Risk of Glucose Intolerance and Diabetes in Hemipancreatectomized Donors Selected for Normal Preoperative Glucose Metabolism

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OBJECTIVE — Hemipancreatectomy (HPx) for the purpose of organ donation has been associated with a 25% risk of developing abnormal glucose tolerance or diabetes in the year after surgery. Since 1997, the University of Minnesota has imposed criteria to prevent potential donors with clinical features associated with an increased diabetes risk from undergoing HPx. We recently assessed glucose tolerance in hemipancreatectomized donors selected since the adoption of the new criteria to determine whether the risk of developing abnormal glucose tolerance was reduced below the 25% rate previously demonstrated.

RESEARCH DESIGN AND METHODS — Individuals who underwent HPx for the purpose of pancreas donation between 1997 and 2003 were contacted and interviewed about their health status. Those not taking diabetes medications were invited to undergo an assessment of their glucose tolerance.

RESULTS — Successful contact was made with 15 of 21 donors who underwent HPx during this period. Two donors reported use of oral diabetic medications and were not studied further. Of the remaining 13, 2 had impaired fasting glucose (fasting blood glucose 100–125 mg/dl), 1 had impaired glucose tolerance (2-h postglucose load blood glucose 140–199 mg/dl), and 3 displayed both. One donor met the diagnostic criteria for diabetes. Six donors had normal glucose values.

CONCLUSIONS — Despite the use of stringent criteria to exclude those at risk for developing abnormalities in glucose metabolism, 43% of healthy humans who underwent HPx between 1997 and 2003 have impaired fasting glucose, impaired glucose tolerance, or diabetes on follow-up. The current preoperative criteria are insufficient to predict those who will develop abnormal glucose metabolism after HPx.

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G lycemic control has long been known to play a critical role in the development of the complications of diabetes. Since the results of the Diabetes Control and Complications Trial (DCCT) first demonstrated that intensive efforts to lower glycemia resulted in a reduction in the rate at which subjects with type 1 diabetes developed microvascular complications (1), clinicians and their patients have attempted to normalize glucose control through many different therapeutic modalities. Exogenous insulin has been used to achieve target glycemia almost universally in the treatment of patients with type 1 diabetes, but the risk of developing severe hypoglycemia has become a limiting factor for many (2). Pancreas transplantation offers an alternative for selected patients with diabetes who seek to achieve normal levels of glycemia without periodic hypoglycemia.

During 2004, >1,400 pancreas transplants were performed in the U.S. (3). The vast majority of these transplants were done using deceased donor organs. However, some centers, including our own, have considered using living donors in situations in which improved outcomes over the use of a deceased donor organ might be expected. Such situations could include the presence of a nondiabetic HLA-identical sibling, a recipient with high panel-reactive antibody levels, or associated morbidities that predict a high risk of mortality while the recipient is on the waiting list.

At the University of Minnesota, the use of living donors in pancreas transplantation dates back to 1977 (4). In this procedure, the distal half of the pancreas is removed from a living donor and placed within the pelvis of the diabetic recipient. Although outcomes for the recipient are at least equivalent to those achieved with a deceased donor organ and perhaps improved for those patients with high panel-reactive antibody levels that prevent an optimal tissue match (4), 25% of the donors were previously found to have glucose intolerance or frank diabetes (non–insulin-dependent) 1 year after hemipancreatectomy (HPx) (5). In addition, even donors with normal glucose tolerance were noted to experience a modest increase in blood glucose and a reduction in insulin and glucagon secretion ≥1 year after HPx (6). Because of these findings, the University of Minnesota changed the criteria used to select hemipancreas donors in 1997 to exclude those with clinical or metabolic features that may be associated with the future development of diabetes.

In this report, we examine the metabolic outcomes in hemipancreatectomized donors selected because they appeared to be at low risk for developing diabetes. Our study was designed to test the hypothesis that the implementation of the revised University of Minnesota criteria would reduce risk of development of abnormal glucose tolerance to less than

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Table 1—*Exclusion criteria used in selecting human donors to undergo HPx for the purpose of organ transplantation at the University of Minnesota, 1997–present*

