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Quality of Life After Islet Transplantation

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This study analyzed quality of life in patients with type 1 diabetes that received islet transplantation. Twenty-three subjects were followed over 3 years. In addition to an interview, patients self-completed two standardized psychometric questionnaires, HSQ 2.0 and DQOL, before and after transplant, and scores were compared. Analysis was also adjusted for potential "confounders" such as graft dysfunction, insulin therapy and adverse events. DQOL: the Impact score significantly improved at all time points of the follow-up; satisfaction and worry scales also significantly improved at selected time points. Longitudinal analysis demonstrated that reintroduction of insulin had a negative effect on all three scales, but significant improvement in Impact scale persisted even after adjusting for this factor. HSQ 2.0: only the Health Perception scale preliminarily showed significant improvement at most time points. Longitudinal analysis showed loss of significance when insulin therapy was considered. Other scores were improved only at selected time points or not affected. Bodily pain scale showed deterioration at selected times. Interview: glucose control stability, not insulin independence, was reported as the main beneficial factor influencing QOL. In conclusion, islet transplantation has a positive influence on patients' QOL, despite chronic immunosuppression side effects. Re-introduction of insulin modifies QOL outcomes.

Key words: Insulin, islets, quality of life, transplantation

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Introduction

Islet allotransplantation with steroid-free (1–6) or steroid-sparing immunosuppression (minimal dose of steroids for islet after kidney transplant recipients) is considered a therapeutic option for selected patients with type 1 diabetes, leading to improvement of glycemic control in the absence of hypoglycemia. While short-term results are excellent (insulin-free patients at 1 year 79%), graft function deteriorates with time, with patients returning to insulin administration (7). The assessment of quality of life (QOL) is a fundamental endpoint to evaluate the efficacy of clinical trials. The use of general-health and disease-specific psychometric measures has been validated in patients with type 1 diabetes (8–11).

We analyzed QOL in patients that underwent islet transplantation at our center. QOL was assessed by standardized tests at selected intervals after transplantation and compared to baseline. Individuals in our study belong to a group of patients that experience severe hypoglycemic episodes or have hypoglycemia unawareness. These are fundamental inclusion criteria, since it is accepted that risks linked to chronic immunosuppression must be outweighed by good glycemic control, as achieved through successful islet transplantation.

We sought to define differences that depended on transplant success, length of insulin-free life, return to insulin therapy and side effects. Our analysis shows QOL improvement after transplantation.

Materials and Methods

Psychometric instruments

Two standardized psychometric instruments and a structured interview were used to get a comprehensive evaluation of the patients' QOL, as part of a general psychological evaluation. The standardized psychometric tests are questionnaires that patients self-complete. The tests utilized are the Health Status Questionnaire, HSQ 2.0 and the diabetes quality of life (DQOL). The former is a generic instrument that assesses health-related QOL in general populations (12, 13) and the latter is disease-specific (8). Both questionnaires have different scales and a numeric score for each scale between 0 and 100 (from worst to best).

The HSQ 2.0 is derived from the Medical Outcomes Study 36-Item Short Form (SF-36) Health Survey. The SF-36 is widely used in clinical trials (14–18), and was constructed to achieve standards of precision necessary for group comparisons in eight conceptual areas. It was formulated to yield a profile useful in understanding the health burden of chronic diseases and the effect of treatments on general health status. HSQ 2.0 has the same 36 items (questions) and 8 scales as the SF-36 and it uses the same scoring algorithm, except for bodily pain, and therefore has excellent consistency and reliability (9, 13). Additionally, the HSQ 2.0 includes three items that screen for dysthymia and major depression as well as an index of health status change, and demographic items that assess factors that affect functioning and well-being.

The HSQ 2.0 has the following eight scales: health perception, physical functioning, role limitation-physical health, role limitation-emotional problems, social functioning, mental health, bodily pain and energy/fatigue.

The DQOL questionnaire was originally designed to measure the patient's personal experience of diabetes care and treatment in the Diabetes Control and Complications Trial and its validity in patients with type 1 diabetes mellitus has been confirmed (8). It covers a broad range of issues relevant to diabetes and its treatment such as satisfaction with treatment, impact of treatment, worry about the future effects of diabetes and social/vocational issues. The questionnaire comprises 46 items with a 5-point Likert-type scale (declarative statements, where the subject is asked to indicate how much he/she agrees from 1 to 5) (19).

