Comparative Evaluation of Simple Indices of Graft Function After Islet Transplantation

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Background. Several simple measures of graft function after islet transplantation have been proposed but a comparative evaluation is lacking. Here, we compared the performance of five indices of β-cell function: β-score, transplant estimated function (TEF), homeostasis model assessment (HOMA) 2-B%, C-peptide/glucose ratio, and Secretory Units of Islets in Transplantation (SUIT).

Methods. Two cohorts of transplanted patients were analyzed. Cohort 1 consisted of 14 recipients with type 1 diabetes of islet transplantation whereas cohort 2 consisted of 21 recipients with type 1 diabetes of cultured islet cell graft. The five surrogate indices were compared against the first- and second-phase insulin response to arginine in cohort 1, and against the C-peptide response to a hyperglycemic clamp in cohort 2.

Results. We found that the performances of the five surrogate indices were close one to each other in cohort 1. The correlation coefficients ranged 0.62 to 0.67 and 0.62 to 0.68 against the first- and second-phase insulin response to arginine, respectively. In cohort 2, we found that the β-score, TEF, C-peptide/glucose ratio, and SUIT were reasonably well correlated with the clamp response (correlation coefficients were in the range 0.71–0.81), whereas HOMA2-B% showed a modest performance (r=0.54). HOMA2-B% could not be evaluated in one patient whose fasting glucose concentration level was below the lower bound indicated by the HOMA calculator (3 mmol/L). SUIT could not be evaluated in three patients whose fasting glucose concentration was below the glucose threshold of the SUIT formula (3.43 mmol/L).

Conclusion. In summary, no single index ouperformed the others. Nevertheless, when the benefit to cost ratio is considered, TEF stands out for its good performance at a very low cost.

Keywords: Islet transplantation, Insulin secretion, Modeling.

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The investigation of a patient's β-cell function after islet transplantation is challenging (*1–8*). The difficulty of performing classical stimulus-response tests has stimulated in recent years the development of simpler surrogate indices of β-cell function. Ryan et al. (*6*) proposed the β-score, an index determined from A1C, daily insulin requirement (DIR), fasting plasma glucose, and stimulated C-peptide response. These measurements, through a simple clinical scoring system, yielded an index that is well correlated with the glucose tolerance displayed during a mixed meal tolerance test (*6*). Borrowing from the homeostasis model assessment (HOMA) of β-cell function (*9*, *10*), Faradji et al. (*5*, *11*), and Yamada et al. (*3*, *8*, *12*) proposed, respectively, the C-peptide/

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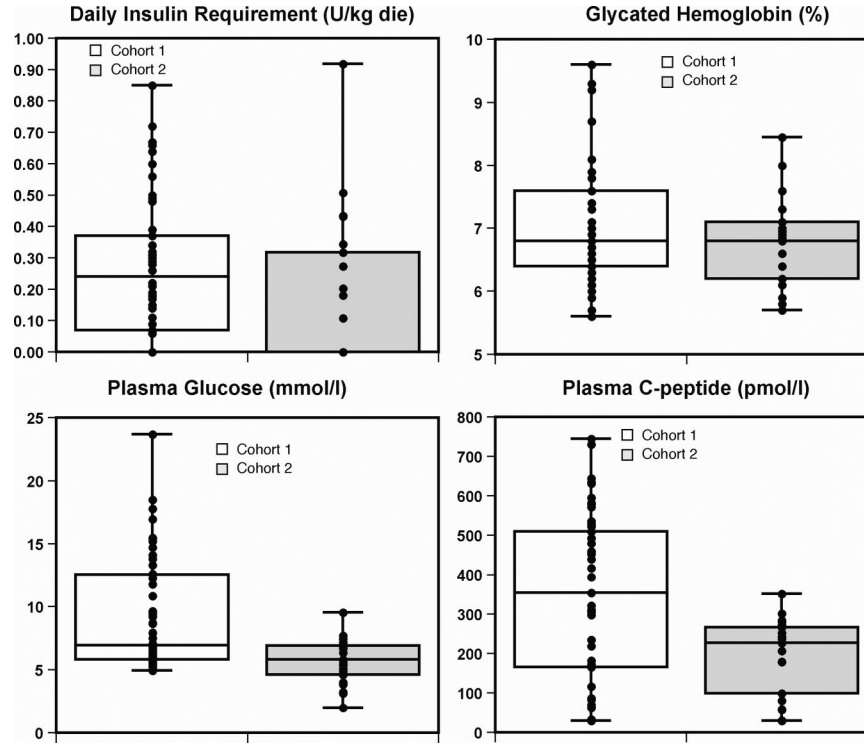