Absolute exclusion criteria
1. History of type 2 diabetes in any first-degree relative (parent, sibling)
2. History of gestational diabetes in the proposed donor
3. Additional first-degree relative with type 1 diabetes (other than proposed recipient)
4. BMI >27 kg/m^2
5. Age >50 years
6. Age of donor <10 years greater than age of diagnosis of type 1 diabetes in proband
7. Any glucose value >150 mg/dl during an oral glucose tolerance test
8. A1C value >6%
9. Glucose disposal rate <1.0% during intravenous glucose tolerance test
10. Presence of elevated titer of islet cell autoantibodies (ICA)

Relative exclusion criteria
1. Basal, fasting insulin values >20 μU/ml (as marker of insulin resistance)
2. Acute insulin response to glucose, arginine, or glucose potentiated arginine <300% of basal insulin
3. Clinical evidence of insulin resistance (e.g., polycystic ovary syndrome)
4. Evidence for >1 autoimmune endocrine disorder (thyroid, adrenal, pituitary, gonads)

the rate of 25% reported using the previous criteria (5). We hoped that our observations would be of benefit to pancreas transplant programs considering the development of a living donor program. Further study of this unique population of healthy hemipancreatectomized humans also provides us with a rare opportunity to gain insight into the effect of β-cell mass reduction on the maintenance of normal glucose tolerance.

RESEARCH DESIGN AND METHODS

Donor selection
In December 1996, the University of Minnesota pancreas transplant program revised the selection criteria for living hemipancreas donors to preclude those believed to be at greatest risk for the development of diabetes from undergoing the procedure (7). The revised criteria are shown in Table 1.

Operative procedure
The operative procedure for HPx has been described in detail elsewhere (4). The procedure results in resection of the distal pancreas where it overlies the portal vein (50% resection), leaving the pancreatic head and proximal tail intact in the donor. More recently, surgeons have made the pancreas transection slightly to the left of the portal vein, resulting in a 40% pancreatectomy.

Follow-up studies
In 2006, all donors who underwent HPx between January 1997 and December 2003 were contacted by phone to ascertain their willingness to participate in a study. This contact was followed by a written explanation of the study. All donors contacted were interviewed on the phone about their current health status. Donors who were not taking diabetes medications were asked to undergo the metabolic evaluation detailed below. This protocol was approved by the University of Minnesota Institutional Review Board, and subjects gave written informed consent before their participation.

The metabolic evaluation was done after the donors had followed a diet consisting of at least 150 g carbohydrate per day for 3 days. On the day of the study, donors presented to the University of Minnesota General Clinical Research Center or to a local clinic in the morning after a 12-h fast. Oral glucose tolerance tests were performed by administering 75 g glucose (Cardinal Health, McGaw Park, IL) orally over a 5-min period. Blood samples were obtained for later determination of serum glucose levels at −10 and −5 min before glucose was administered and at 30, 60, 90, and 120 min after the administration of the glucose load. Fasting samples were also obtained for A1C, insulin, and anti-GAD antibody. Serum glucose was measured on an Analog glucose analyzer system (Analox Instruments, Hammersmith, London, U.K.). Serum insulin was measured using chemiluminescence (Immulite 2000). Samples for anti-GAD antibody levels were analyzed using an immunoradiometric assay (Associated Regional and University Pathologists, Salt Lake City, UT) (8). Blood samples obtained in clinics located away from the University of Minnesota were sent overnight to the University of Minnesota Medical Center for analysis.

Data analysis
Unless otherwise indicated, results are given as means ± SD. The American Diabetes Association criteria for the diagnosis of diabetes, impaired glucose tolerance, and impaired fasting glucose (9) were used to categorize glucose tolerance in donors. The differences between groups were analyzed by two-tailed statistics using the Mann-Whitney test for unpaired data and the Wilcoxon signed-rank test or Student's *t* test for paired data. Correlation was determined using the Spearman rank order correlation coefficient. *P* < 0.05 was considered statistically significant.

RESULTS — Twenty-one individuals underwent HPx for the purpose of organ donation at the University of Minnesota between January 1997 and December 2003. Preoperatively, 17 were noted to have normal fasting glucose values, normal glucose tolerance, normal insulin secretory responses, and an unremarkable personal and family medical history. One individual with a mother who had type 2 diabetes, one individual with a BMI >27 kg/m^2, and three individuals with a single glucose value between 150 and 199 mg/dl on the preoperative oral glucose tolerance test were allowed to serve as hemipancreas donors because they perceived their own risk of donation to be less than the recipient's risk of foregoing the transplant.

