Selection of diabetic patients for islet transplantation. A single-center experience

MC Vantyghem, M Hazzan, S Tourville, F Provost, P Perimenis, N Declerck, G Sergent, J Kerr-Conte, C Noel, F Pattou

Objective: Since the Edmonton protocol, islet transplantation (IT) offers the prospect of adequate glycemic control with no major surgical risk. In our single-center experience of IT, we studied the recruitment of eligible diabetic patients.

Methods: Between 1998 and 2002, we screened 79 diabetic patients that were divided into 2 groups according to their renal status: 41 were not receiving dialysis (ND) while 38 were receiving ongoing dialysis (D).

Results: In the ND group, 20 patients initiated the contact with our team, 8 patients were recruited during hospitalization for very poor glycemic imbalance, and 13 were referred by their dietiologist. 14/41 (34%) patients were ineligible for IT either because of very good glycemic balance, undetectable C-peptide, kidney or liver problems, or plans for future pregnancy. 16/41 (39%) did not wish to proceed, 7 of whom were more interested by a pump. 11/41 (27%) were eligible, among which 8 are currently being assessed, 1 is on the waiting list and 2 have been transplanted. In the D group, 17/38 (45%) had a detectable C-p and received a kidney graft alone. Among the remaining 21 C-p negative diabetic patients, 3 were not eligible for kidney transplantation mainly for psychological reasons, and 4 were enlisted for kidney-pancreas transplantation. The remaining 14 C-p negative patients were kidney-transplanted. Among them, 6 were not eligible for IT, mainly for lack of motivation, slightly positive C-peptide stimulation tests, obesity, cancer, or increased creatininemia. The remaining 8/14 C-p negative kidney-engrafted patients were enlisted for IT. 3 had secondary failure with the pre-Edmonton immunosuppressive (IS) protocol. Five have been transplanted with the Edmonton-like IS regimen.

Conclusion: Twenty-five per cent of the 79 patients for whom islet transplantation was considered underwent pregraft assessment and 12% (10 patients, 8 kidney-transplanted and 2 islet alone) of the 79 patients have been transplanted. The main eligibility criteria were undetectable C-peptide, normal kidney function, average weight, glycemic imbalance, hypoglycemia unawareness, and glycemic brittleness.

Key-words: Type 1 diabetes · Islet transplantation · Kidney transplantation.


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Mots-clés : Diabète de type 1 · Greffe d’îlots · Transplantation rénale.

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he concept of transplanting pieces or extracts of pancreas in patients with diabetes is over a century old. By the 1980s, successful transplantation of islet autografts was reported in humans. By the 1990s, reports of successful allogenic islet transplantation in patients with type 1 diabetes with the use of conventional immunosuppression (antilymphocytes antibodies, corticoids, cyclosporine A and mycophenolate mofetil) began to appear, but internationally, the overall rates of success was less than 10%. In 2000, Shapiro et al. reported an 80% success in a series of patients with a new immunosuppressive protocol (daclizumab, sirolimus and low dose tacrolimus). Centers worldwide have since reproduced their results [1, 2, 3]. Recent studies have gone a step further, showing that islet transplantation can compare with pancreas transplantation in terms of improvement of diabetic complications [4]. Nevertheless, eligibility criteria for this strategy have yet to be defined. Patient motivation, the evolution of diabetic complications, hypoglycemia unawareness and diabetes brittleness have to be balanced against the risks of procedure and long-term immunosuppressive therapy [5]. An attempt at quantified standardization of hypoglycemia unawareness and glycemic brittleness is currently being evaluated [6].