FIGURE 1. Box plot of the raw data (daily insulin requirement, A1C, fasting glucose concentration, and fasting C-peptide concentration) used to calculate the β-score, TEF, HOMA2-B%, CP/G, and SUIT for comparison against reference indices of insulin secretion assessed with the arginine test (cohort 1 in Milan, Italy) and with the hyperglycemic clamp (cohort 2 in Brussels, Belgium).

glucose ratio (CP/G) and the Secretory Units of Islets in Transplantation (SUIT) as surrogate markers of islet graft function. CP/G seemed well correlated with the measures for β-cell function after islet transplantation (90-min glucose after a MMTT and the acute insulin response to an intravenous glucose tolerance tests) and with the clinical scoring system of the β-score. SUIT seemed well correlated with the acute insulin response to glucagon. We recently proposed transplant estimated function (TEF) (*13*, *14*), and index that estimates the patients' daily amount of secreted insulin from the knowledge of the DIR and A1C. TEF can be normalized to the number of transplanted islets, and thus providing an index of function of the single β-cell and is well correlated with the area under the curve of C-peptide concentration over 24 hr, and with the acute insulin response after the intravenous administration of glucose or arginine.

Aim of the present study was to provide a comparative evaluation of such simple indices. We measured β-score, TEF, the HOMA index of β-cell function, the CP/G, and SUIT in two cohorts of transplanted patients. Cohort 1 consisted of 14 type 1 diabetic recipients of islet (7 islet transplant [ITA], 7 islet after kidney transplant [IAK]) transplanted in San Raffaele Scientific Institute (Milan) and not included in our previous work on TEF (*13*). Cohort 2 consisted of 21 type 1 diabetic recipients of cultured islet cell graft transplanted by Beta Cell Bank in Brussels (*15*). The five surrogate indices of β-cell function were compared against reference indices of β-cell secretion that were obtained from the insulin response to intravenous arginine in cohort 1 and from the C-peptide response to a hyperglycemic clamp in cohort 2.

RESULTS

Box plots of the raw data (DIR, A1C, fasting glucose concentration, and fasting C-peptide concentration) used to calculate the β-score, TEF, HOMA2-B%, CP/G, and SUIT are reported in Figure 1.

The scatter plots illustrating the relationship of each surrogate index against the reference indices of insulin secretion derived from the arginine test or the hyperglycemic clamp are shown in Figure 2.

The correlation results obtained in cohort 1 with the arginine test are reported in Table 1 and the correlation results obtained in cohort 2 with the hyperglycemic clamp are reported in Table 2.

In cohort 1, all the surrogate indexes were modestly correlated with the results of the arginine test (Table 1). When IAK and ITA patients were pooled together, the correlation coefficients of the five surrogate indices resulted close one to each other. In fact, the correlation coefficients were in the range 0.62 to 0.67 in the comparison against the first-phase response and in the range 0.62 to 0.68 in the comparison against the second-phase response. When ITA and IAK patients were considered separately, the results were slightly more heterogeneous. In ITA patients, the correlation coefficients against the first- and second-phase response were in the range 0.67 to 0.79 and 0.61 to 0.77, respectively. In IAK patients, the correlation coefficients against the first- and second-phase response were in the range 0.56 to 0.78 and 0.53 to 0.76, respectively. TEF performed slightly worse than the other indices in ITA patients and slightly better than the other indices in IAK patients.

