
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<tr>
<td>Diabetic retinopathy</td>
<td>SPK</td>
<td>Stabilized/improved</td>
<td>6–60 months</td>
<td>[16]</td>
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<tr>
<td>Peripheral and autonomic diabetic neuropathy</td>
<td>SPK</td>
<td>Improved</td>
<td>6–48 months</td>
<td>[17]</td>
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<tr>
<td>Peripheral diabetic neuropathy (action potential)</td>
<td>SPK</td>
<td>Improved</td>
<td>Up to 8 years</td>
<td>[18]</td>
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<tr>
<td>Autonomic diabetic neuropathy</td>
<td>SPK</td>
<td>Improved</td>
<td>12 months</td>
<td>[19]</td>
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<tr>
<td>Peripheral and autonomic diabetic neuropathy</td>
<td>SPK, PAK, PTA</td>
<td>Improved</td>
<td>1–10 years</td>
<td>[20]</td>
</tr>
<tr>
<td>Blood pressure, pulse pressure, cholesterol</td>
<td>SPK</td>
<td>Reduced</td>
<td>1–12 years</td>
<td>[21]</td>
</tr>
<tr>
<td>Progression of coronary artery disease</td>
<td>SPK</td>
<td>Decelerated</td>
<td>3.9 years (mean)</td>
<td>[22]</td>
</tr>
<tr>
<td>Left ventricular ejection fraction</td>
<td>SPK</td>
<td>Improved</td>
<td>4 years</td>
<td>[23]</td>
</tr>
</tbody>
</table>

SPK, simultaneous pancreas–kidney transplantation; PAK, pancreas after kidney transplantation; PTA, pancreas transplantation alone.

<table>
<thead>
<tr>
<th>Table 2. Impact of glycaemic control on renal allograft and patient survival (modified after [1])</th>
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<tbody>
<tr>
<td>Patient survival</td>
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<tr>
<td>-------------------</td>
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<tr>
<td>SPK = DDK</td>
</tr>
<tr>
<td>n.a.</td>
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<td>DDK &gt; SPK &gt; DDK</td>
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<td>DDK &gt; SPK &gt; DDK</td>
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<td>DDK &gt; SPK &gt; DDK</td>
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</tbody>
</table>

SPK, simultaneous pancreas–kidney transplantation; DDK, living donor kidney transplantation; DDK, deceased donor kidney transplantation; n.a., not applicable.
better. The latter group (kidney transplantation alone) would have done better than those patients with kidney transplantation alone. It is a limitation of improved glycaemic control in patients who received a living donor kidney (HR < 0.005). In parallel, there was a lower rate of cardiovascular deaths in recipients of a combined organ transplant (37%) compared to living donor (49%) and deceased donor (46%) kidney transplantation [13]. This effect was mainly attributable to improved glycaemic control in patients who received a simultaneous pancreas–kidney transplant as compared to those patients with kidney transplantation alone. It is a limitation of this registry analysis, however, that no information is available on glycaemic control in patients who received kidney transplantation alone. One might speculate that with intensified treatment, i.e. by the use of insulin pumps, the latter group (kidney transplantation alone) would have done better.

Summary

Simultaneous pancreas–kidney transplantation is now a routine procedure in transplantation. Surgical complication rates are low, and with potent immunosuppressive medication, long-term allograft and patient survival are excellent. From data that were also derived from pancreas transplantation alone, we know that longstanding normoglycaemia can halt or even reverse diabetic lesions in various organs, i.e. heart or kidney. However, data on long-term allograft and patient survival in type 1 diabetes recipients who received a combined transplant in contrast to patients who received a kidney transplant alone (either from a living or a deceased donor) are still scarce. Recent evidence suggests that simultaneous pancreas–kidney transplantation is highly superior to kidney transplantation alone from a deceased donor with respect to allograft and patient survival, and this survival benefit is already visible after only 5 years of follow-up [13]. After 10 years of posttransplant follow-up, patient survival in simultaneous pancreas–kidney transplantation is even superior to that in type 1 diabetic patients who received a kidney transplant (alone) from a living donor. These data clearly argue in favour of simultaneous pancreas–kidney transplantation in type 1 diabetic patients with kidney failure. Therefore, every type 1 diabetic patient with chronic kidney disease stage 4 or 5 should be evaluated for a combined transplant, and this procedure should ideally be performed in a pre-emptive fashion before the patient goes to dialysis. One might speculate that intensified glycaemic control, i.e. targeting a glycated haemoglobin value below 6.5% by the use of insulin, might have comparable positive effects in patients who received a kidney transplant alone in type 1 diabetes, and this may also apply to patients with type 2 diabetes or posttransplantation diabetes mellitus after kidney transplantation. However, it is often difficult to reach those target levels and adverse events such as hypoglycaemia and even an increased rate of death have been reported [14,15].

Conflict of interest statement. None declared.

References

2. Gruessner AC, Sutherland DE. Pancreas transplant outcomes for United States (US) and non-US cases as reported to the United Network for Organ Sharing (UNOS) and the International Pancreas Transplant Registry (IPTR) as of June 2004. Clin Transplant 2005; 19: 433–455

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