Pancreas transplantation has become accepted as the preferred treatment for patients with insulin-dependent diabetes mellitus requiring kidney transplantation for diabetic nephropathy [7, 8, 9]. The current one-year actuarial patient, kidney and pancreas graft survival rates are 95, 92, and 84%, respectively [10, 11]. Nevertheless, the procedure is still associated with significant morbidity in terms of surgical risk and cost. Since the Edmonton protocol, islet transplantation offers the prospect of accurate glycemic control with no major surgical risk [1, 2]. Although islet transplantation with the Edmonton protocol was tested in type 1 diabetes without kidney failure, its application to type 1 diabetic patients already on immunosuppressors for kidney transplantation is particularly easy to support [12]. The aim of this work was to assess the profile of diabetic patients, whether dialysed patients or not, for whom islet transplantation was considered.

Patients

Between January 1998 and December 2002, 79 cases of diabetic patients were assessed by the Islet Transplantation Team: 41 were not dialysed patients while 38 were. Among the 41 non-dialysed patients, the sex ratio was 21 male/20 female. Ages ranged from 18 to 65 years, and weight: from 55 to 105 kg. Thirty one lived in the vicinity of Lille while 10 came from other areas. The patients were divided into three groups according to recruitment: 20 initiated contact (G1), and received information about islet transplantation either by letter or via an information booklet — their family doctors and diabetologists were also informed; 8 were recruited because of emergency hospitalization (G2) for marked glycemic imbalance with either severe ketoacidosis or hypoglycemia; the remaining 13 (G3) were referred by their diabetologist for an appointment. The 38 diabetic dialysed patients were recruited from the Nephrology Department of Lille University Hospital. Their characteristics were as follows: gender — 18 female/20 male; Age range — 20 to 67 years old; weight range — 43 to 127 kg.

Methods

Clinical eligibility criteria

The patients were selected according to the exclusion and inclusion criteria for islet transplantation given in Tables I and II. For diabetic dialysed patients, we modula-

<table>
<thead>
<tr>
<th>Table I</th>
<th>Inclusion criteria for islet transplantation in type 1 diabetic patients with Edmonton-like immunosuppression regimen.</th>
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<tbody>
<tr>
<td><strong>Islet after kidney transplantation</strong></td>
<td><strong>Islet alone transplantation</strong></td>
</tr>
<tr>
<td>Ineligibility for pancreas + kidney transplantation</td>
<td>Brittle diabetes and/or</td>
</tr>
<tr>
<td>Or pancreas transplantation failure</td>
<td>Hypoglycemia unawareness and/or</td>
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<tr>
<td><strong>And</strong></td>
<td>Progression complications</td>
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<tr>
<td>Kidney transplantation &gt; 6 months with discontinuation of corticoids</td>
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<table>
<thead>
<tr>
<th>Table II</th>
<th>Exclusion criteria.</th>
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<tr>
<td>Detectable C-peptide*</td>
<td></td>
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<tr>
<td>Age &lt; 18 or &gt; 65 years</td>
<td></td>
</tr>
<tr>
<td>Diabetes duration &lt; 5 years</td>
<td></td>
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<tr>
<td>Addictions or psychiatric disorders</td>
<td></td>
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<tr>
<td>BMI &gt; 28</td>
<td></td>
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<tr>
<td>Plasma creatinine &gt; 130 (islet alone) or 220 (islet after kidney) micromol/l (or respectively 1.5 and 2.5 mg/dl)</td>
<td></td>
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<td>albuminuria &gt; 300 mg/24 hours</td>
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* In our lab, plasma C-peptide level greater than 0.2 ng/ml.
Selection for islet transplantation

41 diabetic patients not receiving dialysis

Among this series of 41 diabetic patients:
— 14 (34%) did not fit the eligibility criteria, mainly for satisfactory glycemic balance (n = 1), positive C-peptide (n = 2), kidney failure (n = 3), plans for future pregnancy (n = 4) or liver problems (n = 4).
— 16 (39%) did not go beyond the first information step, 7 of these being more interested in a pump. The 9 remaining patients did not wish to proceed mainly because of family disapproval, timing and professional reasons, or unwillingness to submit to constraints by patients that had difficulties accepting their diabetes.
— 11 (27%) undertook pretransplantation evaluation, 8/11 are currently undergoing pretransplantation clinical investigation, and 1/11 is on the waiting list. 2/11 have been transplanted, one of whom was transplanted in Geneva which was geographically nearer to his home, the second in Lille.

