J Mol Med (1999) 77: 148–152

REVIEW

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Indications for clinical islet transplantation today and in the foreseeable future – The diabetologist's point of view

Abstract The treatment of patients with type 1 diabetes mellitus has to focus on short-term and long-term risks of the disease which means to avoid hyperglycemic or hypoglycemic coma as well as late complications. As we know from the DCCT study [1] metabolic control substantially lowers the risk for retinopathy, nephropathy and neuropathy. We also know, that keeping the blood glucose in a nearly normal range inevitably is connected with a marked increase of severe hypoglycemia, an event which occurs more frequently when normoglycemia has been reached and the further slow decline of blood glucose is not recognized by the patient (autonomous neuropathy, hypoglycemia unawareness of other origin, long duration of diabetes etc.). Furthermore, counterregulatory hormones as glucagon and epinephrine may be lacking due to diminished or even lost alpha cells within the islets and as recently observed due to fibrosis of the adrenal medulla in long-term diabetes. The consequences of severe hypoglycemia are manifold: in the actual situation of unconsciousness the risk of heavy injuries and as long-term consequences irreversible brain damage may occur. Finally, the effort of the patient to reach normoglycemia includes the burden of an intensive blood glucose self-control day by day. This broad scenario of all the achievements and of all the problems connected with an intensified insulin treatment has to be regarded when the indication for an islet transplant will be discussed.

From our point of view as clinicans it seems adequate not to give definite recommendations but to express our considerations for islet transplantation in patients with type 1 diabetes mellitus with the following list (table 1). It must be clearly stated, that at present transplantation of isolated islets by no means can serve as a treatment for a larger number of patients and this may hold through also for the foreseeable future. In this context, also the many contraindications should be summarized (table 2).

Consequently we have to deal with several questions and problems which can be subdivided into those regarding the possible benefit for the patients from an islet graft (full success = insulin independence, partial success = lower exogenous insulin requirement due to addditional endogenous insulin, measured by C-peptide levels, more stable glucose metabolism) and those regarding possible side effects (primary risk of implantation, threat for rejection of the primarily transplanted kidney). Furthermore, one may ask for risks when islets are transplanted alone (ITA).

We therefore will address the following areas:

1. Simultaneous islet and kidney transplants
2. Islet transplants after kidney transplantation alone (IAK)

Table 1 Considerations for islet transplantation in patients with type 1 diabetes mellitus

1. previously transplanted kidney
2. end-stage renal failure (simultaneous islet/kidney transplantation)
3. lost function of a pancreatic organ graft
4. defect hypoglycemia counterregulation / life threatening hypoglycemia unawareness
5. autonomous cardiac neuropathy
6. significant clinical problems with insulin therapy (e.g. brittle diabetes)

Table 2 Present contra-indications for islet transplantation in patients with type 1 diabetes mellitus

• age <18 and >65 years
• duration of diabetes <10 years
• manifestation of diabetes after age 30
• Residual C-peptide secretion (stimulated C-peptide 6 min after 1 mg glucagon i.v. ≥ 0.2ng/ml)
• creatinine clearance <45 ml/min
• portal hypertension
• active or chronic infections as hepatitis C or B
• allergy against rabbit or horse serum
• active gastric or duodenal ulcer
• psychosis
• non-compliance
• neoplasia (if not free from relapse >5 years)

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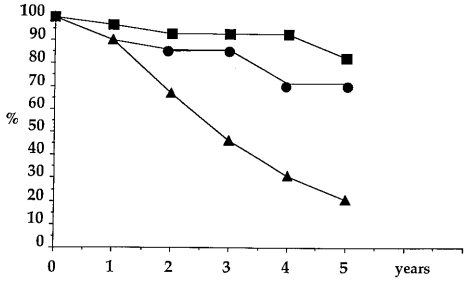

Fig. 1 Actuarial survival rate (%) of IDDM uremic patients admitted to the waiting list for kidney/pancreas transplantation at the San Raffaele Institute (University of Milan). Squares represent patients submitted to kidney/pancreas transplantation, circles represent patients submitted to kidney transplantation, triangles represent patients still on dialysis (not transplanted for technical or immunological reasons)

