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SUIT, secretory units of islets in transplantation: an index for therapeutic management of islet transplanted patients and its application to type 2 diabetes.

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ABSTRACT

Evaluation of a patient's pancreatic β-cell function is important in both diagnosis and treatment of diabetes. We sought to determine β-cell function with a single sampling of blood. Examination of fasting blood glucose (F-BG, mM) and C-peptide (F-CPR, nM) levels in 7 post-islet-transplanted states of 4 patients revealed a linear relationship between F-BG and F-CPR. Assuming that normal subjects aged < 40 years have 100% pancreatic β-cell function, we developed the secretory units of islets in transplantation (SUIT) as an index of β-cell function by the formula: 250 × F-CPR / (F-BG – 3.43). The SUIT index was correlated with the stimulated C-peptide levels not only in islet-transplanted patients ($R^2 = 0.68$, $P < 0.05$) but also in type 2 patients ($R^2 = 0.34$, $P < 0.001$). Since the SUIT index can be calculated from data obtained at a single fasting blood sampling and predict the pancreatic β-cell function, the formula may be a useful tool in clinical management of diabetes.

Key terms

islet transplantation, insulin, diabetes

INTRODUCTION

Diabetes is a heterogeneous group of metabolic disorders characterized by chronic hyperglycemia. As diabetes results from pancreatic β-cell deficiency and/or insulin resistance, a convenient clinical measure of pancreatic β-cell function and insulin sensitivity should be helpful to achieve the tight control of glycemic levels in diabetes.

Glucose is the most important secretagogue of insulin from pancreatic β-cells. Several tools presently available for measurement of pancreatic β-cell function include the hyperglycemic clamp [1], minimal model method [2], and graded glucose infusion [3], either of which determines secretory response of insulin to different glycemic levels and is complicated and time-consuming. In contrast, measurement of pancreatic β-cell mass in human is only possible after autopsy [4] and pancreatic β-cell mass is estimated from *in vivo* functional tests of pancreatic β-cells.

It has been recently shown that islet transplantation offers a prospect of good glycemic control in labile type 1 diabetes [5], and is used worldwide as a treatment of brittle forms of type 1 diabetes [6]. Islet transplantation in such patients involves extraction of islets from donors with normal glucose

tolerance followed by implantation into patients with few islets. Thus, as the patients are under intensive care of blood glucose levels in the postoperative period to avoid gluco-toxicity on islets, each islet transplanted into patients potentially has normal function, and pancreatic β-cell function should be closely related with pancreatic β-cell mass in these patients.

MATERIALS AND METHODS

The proposed SUIT index

Islet isolation was performed using a modification of the Edmonton protocol [5, 7, 8] from pancreata of non-heart-beating donors [9] or a living donor [10]. Islets were infused into the liver after percutaneous transhepatic cannulation of the main portal vein. The study was approved by the ethics committee of the Kyoto University Graduate School and Faculty of Medicine, Japan.

We examined fasting blood glucose (F-BG) and C-peptide (F-CPR) levels in 7 post-transplantation states of 4 patients and found a linear relationship between F-BG and F-CPR in each state. Since the estimation of the summary blood glucose intercept was the ratio estimation, a simple mean of $-a_i/b_i$ was not a good estimator, where a_i was the individual CPR-intercept and b_i was the individual regression coefficient of the lines in Fig. 1. Instead we estimated the summary F-BG intercept by $-\sum_i a_i / \sum_i b_i$. The associated 95% confidence interval was calculated based on the log transformation and the approximate variance using the delta method. We found the point estimate of the summary F-BG intercept to be 3.43 mM and

the 95% confidence interval 3.41-3.45 mM.

Assuming normoglycemic subjects aged < 40 years have normal pancreatic β-cell mass, a SUIT index, the secretory units of islets in transplantation, was assessed from F-BG (mM) and F-CPR (nM).

Application of a SUIT index to type 2 diabetic patients

Type 2 diabetic patients hospitalized in Kyoto University Hospital without renal failure (total 304, male/female 172/132, BMI = 24.0 ± 4.3 (mean ± SD), age = 61.0 ± 13.2 years (mean ± SD)) were recruited. Serum C-peptide levels were measured 6 min after intravenous injection of 1 mg of glucagon [11].

Statistical analyses

Statistical evaluation of results was performed using linear regression. *P* values < 0.05 were considered significant.

RESULTS

Correlation of F-BG and F-CPR

Steady state blood glucose and insulin levels are determined by their interaction in a feed-back loop. We examined fasting blood glucose (F-BG) and serum C-peptide (F-CPR) levels in 7 post-transplantation states of 4 patients, and found a linear relationship between F-BG and F-CPR in each state (Figure 1).

While regression coefficients differ among the states, the slope becomes steeper after sequential islet transplantation (Figure 1, broken lines compared with solid lines in A, B and C). The most interesting feature is that the F-BG intercept is similar in each case. We found the point estimate of the summary F-BG intercept to be 3.43 mM and the 95% confidence interval 3.41-3.45 mM.

Formula of the SUIT index

Assuming normoglycemic subjects aged < 40 years have normal pancreatic β-cell mass, SUIT, the secretory units of islets in transplantation, can be assessed from F-BG (mM) and F-CPR (nM) by the formula: 250 × F-CPR / (F-BG – 3.43), where SUIT index of normal subjects is 100.0 ± 11.7

(mean ± SE).