In cohort 2, we found that the β-score, TEF, CP/G, and SUIT were well correlated with the clamp response; correlation coefficients were in the range 0.71 to 0.81, whereas HOMA2-B% showed a modest performance (r=0.54) (Table 2). Of note that HOMA2-B% could not be evaluated in one patient whose fasting glucose concentration was below the lower bound indicated by the HOMA calculator (i.e., 3 mmol/L). Likewise, SUIT could not be evaluated in three patients whose fasting glucose concen-

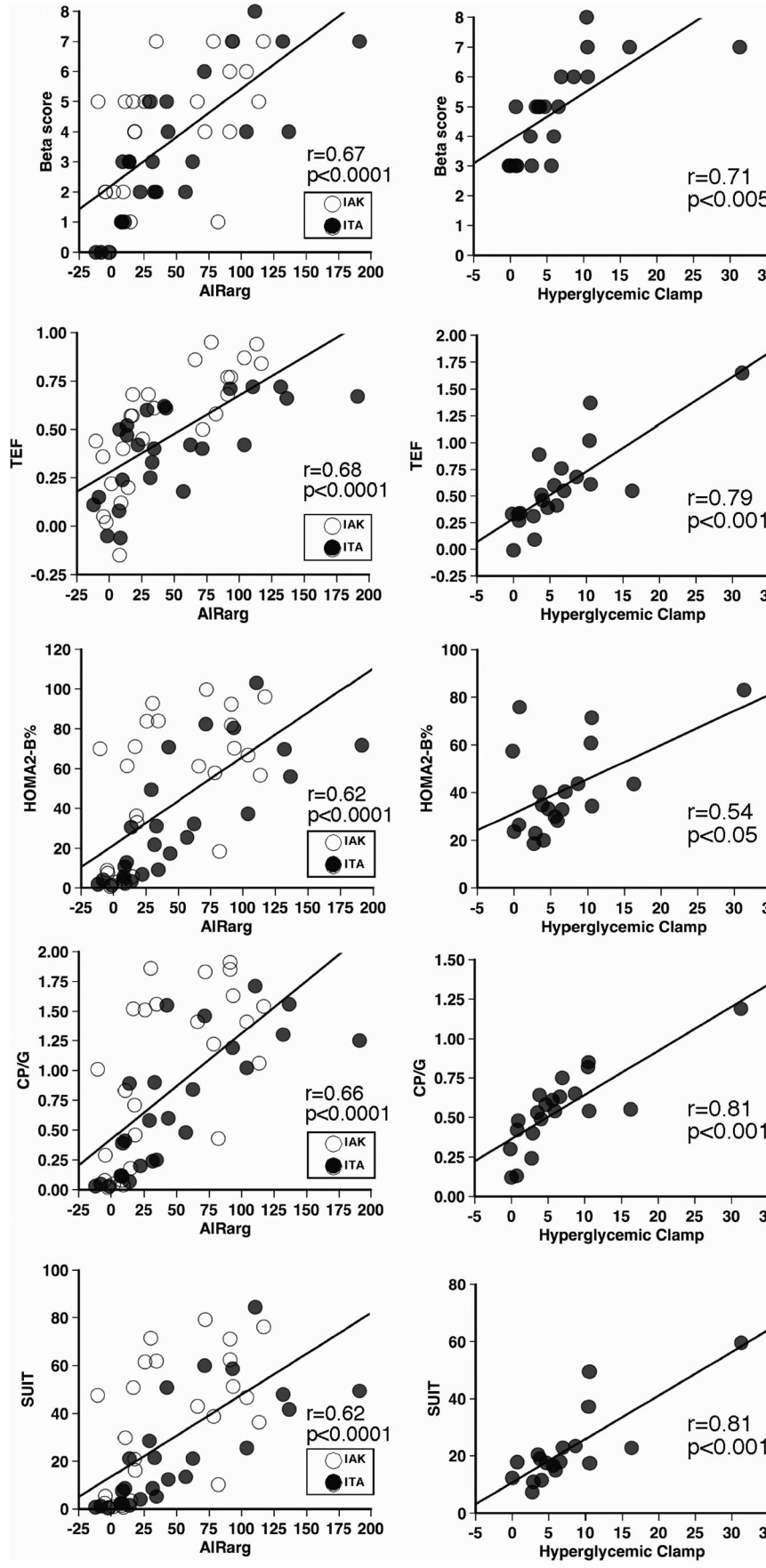

FIGURE 2. Scatter plots illustrating the relationships between each of the five surrogate indices (β-score, TEF, HOMA2-B%, CP/G, and SUIT) and the reference indices of β-cell function derived from the arginine test (*left*) or the hyperglycemic clamp (*right*).

TABLE 1. Comparative evaluation against the arginine test

	First-phase insulin response (AIR_{arg})			Second-phase insulin response		
	ALL (n=50 studies)	IAK (n=25 studies)	ITA (n=25 studies)	ALL (n=50 studies)	IAK (n=25 studies)	ITA (n=25 studies)
β-score	0.67[a]	0.56[b]	0.79[a]	0.62[a]	0.53[c]	0.72[a]
TEF	0.68[a]	0.78[a]	0.67[a]	0.65[a]	0.76[c]	0.61[b]
HOMA2-B%	0.62[a]	0.57[a]	0.77[a]	0.63[a]	0.57[b]	0.75[a]
CP/G	0.66[a]	0.63[a]	0.78[a]	0.68[a]	0.67[b]	0.77[a]
SUIT	0.62[a]	0.58[a]	0.75[a]	0.62[a]	0.56[b]	0.74[a]