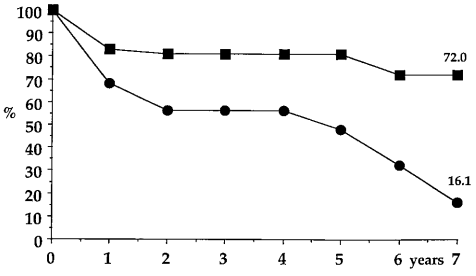

Fig. 2 Pancreas graft function actuarial survival rate (%) at the San Raffaele Institute (University of Milan). Squares represent whole pancreas (bladder diverted), circles represent segmental pancreas (duct obstructed)

3. Islet transplantation after pancreas transplantation failure (P-failure)
4. Defect hypoglycemia counterregulation – life threatening hypoglycemia unawareness as indication for islet transplantation?
5. Autonomous cardiac neuropathy as indication for islet transplantation?
6. Significant clinical problems with exogenous insulin therapy as indication for islet transplantation?

Simultaneous islet and kidney transplantation

End stage renal failure is a growing problem. The number of diabetic patients requiring renal replacement therapy (dialysis or transplantation) has increased from 3.8% (1977) to 17% (1992), as reported by the EDTA Registry [2] (table 3). These data were confirmed at a regional level (Lombardy: 7.7% in 1983, 12% in 1992 [3]), thus emphasizing the widespread diffusion of the problem. Furthermore, it was shown by the Lombardy Registry that 5-year survival of patients under dialysis is significantly lower in diabetic patients (28%) than in non-diabetic patients (61%) (table 4) [3]. On the contrary, diabetic patients receiving a kidney transplant have a higher 5-year actuarial survival rate (75%) than similar patients not submitted to transplantation, but treated with dialysis, and a survival rate even higher in case of combined pancreas/kidney transplantation (fig. 1). From these data it is clear that kidney transplantation must be considered a life-saving procedure in uremic diabetic patients. Metabolic control in diabetic kidney transplanted patients is difficult, as shown by HbA1c levels (table 5), probably as a consequence of the metabolic effects of immunosuppressive drugs (steroids, cyclosporine, FK506). In this particular subset of patients pancreas transplantation can be performed simultaneously to kidney transplantation in order to control blood glucose homeostasis, to prevent the development of diabetic nephropathy on the transplanted kidney, and to improve life quality. This surgical procedure has an 80% success rate at 1 year (fig. 2) [4]. Simultaneous kidney/islet transplantation could be an alternative to simultaneous kidney/pancreas transplantation, having the advantage of requiring minor or no surgery. Furthermore, kidney transplantation for diabetic patients affected by severe macroangiopathy could be indicated, but simultaneous pancreas transplantation could be contraindicated due to surgical and perioperative risks related to the clinical condition of the patient. In this case, islet transplantation could benefit from the immunological advantages related to the simultaneous kidney transplant, as already described for simultaneous pancreas/kidney transplantations (early detection of rejection, uremia-related immunosuppression).

Table 3 New patients starting renal replacement therapy: EDTA registry data [2]

	1977	1992
Diabetes	3.8%	17.0%
Glomerulonephritis	22.0%	11.3%
Pyelonephritis	20.0%	10.0%

Table 4 Survival of patients on dialysis according to the original kidney disease: Lombardy Registry data [3]

	1 year	3 years	5 years
Diabetes	82%	48%	28%
Other	91%	74%	61%

Table 5 HbA1c levels in IDDM patients submitted to kidney (Ktx) or kidney/pancreas (KPtx) transplantation at the San Raffaele Institute (University of Milan)

	Basal	years			
		1	2	3	4
Ktx	7.0±0.3	7.9±0.3	8.1±0.5	8.8±1.1	8.8±1.1
KPtx	6.7±0.2	5.9±0.2	5.7±0.1	5.7±0.1	6.2±0.2
p	ns	0.0001	0.0001	0.0001	0.001

Table 6 Mortality (%) of diabetic patients with autonomous cardiac neuropathy (ACDN)