38 diabetic patients with end-stage renal disease

The results were as follows:
— 17/38 (46%) had positive C-peptide diabetes and received kidney transplantation alone.
— Among the remaining 21 (54%) C-peptide negative diabetic patients, 3 (8%) were ineligible for kidney transplantation mainly for psychological reasons. 18/38 (47%) were eligible for a kidney transplantation. Among these 18 patients, 4 (10%) were enlisted for simultaneous kidney and pancreas transplantation. The remaining 14/38 (37%) were kidney-transplanted, among whom:
— * 6/38 (16%) were ineligible for islet after kidney transplantation (IAK). The reasons for this were as follows: 1 patient had moved away; 1 had negative basal C-peptide but slightly positive stimulation tests; 1 was overweight...
(102 kg); breast cancer was discovered in 1 patient 6 months after kidney transplantation despite negative pre-kidney graft screening; I had post-kidney graft complications with creatinemia > 220 micromol/l (N < 110); I refused islet transplantation mainly because of post kidney transplantation medical problems.

* 8/38 (21%) were eligible for islet after kidney-transplantation (IAK). Three were transplanted with a pre-Edmonton immunosuppressive regimen and exhibited secondary islet failure with the presence or the reactivation of anti-pancreas auto-antibodies [13]. Five have been transplanted with an Edmonton-like protocol.

During the follow-up period and among the 14 kidney transplanted patients, two patients died from sudden stroke, one of whom died three years after an islet transplantation that had been functional for only three months, and the second two years after kidney transplantation that had been detransplanted because of breast cancer.

The main features of type 1 diabetic patients, whether kidney-transplanted or not, finally enlisted for islet transplantation with the Edmonton protocol, are provided in Table III.

**Discussion**

Our aim was to assess the profile of diabetic patients for whom islet transplantation — using the Edmonton protocol — had been considered before transplantation

<table>
<thead>
<tr>
<th>Table III</th>
<th>Patient characteristics. Abbreviation Tx: transplantation.</th>
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<tr>
<td></td>
<td>Islet alone transplantation</td>
</tr>
<tr>
<td>Patients</td>
<td>1</td>
</tr>
<tr>
<td>Age (years)/sex (M/F)</td>
<td>38/M</td>
</tr>
<tr>
<td>Weight</td>
<td>66</td>
</tr>
<tr>
<td>Duration of diabetes</td>
<td>25</td>
</tr>
<tr>
<td>Daily insulin needs (U/day)</td>
<td>60</td>
</tr>
<tr>
<td>Dialysis duration (months)</td>
<td>—</td>
</tr>
<tr>
<td>Time elapsed between kidney and islet Tx (months)</td>
<td>—</td>
</tr>
<tr>
<td>Serum creatinine level (micromol/l or mg/dl)</td>
<td>88 (1.0)</td>
</tr>
<tr>
<td>Microalbuminuria (mg/24h)</td>
<td>13</td>
</tr>
<tr>
<td>HbA1c (N &lt; 6.5%)</td>
<td>8.3</td>
</tr>
<tr>
<td>Main reason for islet Tx</td>
<td>Hypo unawareness</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>Yes/mild</td>
</tr>
<tr>
<td>Other diabetic complications</td>
<td>—</td>
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<tr>
<td>Medical history</td>
<td>—</td>
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evaluation. The patients were divided into two groups according to the presence or absence of end-stage kidney disease. Recruitment and eligibility criteria differed slightly between the two groups. We discuss specific differences before reviewing the main common eligibility criteria for islet transplantation and its place among other treatments of diabetes.