This table reports the correlation results obtained in n=50 arginine tests carried out in cohort 1. Cohort 1 consisted of 14 diabetic patients (7 IAK and 7 ITA). Each patient underwent 2–5 arginine studies.

[a] $P \leq 0.0001$.

[b] $P \leq 0.005$.

[c] $P \leq 0.05$.

ALL, all subjects; IAK, islet after kidney transplant; ITA, islet transplant; TEF, Transplant Estimated Function; HOMA, homeostasis model assessment; CP/G, C-peptide/glucose ratio; SUIT, Secretory Units of Islets in Transplantation.

TABLE 2. Comparative evaluation against the hyperglycemic clamp

	Clamp-based β-cell secretory response
β-score	0.71[a]
TEF	0.79[b]
HOMA2-B%	0.54 (n=20)[c]
CP/G	0.81[b]
SUIT	0.81 (n=18)[b]

This table reports the correlation results obtained in n=21 hypeglycemic clamp studies carried out in cohort 2. The HOMA2-B% index was not evaluated in one subject with a basal glucose concentration lower than 3 mmol/L (in keeping with the HOMA calculator indications). The SUIT index was not evaluated in 3 subjects with a basal glucose concentration lower than the glucose threshold (3.43 mmol/L) of the SUIT formula (*8*). When the correlation analysis of HOMA2-B% vs. clamp was repeated on the same subset of 18 subjects analyzed with SUIT, the correlation coefficient of HOMA2-B% became $r=0.81$.

[a] $P \leq 0.005$.

[b] $P \leq 0.0001$.

[c] $P \leq 0.05$.

TEF, Transplant Estimated Function; HOMA, homeostasis model assessment; CP/G, C-peptide/glucose ratio; SUIT, Secretory Units of Islets in Transplantation.