Authors	Duration of trial (years)	Number of tests	Mortality (%) Pts		Significance (p)
			with ACDN	without ACDN	
Ewing et al. 1980	5	3+S	15	53	<0.05
Hasslacher et al. 1983	5	1	7	19	NS
Navarro et al. 1990	3	2	4	23	<0.05
Sampson et al. 1990	10	1+S	11	37	<0.05
O'Brien et al. 1991	5	4	5	27	<0.05
Ewing et al. 1991	3	5+QTc	8	31	<0.05
Jermendy et al. 1991	5	4+QTc	4	40	<0.05
Rathmann et al. 1993	8	2+QTc	3	23	<0.05
Luft et al. 1993	8	4	5	21	NS
Total	5.8	–	6 (n 41/708)	29 (n 143/495)	Rel. Risk×5

The main disadvantage of this approach is related to the fact that islets might be transplanted even in case of a relatively low quality of the preparation, in contrast to the IAK situation. In fact, these patients cannot wait for the next kidney/islet donor in the case of a poor islet preparation due to the long waiting list for kidney transplantation and the poor survival of diabetic patients on dialysis.

Islet transplantation after kidney transplantation alone (IAK) and after pancreas transplant failure (P failure)

Pancreas transplantation has a 30% probability of failure within the first year for simultaneous pancreas/kidney transplantation, and 50% failure rate in case of pancreas after kidney transplantation, mainly for technical (surgical) or immunological (rejection, recurrence of autoimmune disease) reasons. It was already shown by the International Pancreas Transplant Registry [5] that pancreas retransplantation has a high rate of failure (50%). As a consequence these patients should not undergo pancreas retransplantation due to the low probability of function and the high rate of surgical risks (50% of reoperations) [6]. This particular subset of patients could benefit from an islet transplantation, and similarly those diabetic patients, who have previously received a kidney transplant alone.

These two groups of patients share the advantage of minor surgical risks, of already established immunosuppression (for the kidney), of an easy post-surgical management (when compared to SIK), and of the possibility to select the best islet preparation. The main disadvantages of these two approaches (P failure and IAK) are the requirement of a second course of anti-lymphocyte globuline (ALG) (when patients received ALG for the first transplant) and the risk of inducing kidney rejection as a consequence of an immune "activation" by the antigens presented from the islet graft, if different from those of the transplanted kidney.

Defect hypoglycemia counterregulation, life-threatening unawareness

Although in the last years problems of hypoglycemia counterregulation and unawareness of hypoglycemia have been discussed thoroughly in many journals, symposia and congresses, there is no doubt that the problem of unawareness is more frequently observed today then in the past. Up to now unawareness is very difficult to define and there is no question that this situation increases in patients with long duration of diabetes worldwide.

It is not the time and the place to go into detail about the pathogenic mechanisms leading to severe hypoglycemic episodes or even unawareness, but they may be the cause of death. In recent times several strategies have been developed to regain awareness of low blood glucose values by special training programs. One principle is, to keep the blood glucose temporarily in a higher level to induce a steep gradient when glucose concentration is falling. It has been shown that this situation may evoke sympathetic stimuli which are recognized by the patients and enable them to react. But those learning systems do not change the basic situation of the defects within the counterregulatory system, especially the lacking glucagon. The substitution of such a patient with new islets which contain all types of endocrine cells could help in several aspects: a) functioning beta cells lead to better control of blood glucose changes b) functioning alpha cells may release glucagon when blood glucose decreases, especially in those cases in which after an islet transplant some exogenous insulin is still necessary. In a study reported by Meyer et al. [7] nearly complete awareness could be regained as long as islet function was preserved. Those patients were not only protected against drastic hypoglycemic episodes but they reported also to have regained the feeling for falling blood glucose levels in general.