Research study design

A total of 330 HSQ 2.0 and DQOL questionnaires were retrospectively analyzed. The questionnaires were filled by 23 patients, between November 1996 and November 2004, QOL scores were initially obtained at time 0 (screening), on the waiting list, 3 and 6 months after the first infusion and 3, 6, 9, 12, 18, 24, 30 and 36 months after protocol completion; if applicable, 3, 6, 9 and 12 months post-supplemental infusion or after withdrawal from the trial.

Most patients (n = 18) required two infusions to complete the protocol and reach insulin independence, but in three cases one infusion sufficed. A third (supplemental) infusion was performed in five patients that resumed insulin therapy. Two patients were not completed at the time of the analysis and only results of the questionnaire filled after the first infusion were compared to pre-transplant. Patients included in this study received either islet alone (n = 18) or islet after kidney transplantation (n = 5).

Maintenance immunosuppression was with tacrolimus (target plasma level: 4–6 ng/mL) and rapamycin (target plasma level: 12–15 ng/mL for first 3 months, then 10–12 ng/mL). A fraction of the patients (previous kidney transplant recipients) were on minimal doses of steroids (less than 5 mg/day of prednisone or methyl-prednisolone). Four patients in the islet alone protocol were switched to MMF due to tacrolimus toxicity. None of these patients have had severe hypoglycemia after islet transplantation.

Patient population

Twenty-three patients, 10 males and 13 females, that completed the questionnaires at least at two time points during the follow-up were selected for this retrospective study. At enrollment, the mean age of patients was 41 $\pm$ 9 years and the duration of diabetes was 28 $\pm$ 13 years; diabetes complications were retinopathy in 15, neuropathy in 7, nephropathy in 8 and none in 7 patients. Twenty-two patients were white nonHispanic and one Hispanic. Nine patients attended college, six have an Associate/Bachelor degree and six a post-graduate degree.

Interview

In addition to the compilation of the questionnaires patients underwent an interview with the psychologist. Parameters assessed were as follows: satisfaction with the outcome of islet transplantation, alertness, mood, affect, psychomotor activity, speech, attention/concentration, memory, thought content and process, insight/judgment, presence of dysphoria, energy level, appetite, motivation, interest and sleep pattern. Every patient was specifically asked to describe the most significant benefit from islet transplantation.

Statistical analysis

Preliminary analysis of the QOL scores from baseline was conducted with paired *t*-tests. For each outcome measure, each post-baseline time point was compared with baseline for the preliminary analysis. Paired *t*-test results are illustrated in Table 1.

We then performed an analysis using methods more appropriate to the longitudinal nature of the data collected in this study design. For each of the 11 outcome measures under consideration, we performed a repeated measures analysis of the data using linear mixed model regression.

This method of analysis generalizes linear regression techniques to allow for repeated observations by taking into account the correlation that exists within observations on the same subject to more appropriately estimate variances used for the various tests of significance. Using this approach, we are able to simultaneously estimate differences from baseline at each time point post-baseline while appropriately accounting for the correlation of outcomes within each patient. Correlation within subject is modeled by incorporating a random intercept term to the model. Thus, the intercept (which corresponds to baseline value of the outcome under consideration) is assumed to vary randomly among patients following a normal distribution with some overall population mean and fixed variance. In addition to the effect of time on the QOL outcome measures, we were able to incorporate other factors into the regression models, in order to adjust for potential confounding factors such as insulin therapy (on/off), signs of graft dysfunction regardless of insulin therapy and the presence of adverse events. Thus for each of the 11 outcome measures, we conducted an analysis using linear mixed models regression that considered the change in the outcome measure from baseline as the dependent variable and time point, insulin therapy, signs of graft dysfunction and the presence of adverse events as potential explanatory variables. This analysis included data collected at times 0, on the waiting list and 3, 6, 9, 12, 18 and 24 months after protocol completion (Table 2). In total, the longitudinal model used 132 observations taken from 23 subjects for assessing the effect of all time points post-baseline (where each corresponds to estimating changes from baseline) as well as insulin, adverse events and graft dysfunction.