TABLE 3. The performance of the surrogate indices in insulin-independent compared to insulin-treated patients

	Insulin-independent subjects			Insulin-dependent subjects		
	N	*R*	*P*	N	*R*	*P*
β-score	10	0.76	0.011	11	0.73	0.011
TEF	10	0.70	0.025	11	0.84	0.001
HOMA2-B%	10	0.79	0.007	10	0.06	ns
CP/G	10	0.78	0.008	11	0.85	<0.001
SUIT	10	0.78	0.008	8	0.75	0.032

This table reports the correlation results obtained in n=21 hypeglycemic clamp studies carried out in cohort 2. Ten subjects were insulin-independent and 11 were insulin-dependent at the time of the test. The insulin-independent subgroup included the three patients in which SUIT or HOMA2-B% could not be evaluated because of low fasting glycemia.

TEF, Transplant Estimated Function; HOMA, homeostasis model assessment; CP/G, C-peptide/glucose ratio; SUIT, Secretory Units of Islets in Transplantation; ns, not significant.

tration was below the glucose threshold at the denominator of the SUIT formula (3.43 mmol/L). Because cohort 2 consisted of 10 insulin-independent and 11 insulin-dependent patients, we had the opportunity to test the performance of the surrogate indices in insulin-independent compared with insulin-treated patients (Table 3). The correlation results were similar in the two subgroups and mirrored the results reported in Table 2 for the whole group of 21 patients.

DISCUSSION

In this study, we brought together five surrogate measures of β-cell function after an islet transplant. Many of these indices have not been investigated outside the domain they were introduced in, and not compared with each other. Given this set of surrogate indices, the first question that comes to mind is: which surrogate index of β-cell function is best suited for monitoring patients after islet transplantation? We comparatively tested the performance of such surrogate indices of β-cell function in two cohorts of transplanted patients in which an arginine test (Milan cohort) or a hyperglycemic clamp (Brussels cohort) have been carried out to provide reference indices of β-cell secretion. One key observation is that the performance of the surrogate indices was reasonably good but there was no one best performing measure. Hence, one needs to clarify whether some guidelines for a rational choice among them can be offered.

First of all, it seems that the β-score (which requires four pieces of information: A1C, DIR, C-peptide after a stimulus-response test or in the fasting state, fasting glucose concentration) does not outperform the other indices that only rely on two of the four components. This probably reflects the fact that the components of β-score contain some redundancy, as already suggested in (*1*). Another explanation is that the β-score does not focus on β-cell secretion only, but it blends together different sources of metabolic information to provide an integrated picture of the metabolic status of the

transplanted patient. As a result, the β-score encompasses both β-cell secretion and insulin sensitivity.

The results obtained with TEF against reference indices of β-cell secretion are in line with those obtained with the β-score, at a reduced cost. This confirms previous findings (*1*). Of note is that TEF is the cheapest among the surrogate indices because it only requires the availability of A1C, that is, a measure, which is carried out by default by each transplant center in the transplant follow-up. We made the attempt to quantify the cost of each surrogate index. We found that TEF costs €12.15, each one of the three indices based on glucose and C-peptide concentration (i.e., HOMA2-B%, CP/G, and SUIT) costs €13.08, whereas the β-score costs €25.09 (the cost of the β-score increases considerably if the investigator is willing to measure the time course of C-peptide concentration during a stimulus-response test).

Another observation is that TEF can also be normalized to the number of transplanted cells, thus providing an index (denoted as IEF in Ref. [*1*]) measuring the average secretory capacity of the single islet. By definition, TEF estimates the daily amount of insulin secreted by the transplanted β-cells. Although there is no way of knowing how many cells are alive and functioning after the transplantation, if the secretory output of one β-cell reduces to zero (i.e., that β-cell is dead), such zero output will contribute to decrease the overall secretory output. This diminished secretory output will determine a reduction in TEF and in IEF as well. IEF is a sort of benefit-to-cost ratio because it normalizes the insulin output (measured by TEF) to the effort (i.e., the total number of transplanted islets) made to achieve such insulin output. Such benefit-to-cost is a benchmarking tool that can be useful to compare transplant techniques and conduct comparative studies among different transplant centers.