On follow-up, six donors could not be located. On telephone interview, two reported using a single antidiabetic agent (metformin in one and pioglitazone in the other). The remaining 13 donors completed the follow-up metabolic evaluation. Abnormalities in glucose metabolism were identified in 7 of 13 (54%) reporting for follow-up evaluation (Fig. 1). Table 2 shows the preoperative and postoperative results in the 13 hemipancreatectomized donors who were studied.

In the 13 donors who participated in the metabolic evaluation, no differences were noted with respect to age at donation (47 ± 6 vs. 41 ± 14 years) or months since donation (60 ± 10 vs. 55 ± 12 months) between those with normal versus abnormal glucose tolerance at follow-up. Despite the elevated postoperative serum glucose levels in those with abnormal glucose tolerance, fasting serum insulin values were similar to those measured in the donors with normal postoperative glucose tolerance (5.3 ± 3.0 vs. 6.4 ± 3.6 μU/ml, *P* = 0.58). There was a trend toward a higher BMI in the group with ab-
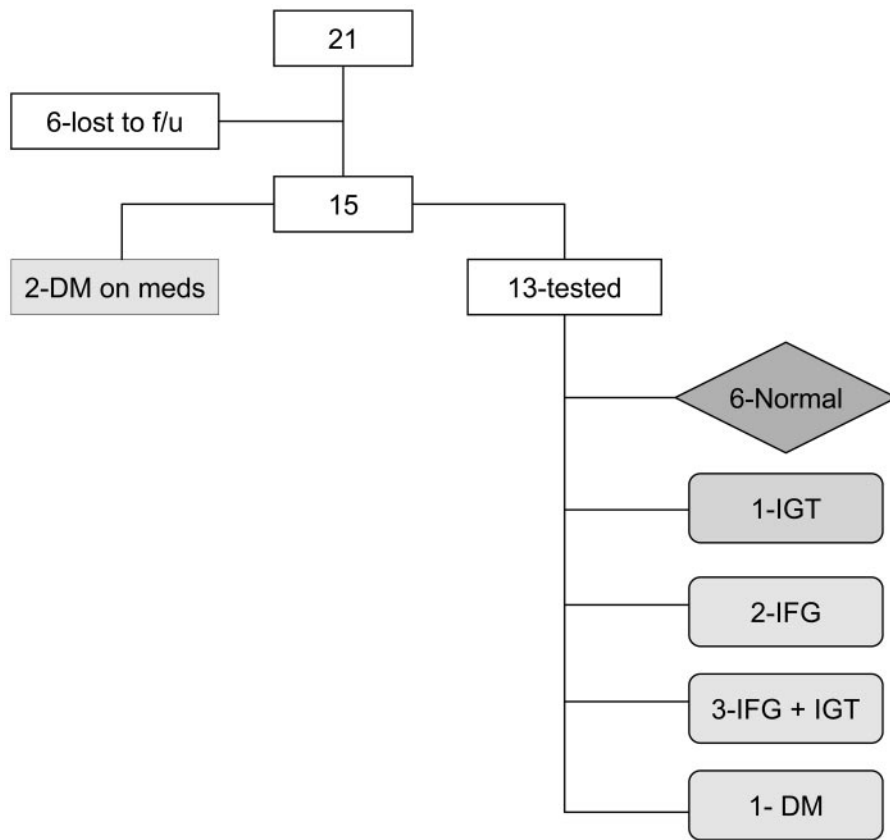
Figure 1—*Status of hemipancreatectomized human donors on follow-up. Human donors were contacted between 3 and 10 years after undergoing HPx for the purpose of organ donation.*

>27 kg/m², and two of the three subjects who were allowed to donate despite achieving a glucose value between 150 and 199 mg/dl on the preoperative oral glucose tolerance tests showed abnormal glucose tolerance on follow-up. HLA typing data are available for all 15 donors contacted. Only two donors were heterozygous for the DRB1*3/4-DQB1*0302 (DQ8) genotype that confers higher risk for type 1 diabetes (10). One of these donors had impaired fasting glucose, and the other was taking an oral antidiabetic agent on follow-up. Table 3 summarizes the characteristics and variables of the 13 hemipancreatectomized donors studied.