In longitudinal models, as with cross-sectional analysis, power for estimating any of the effect sizes modeled with covariates depends on many factors such as sample size, number of covariates, measurement variations, meaningful differences to be detected (the hypothesized effect size) and type 1 error. Additionally, for longitudinal models, power is affected by the number of observations per subject, as well as the degree and direction of correlation among observations within the same subject. Having positive correlation within observations from the same subject generally decreases the required sample size when estimating changes in outcome over time. In cross-sectional studies, having 10 observations for every covariate effect that we wish to estimate is generally considered to be adequate for estimation of the effects. Since we have at least that ratio of observations to parameters in our model, and given the correlated nature of the longitudinal data for this analysis, this study is sufficiently powered to estimate and assess the significance of the effects in the model, particularly the effects corresponding to changes in outcome from baseline at each follow-up time point.

Definitions

Insulin therapy. Insulin restarted chronically (at any dose) post-islet transplant.

Graft dysfunction. Fasting glucose >140 mg/dL and/or 2 h post-prandial glucose >180 mg/dL in three or more occasions in 1 week.

Occurrence of adverse events. The presence of any adverse event (grades 3 and 4, according to NCI criteria) or serious adverse event, as defined by FDA (requiring hospitalization, unexpected, causing disabilities), at the time of QOL assessment and in the three preceding months.

Table 1: T-test mean score changes at the indicated time points (Score: 1–100)

	DQOL			HSQ 2.0							
	Satisfaction [Baseline: 73 ± 13.94]	Impact [Baseline: 69.1 ± 9.96]	Worry [Baseline: 71 ± 15.83]	Health perception [Baseline: 64.9 ± 17.52]	Physical function [Baseline: 94.1 ± 8.48]	Role Limit-physical health [Baseline: 94.6 ± 18.4]	Role Limit-emotional problems [Baseline: 94.2 ± 19.26]	Social function [Baseline: 91.9 ± 13.9]	Mental health [Baseline: 85.7 ± 7.32]	Bodily pain [Baseline: 90.1 ± 12.74]	Energy/ fatigue [Baseline: 72.4 ± 15.87]
Waiting List	9.66 ($p < 0.001$)	3.97 ($p = 0.036$)	ns	5.06 ($p = 0.021$)	ns	ns	ns	ns	5.25 ($p = 0.001$)	ns	7.03 ($p = 0.019$)
3 mo post-first infusion	ns	14 ($p = 0.050$)	ns	ns	ns	ns	ns	ns	ns	ns	ns
6 mo post-completion	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	5 ($p < 0.001$)
3 mo post-completion	8.22 ($p < 0.001$)	10.28 ($p < 0.001$)	12.39 ($p = 0.003$)	12.72 ($p = 0.001$)	ns	ns	ns	ns	ns	ns	ns
6 mo post-completion	12.76 ($p = 0.001$)	14.41 ($p = 0.001$)	13.47 ($p = 0.004$)	12.12 ($p = 0.05$)	ns	ns	ns	ns	ns	ns	ns
9 mo post-completion	ns	13.29 ($p < 0.001$)	14.86 ($p < 0.001$)	ns	ns	ns	ns	ns	ns	ns	ns
12 mo post-completion	13.06 ($p < 0.001$)	15.53 ($p < 0.001$)	13.73 ($p = 0.003$)	16.06 ($p = 0.003$)	ns	ns	ns	ns	ns	ns	ns
18 mo post-completion	10.18 ($p = 0.03$)	15.73 ($p < 0.001$)	20.82 ($p < 0.001$)	12.91 ($p = 0.03$)	ns	ns	ns	ns	3.27 ($p = 0.031$)	ns	ns
24 mo post-completion	ns	12.89 ($p = 0.033$)	ns	ns	ns	ns	ns	ns	ns	ns	ns
30 mo post-completion	ns	19.67 ($p = 0.02$)	ns	20.33 ($p = 0.017$)	ns	ns	ns	ns	ns	ns	ns
36 mo post-completion	ns	22 ($p = 0.013$)	13.67 ($p = 0.03$)	17.67 ($p = 0.007$)	ns	ns	ns	ns	ns	ns	ns
3 mo post-suppl infusion	ns	ns	ns	ns	ns	ns	ns	ns	−18.4 ($p = 0.038$)	ns	ns
6 mo post-suppl infusion	ns	ns	ns	ns	ns	ns	ns	ns	−11.8 ($p = 0.032$)	ns	ns
9 mo post-suppl infusion	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
12 mo post-suppl infusion	ns	ns	ns	ns	ns	ns	ns	ns	−9.6 ($p = 0.024$)	ns	ns
Post-withdrawal	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns

Significant values are listed, ns = non-significant. Sample sizes corresponding to each time point were as follows: Baseline (n = 23) on waiting list (n = 16), 3 (n = 6) and 6 (n = 3) months after first infusion; 3 (n = 18), 6 (n = 17), 9 (n = 14), 12 (n = 16), 18 (n = 11), 24 (n = 9), 30 (n = 3) and 36 (n = 3) months post-protocol completion; 3 (n = 5), 6 (n = 5), 9 (n = 4) and 12 (n = 5) months post-supplemental infusion and post-trial withdrawal (n = 2).

Table 2: Longitudinal Analysis

	DQOL			HSQ 2.0							
	Satisfaction [Baseline: 73 ± 13.94]	Impact [Baseline: 69.1 ± 9.96]	Worry [Baseline: 71 ± 15.83]	Health perception [Baseline: 64.9 ± 17.52]	Physical function [Baseline: 94.1 ± 8.48]	Role Limit-physical health [Baseline: 94.6 ± 18.4]	Role Limit-emotional problems [Baseline: 94.2 ± 19.26]	Social function [Baseline: 91.9 ± 13.9]	Mental health [Baseline: 85.7 ± 7.32]	Bodily pain [Baseline: 90.1 ± 12.74]	Energy/ fatigue [Baseline: 72.4 ± 15.87]
Waiting list	9.62 (p = 0.009)	4.31 (p = 0.042)	ns	8.69 (p = 0.045)	ns	ns	ns	ns	4.44 (p = 0.030)	ns	ns
3 mo post-completion	ns	ns	ns	ns	ns	ns	ns	ns	ns	−23.22 (p = 0.003)	ns
6 mo post-completion	ns	7.57 (p = 0.029)	ns	ns	ns	ns	ns	ns	ns	−15.82 (p = 0.029)	ns
9 mo post-completion	ns	8.57 (p = 0.011)	ns	ns	ns	ns	ns	ns	ns	−17.38 (p = 0.017)	ns
12 mo post-completion	ns	9.38 (p = 0.002)	ns	ns	ns	ns	9.78 (p = 0.018)	ns	ns	ns	ns
18 mo post-completion	ns	11.61 (p = 0.0002)	14.63 (p = 0.0013)	ns	ns	ns	ns	ns	ns	ns	ns
24 mo post-completion	ns	8.77 (p = 0.004)	ns	ns	−8.32 (p = 0.036)	ns	ns	ns	ns	−16.70 (p = 0.009)	ns
Insulin therapy	−11.09 (p = 0.016)	−8.43 (p = 0.0007)	ns	−12.41 (p = 0.014)	−6.98 (p = 0.026)	ns	ns	ns	−4.85 (p = 0.039)	−13.53 (p = 0.008)	−10.35 (p = 0.047)
Adverse events	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
Graft dysfunction	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns

Significant values are listed, ns = non-significant.

Sample sizes corresponding to each time point were as follows: Baseline (n = 23) on waiting list (n = 16), 3 (n = 6) and 6 (n = 3) months after first infusion; 3 (n = 18), 6 (n = 17), 9 (n = 14), 12 (n = 16), 18 (n = 11), 24 (n = 9), 30 (n = 3) and 36 (n = 3) months post-protocol completion; 3 (n = 5), 6 (n = 5), 9 (n = 4) and 12 (n = 5) months post-supplemental infusion and post-trial withdrawal (n = 2).