Another observation is that among the three indices based on fasting C-peptide and glucose concentration, the CP/G index could be evaluated in all the subjects of both cohorts, whereas HOMA2-B% and SUIT could not be evaluated in some subjects of cohort 2 exhibiting low fasting glucose levels before the clamp study. In fact, —in keeping with the recommendations of the HOMA calculator (i.e., the computer program)—HOMA2-B% was not evaluated in one subject having fasting glucose concentration below 3.0 mol/L. Likewise, SUIT became negative and thus meaningless in three subjects having fasting glucose levels below 3.43 mmol/L. The results of Table 2 show that the performance of HOMA2-B% was worse than those of SUIT and CP/G (r=0.54 vs. 0.81). However, to be fair with the HOMA index, when the HOMA2-B% vs. clamp correlation analysis was repeated in the same subset of 18 subjects analyzed with SUIT, the correlation coefficient of HOMA2-B% became r=0.81 and thus identical to those of SUIT and CP/G. This indicates that the performance of HOMA2-B% is penalized by the presence of two subjects having fasting glucose levels in the range 3 to 3.5 mmol/L. Because islet transplant recipients who receive exogenous insulin therapy may exhibit low fasting glucose levels, the earlier mentioned difficulties shared by HOMA and SUIT should be taken into account by the investigators planning to use such indices to assess β-cell function. All in all, our results suggest that HOMA2-B%, CP/G, and SUIT provide similar performances provided that the subject's fasting glucose concentration is more than 3.5 mmol/L.

A final remark, common to all methods based on C-peptide fasting concentration, is that C-peptide concentration may become less reliable as marker of β-cell secretion in those patients in which kidney function is impaired. Faradji et al. (*5*) used the creatinine level to correct the CP/G ratio, but such correction did not lead to any improvement, probably because the subjects investigated in their study had normal and stable kidney function. As pointed out by Faradji et al. (*5*), it will be necessary to undertake a large study in patients with progressive nephropathy to gain a more thorough understanding of whether the correction based on the creatinine level can improve the performance of the indices based on C-peptide concentration.

Another remark is that in the validation study based on arginine data (cohort 1) TEF and CP/G exhibited complementary performances in IAK and ITA patients, that is, one performed well whereas the other performed modestly and vice versa. The finding that CP/G performed worse in IAK than in ITA patients may be due to the fact that in IAK patients, who often have a suboptimal kidney function, the C-peptide level becomes less reliable as a marker of β-cell secretion. The reason why TEF performed worse in ITA than in IAK patients is unclear and needs to be elucidated. In this regard, it should be noted that TEF is based on a population estimate of the ability of insulin to affect A1C (parameter k=5.43). It stands to reason that such a value becomes less efficient in representing an entire group when the range of insulin sensitivities is wide. Thus, it would be interesting to ascertain whether ITA patients exhibit a wider range of insulin sensitivities than IAK patients do. In any case, it is worth emphasizing that in the validation study based on hyperglycemic clamp data and carried out in ITA patients exclusively (cohort 2), the performances of TEF and CP/G were superimposable.

In summary, we compared β-score, TEF, HOMA2-B%, CP/G, and SUIT and found that no index was clearly superior to the others and the degree of correlation against reference indices measured with the arginine test and the hyperglycemic clamp was reasonably good. Some caveats have been given for the assessment of β-cell function with HOMA2-B% or SUIT in transplanted patients who are not insulin free and that exhibit low fasting glycemic levels. When the benefit to cost ratio is considered, TEF stands out for its good performance at a low cost.

MATERIALS AND METHODS

Subjects

The performance of the surrogate indices of β-cell function was evaluated by comparing the relationship of each index against reference indices of insulin secretion derived from an arginine test (*3*) or a hyperglycemic clamp. Two cohorts of transplanted patients were analyzed, one in Milan and the other in Brussels. The study protocol was approved by the institutional review board for each center. All patients provided written informed consent. All the patients transplanted were involved in intensive diabetes management defined as self-monitoring of glucose values no less than a mean of three times each day averaged over each week and by the administration of three or more insulin injections each day or insulin pump therapy. Such management, as for inclusion criteria, must be under the direction of an endocrinologist, diabetologist, or diabetes specialist with at least three clinical evaluations during the 12 months before enrollment in transplant program.