CONCLUSIONS — The purpose of this study was to determine whether the application of stringent metabolic criteria during the selection of living pancreas donors would reduce the risk of development of abnormal glucose tolerance after HPx to below the 25% rate reported previously (5). Whereas four of the current donors who developed abnormalities in glucose tolerance were allowed to donate despite failing to meet all of the selection criteria, five of the donors who met the strict criteria developed to minimize the risk of post-HPx disturbances in glucose tolerance had either been given a diagnosis of diabetes by their primary physician or had abnormal glucose tolerance on a standard glucose tolerance test 3 to 10 years after organ donation. The preoperative criteria, which are the gold standard in the pretransplant workup for potential

normal glucose tolerance compared with group with normal glucose tolerance both before (26.1 ± 3.6 vs. 23.6 ± 2.2 kg/m², $P = 0.14$) and after (26.4 ± 4.4 vs. 23.5 ± 2.4 kg/m², $P = 0.23$) donation; however, these differences were not statistically significant. An increase in weight over time did not correlate with higher fasting glucose values in these 13 donors (Spearman $r^2_s = 0.21$, $P = 0.28$). All subjects had immeasurable levels of GAD. The subject who was selected despite a family history of diabetes, the subject allowed to donate despite having a BMI

Table 2—*Preoperative and postoperative results in 13 hemipancreatectomized donors studied*

Donor	Fasting glucose (mg/dl)		2-h postprandial glucose (mg/dl)		A1C (%)		Fasting insulin (μU/ml)	
	Before	After	Before	After	Before	After	Before	After
1	82	110	98	167	NA	5.8	9	10
2	83	101	73	118	5.1	5.7	7	3
3	80	127	90	266	NA	6.3	4	11
4	NA	93	NA	122	NA	4.8	NA	9
5	85	92	NA	188	4.5	6.6	3	8
6	80	81	NA	101	NA	5.3	3	5
7	84	79	123	NA	NA	5.5	NA	6
8	87	103	NA	152	5.7	6.3	6	1
9	93	92	69	81	5.1	5.6	9	8
10	83	94	NA	118	4.8	5.4	3	1
11	78	91	NA	138	5.0	5.7	3	3
12	88	109	NA	NA	5.4	5.9	NA	7
13	76	116	56	145	5.5	5.8	1	5
Average	83 ± 5	100 ± 14*	77 ± 17	155 ± 62†	5.1 ± 0.4	5.9 ± 0.4*	4.8 ± 2.8	5.5 ± 3.6

Data are means ± SD unless otherwise indicated. *$P < 0.01$; †$P < 0.05$. NA, not applicable.

Table 3—*Characteristics and variables of 13 hemipancreatectomized donors*

Donor	Year of surgery	Surgeon (A, B, C, D, E)	Preoperative BMI (kg/m^2)	ICA (titer)	Related/ Unrelated	Time to follow-up (months)
1	1999	A,B	31.8	<4	R	82
2	2000	C	27.3	<4	U	63
3	1998	C	20.2	<4	U	87
4	1998	C	NA	NA	R	87
5	2000	B	26.0	<4	U	67
6	2000	C	21.6	NA	U	70
7	1997	E	21.7	NA	R	106
8	2000	D	27.2	<4	U	64
9	2002	E	26.1	<4	R	50
10	2000	D	22.4	<4	U	70
11	2000	C	23.1	NA	R	75
12	1997	D	25.7	<4	R	115
13	2003	D	23.8	<4	U	39
Average			24.7			75

ICA, islet cell antibody; NA, not applicable.

hemipancreas donors (11), were not successful in identifying donors at risk for the development of diabetes and impaired glucose tolerance after β-cell mass reduction. Thus, the risk for postdonation glucose intolerance cannot be completely eliminated even with the application of these narrow criteria. Our findings raise concerns about the expanded use of living donors in pancreas and islet transplantation programs.

The metabolic effects of HPx for the purpose of organ donation have been studied previously. Bolinder et al. (12) were the first to demonstrate that fasting blood glucose concentrations were higher after hemipancreas donation than they were before surgery. This observation was quickly followed by that of Kendall et al. (5) who noted that 25% of healthy individuals providing a hemipancreas to a first-degree relative with type 1 diabetes developed abnormal glucose tolerance or diabetes within 1 year of surgery. Subsequent work demonstrated that HPx is associated with reductions in glucose, arginine, and glucose-potentiated arginine-induced insulin secretion (6) as well as an increase in serum proinsulin concentrations (13). β-Cell mass reduction has been presumed to be the cause of these metabolic abnormalities after HPx. This assumption is supported by recent work in humans in which β-cell mass was found to be reduced in an autopsy study of individuals with type 2 diabetes (14), and the magnitude of the reduction appeared to have a curvilinear relationship with fasting glucose (15). These previous studies, as well as the current study, sup-

port the hypothesis that a deficit in β-cell mass contributes to the pathogenesis of hyperglycemia and further emphasize the need to maintain β-cell mass to maintain normal glucose tolerance.