Autonomous cardiac neuropathy

Autonomous cardiac diabetic neuropathy may be a definite threat for the patient with long duration of diabetes. The mortality is much higher in patients with this type of neuropathy than in those without as shown by several groups (table 6) [8]. This may be indicated by lack of pain when coronary heart disease inhibits sufficient oxygen supply for the heart muscle. This lack of the warning system may adversely affect rational behaviour of the patient as well as rapid medical care. Furthermore, dangerous arrhythmias have been observed frequently and seem to be responsible for most of the cases with sudden death in diabetic patients. As we know from pancreatic organ transplantation not only peripheral but also autonomous neuropathy may be ameliorated when normalization of blood glucose has been obtained after transplantation [9]. Several hypotheses have been developed to explain this phenomenon. Up to now it remains open whether it is simply normalization of blood glucose which among other aspects means reduced glycosylation of tissue proteins or other cell systems corresponding to the observation of the DCCT study. In this it was shown, that better metabolic control in type 1 diabetes lowered the risk for neuropathy in general. However, perhaps other mechanisms may be involved: as recently shown by Wahren and his group in Stockholm C-peptide alone seems to have functional influences on several organ systems.

C-peptide indirectly activates sodium/potassium ATPase which is decreased in the nervous system in diabetes mellitus. Those studies suggest that C-peptide administration to patients with diabetic autonomous neuropathy is accompanied by significantly improved autonomous neurofunction [10].

Significant clinical problems with insulin therapy (e.g. “brittle diabetes”)

There is no doubt that patients which may be classified into the category of “brittle diabetes”, whatever this definitely may be, are seeking for help in centers where pancreatic organ transplants or islet transplantation are performed.

Some diabetologists feel that every so called “brittle diabetes” can be converted into the “normal” situation of a type 1 diabetic patient when intensive education, blood glucose self-control and intensified insulin treatment schedules including pumps are used and if no psycho-social factors are involved. Nevertheless, this type of patient does exist and is usually associated with several keto-acidotic comas and hospitalizations per year frequently combined with the incapacity for a daily work. Therefore, we have reason enough to think about the life change for those persons which could be reached by a functioning islet transplant leading to a much more stable metabolic situation.

In conclusion it can be stated that in principal categories 4 to 6 offer the indication for an islet transplant. Although at present times we have no definite proof yet that the initiative for all the necessary expenditure regarding organisation, organ procurement, hospitalization, patient pretreatment, and the transplant procedure itself is indeed justified, we nevertheless should have clearly in mind:

The foreseeable future for those patients does not offer any better chance to change their life. The number of pancreatic organs available for the moment is not a limiting factor and transplant groups doing pancreatic organ grafting are not hampered by the activity of the islet transplanting groups at least within Europe.

Finally the overall situation in islet transplantation might be subdivided in

1. patients, who receive islets simultaneously with or consecutively to a renal transplant;
2. patients receiving islets alone.

Coming back to the questions asked initially in regard to the potential advantages of islet transplants there is no doubt that at present times much better results can be obtained for patients with category 1. This has been outlined already in previous reports. As argued for many years in connection with pancreatic organ transplantation longer lasting renal insufficiency may act as an immunosuppressive condition which facilitates the survival of transplanted islets in patients receiving the graft simultaneously with a kidney. This scenario would not apply to diabetics who receive an islet transplant after a successful renal graft which has led to normalization of blood creatinine and urea nitrogen. Only the progress of clinical islet transplantation will allow further insights in this area.

There is now definite proof for the fact that islet transplants whether with a kidney or after a kidney graft may lead to insulin independence for many months and even years which may be defined as full success. However, also with a partial success (which means that in addition to the transplanted islets there is still the need for additional exogenous insulin supplements per day) the basic situation for the patient has definitely changed. The daily blood glucose excursions now are more stable, hypoglycemic attacks are abolished and due to the better overall metabolic situation also the risk of late complications may be lower.

For the moment, there is a challenge to develop still better immunosuppressive regimen to increase the number of islets from one gland and to learn from further transplants, and to further explore how the overall results can be optimized and sustained in a type of treatment which in principal offers so many advantage for the diabetic patient. A final remark should address the relative ease and safety of the islet transplant procedure:

Until now according to the International Islet Transplant Registry islet transplantation itself is a minor and safe procedure, it can be performed in local anesthesia via a percutaneous cannulation of a portal vein branch under x-ray control. With pure islet suspensions neither vein thrombosis nor increase of portal pressure have been observed. Three cases of death several weeks after islet transplantation due to lung embolism or cardiac infarction are apparrently not attributed to islet transplantation itself.

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