Cohort 1: San Raffaele Scientific Institute, Milan. The subjects included in the present study were new transplanted patients who did not participate in our previous work on TEF (*13*). Seven type 1 diabetic subjects (mean age 44±6 years and mean duration of diabetes 30±10 years) who received an IAK (with anti CD25 Ab, calcineurin inhibitors, and mycophenolate mofetil as immunosuppression) and seven type 1 diabetic subjects (mean age 33±8 years and mean duration of diabetes 12±6 years) who received islet transplant (ITA) (with anti-thymocyte globulin, rapamycin, and mycophenolate mofetil as immunosuppression) were included in this analysis. The subjects underwent identical arginine tests on more than one occasion (the median number of studies in each subject was three and the interquartile range was 2.2–5). The median time after transplantation at which the subjects received the arginine test was 3 months and the interquartile range was 1 to 6 months. Overall, 50 arginine studies were performed: nine studies in four patients who were tested when they were insulin independent, and 41 studies in 14 patients who were tested when they were insulin dependent. The arginine test (30 g of arginine hydrochloride administered in 30 min) was performed under fasting conditions and after overnight withdrawal of insulin administration. Blood samples were collected for the measurement of insulin, glucose, and C-peptide concentrations at baseline and at 5, 10, 20, 30, 40, 50, and 60 min. Such experimental protocol has been shown capable to elicit both first- and second-phase insulin responses (*16*) and has been frequently used by the Milan group to assess insulin secretion in pancreas or β-cell transplant recipients (*17*). Serum insulin levels were assayed with a microparticle enzyme immunoassay (IMx; Abbott Laboratories, North Chicago, IL) in which the lowest insulin sensitivity was 1 μU/mL. Serum C-peptide levels (intra-assay coefficient of variation 3.0% and interassay coefficient of variation 3.0%) were assayed by radioimmunoassay using commercial kits (Dako, Cambridgeshire, UK). The plasma glucose concentration was determined by the glucose oxidase method on a glucose analyzer (Beckman Coulter, Fullerton, CA). A1C was measured by the Variant II Hemoglobin A1C program (Bio-Rad, Hercules, CA), which uses the principle of ion (cation)-exchange high-performance liquid chromatography. Indices of the first-phase (acute insulin response to arginine, AIR_{arg}) and second-phase insulin responses were calculated as the incremental area under the insulin curve in the intervals 0 to 10 min and 10 to 30 min, respectively. The A1C level that was used for the calculation of the β-score and TEF was measured within 3 days before the day of the arginine test. The fasting levels of C-peptide and glucose that were used to calculate the β-score, HOMA2-B%, CP/G, and SUIT were measured within 3 days before the day of the arginine test. This was done to avoid the potentially confounding effect of deriving these indices from the basal values of the same test used for validation. Cohort 2: Beta Cell Bank in Brussels. This cohort of patients has been previously described (*15*). Twenty-one nonuremic C-peptide-negative patients who received an intraportal graft with $0.5-5.0\times10^6$ β cells per kilogram of body weight under antithymocyte globulin and mycophenolate mofetil plus tacrolimus were included in this analysis. Ten patients were insulin-independent and 11 patients were insulin-dependent. Each subject underwent a hyperglycemic clamp after 12 months from the transplant. In this cohort of patients, plasma C-peptide (C-peptide TRFIA; PerkinElmer, Turku, Finland) and corresponding glycemia, and A1C concentrations were measured in the central laboratory of the Belgian Diabetes Registry (*15*). A clamp-based index of secretory capacity was obtained by dividing the incremental steady-state level of C-peptide concentration to the incremental steady-state level of glucose concentration. Steady-state levels of C-peptide and glucose were obtained by averaging the data collected at minutes 120, 135, and 150 min of the clamp. The A1C level that was used for the calculation of the β-score and TEF was measured within 3 days before the day of the clamp test. The fasting levels of C-peptide and glucose measured immediately before the hyperglycemic clamp were used to calculate the HOMA2-B%, CP/G, and SUIT (unfortunately, fasting measurements taken at different days of the clamp were not available). The same data, together with the patient's DIR and A1C, were used to calculate the β-score. TEF only relied on DIR and A1C.