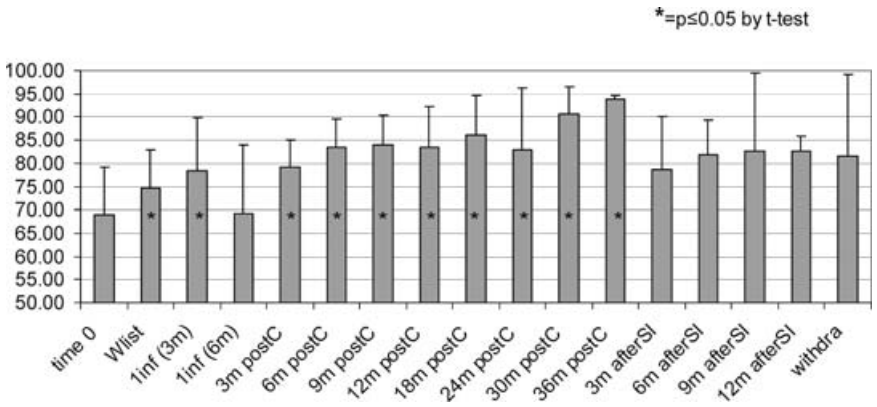

Figure 1: Representation of changes in the average scores of Impact Scale of the DQOL questionnaire at the indicated time points. Results are expressed as mean ±SD. Significant changes were determined by *t*-test and are represented by an asterisk.

Results

Initial evaluation of QOL

A preliminary analysis of scores collected at time 0 (during screening) was compared to subsequent scores with a paired *t*-test. The time points analyzed were as follows: on waiting list (n = 16), 3 (n = 6) and 6 (n = 3) months after first infusion; 3 (n = 18), 6 (n = 17), 9 (n = 14), 12 (n = 16), 18 (n = 11), 24 (n = 9), 30 (n = 3) and 36 (n = 3) months post-protocol completion; 3 (n = 5), 6 (n = 5), 9 (n = 4) and 12 (n = 5) months post-supplemental infusion and post-trial withdrawal (n = 2).

DQOL data are summarized in Table 1, expressed as baseline average ±SD, and average change in scores. All three scales (satisfaction, impact and worry) improved significantly at selected time points in the first 3 years; specifically, Impact score significantly improved at all time points after completion and approached significance 3 months after first islet infusion (Figure 1); Satisfaction score improved significantly 3, 6, 12 and 18 months post-completion, and Worry scale significantly improved at 3, 6, 9, 12, 18 and 36 months post-completion. None of the scores of the three scales improved significantly at any time point after supplemental infusion and after withdrawal from the trial.

Analysis of the scores of the *HSQ 2.0 questionnaire* showed that only the Health Perception score improved significantly in the first 3 years after protocol completion (except at 9 and 24 months) (Table 1). After supplemental infusion, Mental Health scale score appeared to deteriorate.

Longitudinal analysis

Results from the longitudinal regression models are illustrated in Table 2, and are expressed as estimated changes in outcome measure from baseline at each time point along with the associated p-values where statistically significant.

DQOL questionnaire score analysis showed (Table 2) statistically significant improvements in Impact at all time points except 3 months post-completion. Marginally significant improvement was seen when the scores obtained on the waiting list were compared to control values.

Satisfaction scale analysis showed significant improvement while on the waiting list, albeit no significant improvement was seen at any time point after transplantation. Analysis of scores in the Worry scale showed significant improvement at 18 months post-completion.

Importantly, independent of time, re-introduction of insulin therapy had a significant negative impact on Satisfaction and Impact scales. Overall, adverse events and signs of graft dysfunction (regardless of insulin therapy) did not negatively alter the scores of all three scales.

HSQ 2.0 score analysis showed that (Table 2) Health Perception was not significantly improved at any time point in the first 2 years post-transplant, and only marginally improved on the waiting list. Physical Function was not affected at any time point except at 24 months post-completion, where a significant deterioration was observed. Role Limitation-Physical Health (as well as Social Function and Energy/Fatigue) was unaffected at all times.

Role Limitation/Emotional Problems was improved at 12 months post-completion. Mental Health was not affected at any time, except on the waiting list, where improvement was observed. Bodily Pain score showed significant deterioration at 3, 6, 9 and 24 months post-completion.