Interesting new observations suggest that a reduction in β-cell mass may also reduce glucose disposal in the peripheral tissues (16). In dogs studied by Matveyenko et al. (16), a 50% pancreatectomy resulted in impaired fasting glucose or impaired glucose tolerance, a reduction in the pulse mass of glucose-induced insulin secretion, a decrease in hepatic insulin extraction, and a 40% reduction in insulin-stimulated glucose disposal. The findings raise the provocative possibility that β-cell mass reduction may not only have effects on insulin secretion that are important in the pathogenesis of type 2 diabetes but may also play a role in the impaired insulin action present in this disorder in the dog. Whether β-cell mass has an effect on insulin action in humans is not as clear. Hemipancreatectomized human donors have been found to have normal insulin sensitivity as measured by the hyperinsulinemic-euglycemic clamp and by the frequently sampled intravenous glucose tolerance test (17), but the effect of β-cell mass reduction on the pulse mass of insulin secretion and on hepatic extraction has not been examined.

Why one group of donors went on to develop abnormal glucose tolerance whereas another group maintained normal glucose tolerance is not clear from our data. There was a trend toward higher BMIs among those who developed abnormal glucose tolerance, but this difference

was not statistically significant. In a previous study, obesity was more related to the development of diabetes or glucose intolerance in donors after HPx than family history of type 2 diabetes or age (18). In our cohort, the stringent criteria of 1997 recommended that no one with a BMI >27 kg/m^2 be allowed to provide a hemipancreas to a recipient with type 1 diabetes, although one donor with a BMI of 30.8 was permitted to undergo the procedure. Because nearly half of our relatively lean cohort were found to have abnormal glucose tolerance on follow-up, it is possible that even BMI <27 kg/m^2 is still too high to ensure the maintenance of normal glucose homeostasis in the setting of β-cell mass reduction.

Nine of the donors in our group were not biologically related to the recipient of their hemipancreas. Five of these individuals are known to have developed abnormal glucose tolerance on follow-up. It is interesting that the proportion of first-degree relatives known to have developed diabetes or abnormal glucose tolerance (4 of 12) is actually lower than the proportion in those unrelated to their recipient (5 of 9), suggesting that a family history of diabetes may not be predictive of abnormal glucose tolerance after HPx.

The present study has certain limitations. Six of the 21 donors operated on between 1997 and 2003 were lost to follow-up and as a result we lack a complete description of the outcomes in this patient group. However, even if all six of these donors were found to have normal glucose tolerance, 43% (9 of 21) of those undergoing HPx during this period were

found to have abnormal glucose tolerance on follow-up. Our conclusion that the new criteria do not successfully exclude subjects at risk for developing abnormal glucose tolerance after HPx still stands.

All of these donors underwent a surgical HPx, but it is unclear whether small differences in technique among surgeons could play a role in donor outcomes. Determining the exact percentage of islet tissue removed is difficult because of the heterogeneous nature of the pancreas. However, Robertson et al. (18) found that probable differences in β-cell mass between donated and retained pancreatic segments did not appear to influence clinical outcomes.

In summary, our results indicate that the development of abnormal glucose tolerance is a risk inherent to HPx. Despite the use of stringent criteria to exclude those at risk for developing abnormalities in glucose metabolism, 43% of healthy humans who underwent HPx between 1997 and 2003 at the University of Minnesota (60% of those who reported for examination) had impaired fasting glucose, impaired glucose tolerance, or diabetes on follow-up. Given our inability to accurately predict those who will develop abnormalities in glucose tolerance and the fact that, in most circumstances, whole pancreas transplantation from a deceased donor would be comparably effective (4), we conclude that living donors should be used only in very special circumstances. Such circumstances may arise in the presence of an HLA-identical sibling or a recipient with high panel-reactive antibody levels, which would make tissue matching very difficult, or associated morbidities that predict a high risk of recipient mortality while on the waiting list. As in the case of all living organ donation, the donor should always be expected to experience consequences. In the future, preoperative genotyping might be useful in excluding those potential donors with the greatest risk for developing diabetes, but until then our data demonstrate that even subjects with nor-mal preoperative metabolic characteristics are at significant risk of developing abnormalities in glucose tolerance after HPx.

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