Calculation of the Surrogate Indices of β-Cell Function in Patients In Vivo

The β-score was calculated from the DIR, A1C, fasting plasma glucose concentration, and stimulated/fasting C-peptide levels according to the method described by Ryan et al. (*6*). Briefly, each metabolic component is subjected to a staircase function that maps its value into a discrete score (0, 1, or 2 points). The β-score ranges from 0 (no graft function) to 8 (interpreted as an index of excellent graft function).

TEF was calculated from the DIR and A1C according to the method previously described (*13*). By definition, TEF represents the daily endogenous β-cell secretion (units/24 hr) and can be assessed at any time after the transplant using the current and pretransplant measures of DIR and A1C:

$$\mathrm{TEF}=\left[\mathrm{DIR}_{\text{pre-tx}}+\frac{\mathrm{A1C}_{\text{pre-tx}}}{5.43}\right]-\left[\mathrm{DIR}+\frac{\mathrm{A1C}}{5.43}\right]$$

The HOMA index of β-cell function is based on a model of the feedback-loop between β-cell secretion and blood glucose under fasting, steady-state conditions. Such index is present in the literature in two versions, HOMA1-%B and HOMA2-%B (*6*,*10*). HOMA1-%B is given by a simple formula that approximates the homeostasis model solution (*6*):

$$\mathrm{HOMA1-B\%}=\frac{20\times \mathrm{I_b}}{(\mathrm{G_b}-3.5)}$$

where I_b is fasting plasma insulin concentration (μU/mL) and G_b is fasting plasma glucose concentration (mmol/L). HOMA1-B% cannot be used to assess β-cell function in patients taking exogenous insulin because of the inability of the insulin assays to differentiate between endogenously secreted and exogenously administered insulin. In contrast, HOMA2-B%, the updated version, can be used in transplanted patients because it can be calculated relying on paired fasting plasma glucose and C-peptide concentrations (*10*). At variance with HOMA1-B%, the updated index cannot be evaluated through a closed formula but requires the use of a computer program (HOMA calculator) that can be freely downloaded from www.dtu.ox.ac.uk/index.php?maindoc=/homa/index.php. In the present article, we present the results obtained with the HOMA2 method.

CP/G was calculated from the fasting blood glucose (mg/dL) and C-peptide (ng/mL) levels according to the method described by Faradji et al. (*5*):

$$\mathrm{CP}/G=\frac{100\times \mathrm{CP_b}}{G_b}$$

where CP_b is fasting C-peptide concentration (ng/mL) and G_b is fasting plasma glucose concentration (mg/dL). SUIT (Secretory Unit of Islets in Transplantation) was calculated from the fasting blood glucose (mM) and C-peptide (nM) levels according to the method described by Yamada et al. (*3*,*8*). Assuming normoglycemic subjects were younger than 40 years have normal pancreatic β-cell mass, SUIT can be assessed from fasting blood glucose and C-peptide by the formula:

$$\mathrm{SUIT}=\frac{250\times \mathrm{CP_b}}{(G_b-3.43)}$$

where SUIT index of normal subjects is 100.

Statistical Analysis

Descriptive statistics of DIR, A1C, fasting glucose concentration, and fasting C-peptide concentration makes use of box plots showing median and interquartile range. Standard linear regression was used to evaluate the relationship between surrogate and reference indices. A P value of less than 0.05 was considered statistically significant. The statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS version 13.0; SPSS, Chicago, IL).

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