The SUIT index in patients receiving exogenous insulin therapy

Measurement of immunoreactive insulin is the standard method for evaluating the pancreatic β-cell function. However, insulin assays cannot differentiate endogenous insulin from exogenous insulin and the measurement of peripheral concentrations of C-peptide is the most common approach in patients receiving exogenous insulin therapy. We then calculated the SUIT index in a case of living donor islet allo-transplantation [10] requiring 0-17 units of exogenous insulin daily after islet transplantation. The SUIT index of 37.1 ± 1.3 (mean ± SE) was independent of the amount of exogenous insulin in this case (Figure 2) as well as in other cases (data not shown).

The SUIT index to evaluate the efficacy of islet transplantation

The efficacy of islet transplantation has been evaluated by measuring the stimulated C-peptide levels [12]. We then compared the SUIT index with the results of a glucagon stimulation test of islet secretory capacity in patients after islet transplantation (Figure 3A). The acute insulin response to glucagon (1 mg) is clearly correlated with the SUIT index (R^2 =

0.68, $P < 0.05$). We next compared the SUIT index against the post-operative days (Figures 2 and 4) and found that the index is similar around the course. These results indicated that the SUIT index was able to predict the efficacy of islet transplantation just after post-operative day 7.

Application of the SUIT index into type 2 diabetes

The SUIT index was then compared with the results of glucagon stimulation test in type 2 diabetic patients (Figure 3B). The acute insulin response to glucagon was similarly correlated with the SUIT index ($R^2 = 0.34$, $P < 0.001$).

DISCUSSION

The measurement of the pancreatic β-cell function is critical in the management of diabetic patients. In type 1 patients, intensive insulin therapies aimed at preserving or improving endogenous insulin secretion are associated with better metabolic control and lower risk for hypoglycemia and chronic complication [13, 14]. In type 2 patients, the United Kingdom Prospective Diabetes Study revealed that the glycemic deterioration is associated with progressive loss of the pancreatic β-cell function [15].

The pancreatic β-cell function is determined by two factors: quantity of pancreatic β-cells and quality of each β-cell. Characterization of maturity-onset diabetes of the young (MODY) shows that each of the factors plays an important role on glucose-induced insulin secretion. Glucokinase, a rate-limiting enzyme of the glycolytic pathway, plays a key role in glucose sensing by the insulin-secreting pancreatic β-cells. In subjects with glucokinase mutations (MODY2), the dose-response curve relating glucose and insulin secretion rate during graded intravenous glucose infusions was shifted to the right, indicating that quality of pancreatic β-cells can determine insulin-secretory capacity *in vivo* [16]. In contrast, inactivating

mutation of the *IPF1* gene leads to MODY4 [17] and partial deficiency of the IPF1, known as PDX-1 in mice, showed that pancreatic β-cell mass was decreased but single β-cells had normal glucose sensing and insulin secretion, indicating that quantity of pancreatic β-cells can also determine insulin-secretory capacity [18]. Therefore, measurement of pancreatic β-cell mass in human is necessary but is only possible after autopsy [4].

In this study, we have shown that in islet-transplanted patients, fasting blood glucose and fasting serum C-peptide levels have a linear relationship and pancreatic β-cell mass can be estimated from the formula by a single sampling of blood after over-night fast. This formula resembles that in the computer-solved model of pancreatic β-cell function, HOMA-β, which is 20 × insulin (mU/L) / (F-BG – 3.5) [19]. However, HOMA-β cannot be used to assess β-cell function in those taking exogenous insulin [20], due to the inability of insulin assays to differentiate endogenous insulin from exogenous insulin. We have not yet determined the range of the linear regression of F-BG and F-CPR. However, the SUIT index is independent of the amount of exogenous insulin. Therefore, it would be possible to know the β-cell function after injection of long-acting insulin.

After islet transplantation, not all of the grafted islets survived in the recipients but some islets were damaged and insulin were released from the eliminated islets especially in the early stage of islet transplantation, resulting in dysregulated elevation of serum C-peptide levels during a few days of post-transplantation. Our study showed that the SUIT index could predict the efficacy of islet transplantation just after post-operative day 7.

Calculation of the SUIT index by a single sampling of blood after over-night fast can predict pancreatic β-cell function not only in islet-transplanted patients but also in type 2 diabetic patients, and should be a useful tool in the clinical management of diabetes.

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FIGURE LEGENDS

Figure 1 Linear relationship of fasting blood glucose and C-peptide levels

Seven cases of islet transplantation of 4 patients (A-D) were plotted. Data from the first transplantation were shown in filled circles and solid lines and data from the second transplantation (A, B and C) were shown in open circles and broken lines. Coefficient of determination (R^2) and P-value (P) are shown.

Figure 2 The SUIT index in a patient receiving exogenous insulin therapy

The clinical course of the SUIT index in a patient after islet transplantation was shown. Amount of exogenous insulin injection and the SUIT index were plotted against post-operative day.

Figure 3 Validation of the SUIT index as pancreatic β-cell function

Correlation of the SUIT index and the acute insulin response to glucagon were shown in islet-transplanted patients (A) and type 2 diabetic patients (B). Serum C-peptide levels were measured 6 min after intravenous injection of glucagon (1 mg). Coefficient of determination (R^2) and P-value (P) are