The group of patients who did not exhibit signs of end-stage kidney disease was divided into three groups according to recruitment. Results suggest that patients seen in the emergency room for serious diabetic imbalance are poor candidates for islet transplantation (only 1/8 patients in G2 were recruited for further evaluation, while 5/20 were recruited in group G1 and another 5/13 in group G3). All in all, about 25% of the diabetic patients for whom islet transplantation was considered actually underwent pretransplantation evaluation. Apart from eligibility criteria given in Tables I and II, three main reasons led us to exclude patients from the IT protocol (still at the clinical research stage in France): 1) future plans for pregnancy in young women, the risk of immunosuppressive therapy for the fetus not being documented, 2) incipient nephropathy, and this is a difficult situation in which no standard therapy is proposed, and 3) liver problems related to alcohol and/or iron overload, as this may increase the risk of liver steatosis and fibrosis, especially under immunosuppressive therapy.

As for the group of diabetic patients receiving ongoing dialysis, our main initial challenge was to recognize type 1 from type 2 diabetes. Epidemiological studies have shown how dramatically the prevalence of diabetes increases among dialysed patients (13%, among whom 13% of type 1 and 15% with severe macrovascular complications) [15]. Also, an increasing number of type 2 diabetic patients require insulin because of relative insulinopenia in the course of their disease, not to speak of the earlier onset of type 2 diabetes due to the increasing prevalence of obesity. Moreover, about 20% of type 1 diabetes are of late-onset. These facts make the diagnosis of type 1 diabetes difficult, especially in dialysed patients, since the classical criteria of Type 1 diabetes (young age of onset, requirement for insulin therapy) often do not apply. In the Edmonton protocol, one of the main criteria of eligibility was undetectable levels of C-peptide in the end of hypoglycemic episodes, an especially important marker of the type 2 diabetes phenotype [16], a previous application of C-peptide determinations became possible in dialysed diabetic patients [17]. Also, it is a well known fact that diabetic patients remaining on the waiting list for months worsen their vascular status to such an extent that it is preferable to transplant a kidney alone, (possibly before transplanting islets). It must also be noticed that, although little available in France, living-donor kidney transplantation is associated with a similar life expectancy [17, 18]. The strategy for islet transplantation probably also depends on other factors such as the necessity to be transplanted in a distant center which is often a burden to these sometimes severely disabled patients.

In summary, among this series of 38 diabetic patients under dialysis, over 90% were eligible for kidney transplantation. Nearly 50% were ineligible for pancreas or islet transplantation because of a positive C-peptide. About 20% were eligible for islet transplantation. These results suggest the importance of C-peptide determination in dialysed diabetic patients to identify eligible patients for pancreas or islet transplantation.

Finally, islet transplantation indications may vary according to the theoretical benefits and potential drawbacks. Ideally, the benefits of islet transplantation are 1) the end of hypoglycemic episodes, an especially important benefit when patients are no longer aware of their hypoglycemias; 2) discontinuation of insulin with satisfactory glycemic balance, evidenced by normal levels of glycated hemoglobin over long periods; and 3) stabilization or prevention of chronic complications of diabetes. Potential drawbacks include 1) the need to transplant at least two pancreases; 2) acute complications potentially linked to portal puncture; and above all 3) the need for an immunosuppressive regimen.
Therefore, the level of glycemic imbalance regarded as sufficiently unsatisfactory to consider islet transplantation differed between the dialysed and non-dialysed patients because of the need for immunosuppressive therapy. IA was considered in patients with brittle type 1 diabetes, hypoglycemia unawareness or progressive complications. In clinical practice, this means considering IA after failure or refusal of an ambulatory pump, each time hypoglycemia has required outside help or caused traumatism, when HbA1c levels remains above 7% with progressive complications, and/or in case of brittle diabetes evidenced during hospitalization or by continuous glucose monitoring sensing. An attempt to quantify both hypoglycemia unawareness and brittleness has recently been made in order to allow between-center comparison [6]. Islet transplantation could be balanced against solitary pancreas transplant. Nevertheless, a recent study demonstrated that survival in patients with diabetes and preserved kidney function receiving a solitary pancreas transplant was significantly lower than the survival of patients on the waiting-list receiving conventional therapy, mainly in reason of post-surgery complications.