Insulin therapy had a global negative impact of statistical significance on Health Perception, Physical Function, Mental Health, Bodily Pain and marginal negative impact on Energy/Fatigue. As in the case of DQOL score analysis, adverse events and graft dysfunction did not significantly influence the overall results in any of the scales.

Discussion

In this study, we used psychometric instruments to evaluate QOL in a cohort of patients that underwent islet

transplantation. Results of an initial analysis showed significant improvement in the Impact scale of DQOL at all time points in the 3 years of follow-up post-islet transplantation. The Worry scale was improved in the first 18 months, as was Satisfaction scale (with the exception of the 9 months time point). Also, the score that addresses the patient Health Perception in the HSQ 2.0 was significantly higher at most of the time points in the first 3 years. This means that when each patient was compared to himself, with time post-islet transplant as the only variable, islet transplantation showed an overall beneficial influence on the health-related quality of life in the first 3 years. Worry about illness was lower than before, the impact of islet transplant as a treatment was positive on the patient, and general perception of health was improved. Interestingly, the Impact scale was already marginally improved and the Satisfaction scale was significantly improved on the waiting list. These outcomes could be related to the high expectations and the psychological positive effect of waiting for a transplant. It is often difficult to reach statistical significance when performing comparisons with very small sample sizes, and statistical significance from analytical methods of comparison would likely require extremely large differences. This might be the explanation as to why, at selected time points, the initial comparisons made in our preliminary analysis of the data using paired *t*-test (illustrated in Table 1) were not able to reach statistical significance. However, these comparisons were only meant as preliminary analysis of the data, and a more appropriate repeated measures analysis of the longitudinal data was conducted as described in the statistical methods section.

When we analyzed in greater detail the scores of our patients' questionnaires, using a longitudinal statistical analysis of the first 2 years post-transplant, and additionally considering factors that could represent statistical 'confounders', we found that, albeit somehow reduced, the overall benefit persisted. Confounders significant for any of the outcomes considered included return, at any time point, to insulin therapy; and any important health problem likely related to immunosuppressive therapy (adverse events grade 3 and 4 NCI) in the 3 months before the test. Indeed, when considering the occurrence of an adverse event and, most importantly, reinstatement of insulin therapy, we found that these factors influenced the outcome, independently of the time, as most of the scores lost statistical significance; one of the scales (bodily pain in HSQ 2.0) showed significant deterioration in the first 2 years after islet infusion.

Impact was the only scale of the DQOL questionnaire that appeared not influenced by these factors, after 3 months post-completion and onwards. The positive influence ('Impact') of islet transplantation on the life of these patients remains, therefore, independent of the events that follow the transplant, such as restarting insulin therapy and experiencing adverse events.

Satisfaction scale and worry scale of DQOL and Health Perception scale of HSQ 2.0 lost their significance, when corrected for insulin therapy and presence of adverse events, showing that these very factors had a confounding role on the benefit observed in the initial analysis, where time post-transplantation was the only variable considered.

The day of the compilation of the questionnaires, patients met the psychologist for a verbal evaluation of the personal satisfaction about different aspects of life after islet transplantation. During these conversations, the most frequently reported beneficial effect of islet transplantation was stability of glucose control and absence of hypoglycemic episodes resulting in a feeling of independence and reliability, not experienced before the transplant. Also, transplanted patients reported that being part of and helping research for future generations, was worthy the adverse events that they tolerated. In this colloquial analysis, being able to remain insulin-free was not, in general, indicated as a fundamental element in the patients' well-being, even if this was mentioned as desirable.

The apparent discordance between the results of the two standardized instruments (DQOL and HSQ 2.0) and the verbal communication with a professional in the evaluation of QOL, when insulin therapy was specifically examined, may be explained as follows: the interview looks for the patient global (general) QOL, while questionnaires force the patients to dissect QOL in different aspects, explore different areas and analyze the specific components of QOL; this is probably why the importance of insulin was revealed more by these tests than by the interview.

