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（分担）研究報告書

日本人２型糖尿病のインスリン抵抗性に寄与する因子に関する研究

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研究要旨
食事療法の指示にあたり、個々の糖尿病症例のインスリン分泌量は重要である。膵島移植症例から開発したインスリン分泌の指標SUITは、2型糖尿病においてもインスリン分泌量を反映する指標である。空腹時の1回の採血で得られることならびにインスリン注射施行中の症例にも応用できることが特徴である。さらに、SUITはインスリン治療の必要性を決定する因子であり、2型糖尿病患者の管理に有用であることを明らかにした。

A.研究目的

糖尿病の病態を考えるにあたり、インスリン分泌障害とインスリン抵抗性がその大きな成因であると考えられている。消化管ホルモン分泌の低下はインスリン分泌を低下させ耐糖能を悪化させる一方、消化管ホルモン分泌の増加は肥満・インスリン抵抗性を来たし耐糖能を悪化させる。したがって、食事による消化管ホルモン分泌増加はインスリン分泌障害を有する症例では必要だが、インスリン抵抗性の症例ではかえって病態を悪化させる。したがって、インスリン分泌能を明らかにすることは、より的確な食事療法を行うにあたり非常に重要であると考えられる。しかしながら、簡単にインスリン分泌能を評価する指標はない。

膵島移植はアルバータ大学のグループが2000年に新たな免疫抑制薬などを用いた方法を発表して以来、欧米で急速に普及してきた。欧米では脳死ドナーからの膵島単離であるが、本邦においては、法律によって脳死からの単離は認められておらず、心臓死ドナーから提供された膵島を移植に用いる必要があり、より単離法が困難なため実施が遅れていたが、2004年4月に京都大学で開始された。本治療のいては、膵島をほとんど有していないレシピエントに正常な機能を有するドナーの膵島を移植するため、移植後に得られるレシピエントのインスリン分泌能は基本的に膵島の数によって規定されているものと考えられる。研究者らが遂行したわが国における膵島移植の臨床応用から、膵島量を反映する新たなインスリン分泌能SUIT (Secretory Units of Islets in Transplantation)の指標を作製したので、本指標を2型糖尿病症例に応用し、インスリン分泌能症例を的確に診断できるかどうか検討した。

B.研究方法

1) 当院に入院した304名の2型糖尿病患者において、SUITと、グルカゴン負荷によるインスリン分泌能の評価ならびにインスリン治療の必要性との相関を解析した。

C.研究成果

1) SUITはグルカゴン負荷6分後のCペプチドと有意の相関を示した。また、SUITとインスリン治療の必要性は、ロジステック解析により有意な相関が得られ、SUITはインスリン治療の必要性を決定する因子となることが明らかにした。したがって、空腹時の1回の採血で評価可能なSUITは2

型糖尿病症例においてもインスリン分泌の良好な指標となると考えられた。

D.考察

膵島移植症例から開発したインスリン分泌の指標SUITは、2型糖尿病においてもインスリン分泌量を反映する指標である。空腹時の1回の採血で得られることならびにインスリン注射施行中の症例にも応用できることが特徴である。さらに、SUITはインスリン治療の必要性を決定する因子であり、2型糖尿病患者の管理に有用であることを明らかにした。

E.結論

食事療法にあたり、その症例のインスリン分泌能の的確な評価は必須であるが、簡単な指標が存在しない。研究者らが作製した膵島量を反映する新たなインスリン分泌の指標であるSUITは、2型糖尿病症例においても、インスリン治療の必要性を決定する因子であり、2型糖尿病患者の管理に有用であることを明らかにした。

F．健康危険情報

なし

G．研究発表

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H．知的財産権の出願・登録状況

なし

研究成果刊行一覧表

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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: $250 \times$ 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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