By contrast, islet after kidney transplantation (IAK) was systematically proposed to kidney-transplanted patients insofar as HbA1c remained above 7% and inclusion criteria were respected, since the constraints of immunosuppressive treatment did not have to be balanced against the risk of diabetic complications.

Another important factor for patient selection is BMI and/or insulin needs. In international trials, daily insulin requirement varied between 0.7 and 1.2 U/kg/day. None of our enlisted patients had insulin needs greater than 1 U/kg/day. But daily insulin needs are known to vary according to numerous factors such as administration route, diet, stress or occasional diseases, weight, former diabetic imbalance or drugs, and especially immunosuppressive drugs. Therefore this parameter should be considered with caution, and we did not include it in our eligibility criteria. Patient weight was more of a concern, since the number of islets needed to achieve insulin independence is about 10 000 IEQ/kg, according to the Edmonton protocol. The greater the weight, the more islets need to be transplanted. This increases the risk of acute complications and may be a burden in our context of relative donor shortage. In clinical practice, we did not include patients weighing more than 80 kg, but this point may be balanced against daily insulin needs.

Currently, checking that serum C-peptide level is undetectable is an important step, since this parameter is one of our success criteria. Stimulation tests with glucose and arginin seem justified on account of the difficulty to detect borderline values of plasma C-peptide and/or the lack of sensitivity of the assay in low values, especially in kidney-transplanted patients. Nevertheless, once islet transplantation is validated, one may discuss its indication in type 1 diabetic patients with minimal residual C-peptide function.

Last, checking kidney function is currently one of our inclusion criteria on account of potential nephrotoxicity of immunosuppressive drugs, especially tacrolimus. A specific point to discuss is the cut-off serum creatinine level-which was higher for IAK than for IA. We decided to include patients with slightly increased serum creatinine levels for IAK because 1) we did not want to exclude patients with steady creatinine levels, and 2) these levels are often slightly increased in kidney-engrafted patients due to the potential nephrotoxicity of tacrolimus, especially on a transplanted-kidney alone. Note that the dose of tacrolimus used in the Edmonton protocol is about one third lower than the one used in kidney-transplanted patients. We hoped to stabilize kidney function with normoglycemia reached through islet transplantation better than with standard insulin therapy, since immunosuppressive regimen was already required for kidney transplant.

Last, islet transplantation may be in competition with insulin pumps, especially for patients who are aware of their hypoglycemia. A recent publication comparing the results of islet or pancreas transplantation vs. intraperitoneal delivery of insulin with a pump demonstrated the superiority of glycemic balance obtained after transplantation [20]. Nevertheless, the gain of glycemic balance has to be weighed against the risk of long-term immunosuppression. For the time being, we suggest some reasonable treatment strategies in severe forms of C-peptide negative diabetes: an insulin pump could be proposed to patients weighing more than 80 kg, young women planning a future pregnancy, patients with renal disease (serum creatinine level > 130 micromol/l and/or microalbuminuria > 300 mg/24 h). Islet cell therapy could be offered to patients having failed or refused an insulin pump, demonstrating progressive complications despite optimized insulin therapy, hypoglycemia unawareness evidenced by an increased hyposcore or brittle diabetes. Patient motivation and distance to the transplantation center should also be taken into account. Of course, the definitive answer will require clinical trials comparing islet transplantation and ambulatory or implanted insulin pump as soon as islet transplantation is validated as a possible alternative treatment for severe forms of type 1 diabetes.

Conclusion

According to the analysis of our series, the constitution of active files of patients eligible for islet transplantation requires that patients, diabetologists, but also nephrologists be informed. All in all, about 25% of the 79 patients for whom islet transplantation was considered underwent pre-graft assessment and 12% (8 kidney-transplanted and 2 islet alone) of those 79 have been transplanted. The main eligibi-
lity criteria were undetectable C-peptide, normal kidney function, average weight, glycemic imbalance, hypoglycemia unawareness, and glycemic brittleness.

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