Notwithstanding that the positive influence (as the Impact scale showed) of islet transplantation on the life of the patients was confirmed by our study, we expected a better outcome, with significant improvement of other scales of the questionnaires. One possible explanation could be related to the high educational and socioeconomic status of this selected cohort of patients and the consequent general better health status than the average population with type 1 diabetes mellitus. The high baseline QOL of this particular group of subjects can, possibly, reduce the magnitude of the improvement after islet transplantation.

Another important factor is that insulin independence, after the completion of an islet transplant protocol, probably leads patients to consider themselves cured, and consequently to compare themselves and their QOL to a nondiabetic population. Even if this can be understood from a psychological perspective, it is not correct from a clinical standpoint, since type 1 diabetes is a complex chronic disease, with metabolic alterations and complications, and islet transplantation has resulted in adequate but transient glycemic control without insulin administration, while several features of type 1 diabetes persist.

The longitudinal regression analysis employed in this study allowed us to simultaneously assess changes from baseline at multiple time points. Additionally, using these regression-modeling methods allowed us to assess 'a confounding effect', i.e. whether inclusion of another variable (the potential confounder) in the model resulted in a different interpretation of the relationship of interest. Thus, adjusting for insulin therapy, graft dysfunction and adverse events may affect ('confound') the estimate of the relationship between time and the outcome of interest (e.g. Satisfaction).

Analysis of the scores adjusted for confounders revealed changes in the significance of the results, different from our initial unadjusted analysis and from our expectations. Still, we feel that the discrepancy between the scores obtained with questionnaires and the outcome of the interviews might indicate that the former is not enough to get a complete picture of the patients' QOL. And this suggests that additional objective psychometric instruments might be needed and that the verbal consultation with a professional must be integrated in the overall QOL evaluation. At the visit, during follow-up with the psychologist, even if the reason for satisfaction is very subjective and the expectations of most patients change with time, the most frequent factor for the recipient's well-being was good glycemic control and disappearance of brittle diabetes, because metabolic stability and absence of hypoglycemia led the patients to independency from other people and the ability to conduct normal life and take responsibilities. These factors persist even if insulin therapy is restarted, and none of the patients ever regretted his/her islet transplant, since overall QOL improved, even if he/she was back on insulin.

The enhanced daily functioning, as a function of independency, is usually best described by the scale Role Limitation-Physical Health of the HSQ 2.0 questionnaire. No significant improvement was observed on this scale at any of the time points studied. In a previous study (10) this very scale demonstrated a good correlation with the Impact scale of the DQOL, which instead is significantly improved in our study. We believe that a further analysis by more deeply investigating some aspects of this scale and by increasing the number of patients will result in improved outcome.

The lack of better QOL scores could also be explained by the analysis of two heterogeneous populations, islet after kidney and islet alone recipients. As soon as the number of patients in each population is larger, we will analyze them independently in order to test this hypothesis.

Also we believe that, in addition to the psychometric instruments utilized for this study, the use of a hypoglycemia-fear specific questionnaire would be very useful to capture the fundamental benefit for a patient with type 1 diabetes that receives an islet transplant (20).

We also want to analyze in detail the deterioration of the bodily pain scale score, trying to correlate it with the presence of other adverse events, even at lower grade of severity according to NCI. These can be very discomforting for the patient under immunosuppression (e.g. mouth ulcers, a common side effect of rapamycin) and can possibly explain the lower scores of this specific scale after transplantation.

A recent report on QOL in a small group of patients that were followed up for 12 months suggested that while hypoglycemia fear improved significantly after transplant, all scores of the SF 36 questionnaire did not (20). This is quite consistent with our observations obtained in a larger group of patients and with a longer follow-up; it is therefore conceivable that rather than an improvement in general health related QOL, diabetes-specific aspects of QOL are more likely to show benefit from an islet transplant.

In summary, our data showed that islet transplantation results in improvement of selected aspects of QOL, and that there is little, if any, negative impact of the procedure, an important observation in view of the question as to whether chronic immunosuppression side effects might outweigh the benefits of improved metabolic control (21). We also show that re-introduction of insulin therapy is a fundamental independent variable that affects QOL outcomes, and we suggest that larger patient samples and longer follow-ups will strengthen our conclusions. We also suggest that the definition of more specific psychometric instruments should be considered.

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