The Role of Diminished β Cell Reserve and Insulin Resistance in Secondary Sulfonylurea Failure of Type 2 Diabetes Mellitus

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Abstract

Introduction : The correction of hyperglycemia by insulin treatment has been shown to ameliorate β cell function and insulin sensitivity in SU failure patients, and there also appears to have disparity between tests of β cell function among these patients. The objectives of this study were to determine β cell secretory reserve and insulin resistance of secondary SU failure type 2 diabetic patients who had fairly good glycemic control compared with those who were SU responsive and the disparity of β cell responses to glucose and non-glucose stimuli were examined in these two groups.

Subjects and Method : Eight secondary SU failure, insulin-treated and 11 SU responsive type 2 diabetic patients who were matched for age, degree of obesity, duration of diabetes as well as HbA1c were studied. Intravenous glucagon and oral glucose tolerance tests (OGTT) as well as short intravenous insulin tolerance test using arterialized venous blood were randomly performed on separate occasions to assess β cell secretory reserve and insulin sensitivity, respectively.

Results : Basal (0.37±0.05 (SEM) *vs* 0.80±0.14 nmol/l; p=0.02) and stimulated c-peptide levels (0.66±0.08 *vs* 1.16±0.14 nmol/l; p=0.007) after glucagon as well as basal (0.46±0.06 *vs* 0.73±0.10 nmol/l; p=0.046) and maximal c-peptide responses (1.41±0.14 *vs* 1.97±0.14 nmol/l; p= 0.021) to glucose stimulation were significantly lower in SU failure than SU responsive patients. However, the incremental changes of c-peptide over basal after glucagon (0.29±0.06 *vs* 0.37±0.09 nmol/l) and glucose (AUC : 36.9±7.6 *vs* 47.9±4.5 nmol/l/h) were not different between both groups. There were strong positive relationships between basal and stimulated c-peptide responses to glucagon (r=0.818; p=0.002) and glucose (r=0.85; p=0.001) in SU responsive patients but these relationships were not as strong in SU failure patients (r=0.682; p=0.062 and r=0.41; p=NS, respectively). Insulin sensitivity did not differ between the two groups.

Conclusion : This study demonstrated that decreased basal, but not stimulated, insulin secretion was possibly a major factor associated with secondary SU failure in type 2 diabetic patients.

With comparable glycemic control, there was no disparate β cell responses to glucose and glucagon in patients with or without secondary SU failure.

Key word : Glucagon Test, Oral Glucose Tolerance Test, Insulin Resistance, Insulin Tolerance Test, Sulfonylurea Failure, Type 2 Diabetes Mellitus

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It is well established that hyperglycemia of type 2 diabetes mellitus results from the interplay of insulin resistance and insulin insufficiency[1]. The capacity of β cell to secrete insulin is a major determinant of glucose intolerance severity. At the early stage of the disease when insulin secretory capacity of β cell is minimally impaired, any treatment which results in lowering of insulin resistance or increasing insulin secretion would be able to correct hyperglycemia. However, for uncertain reasons, the capacity of β cell progressively deteriorates after years of diabetes[2]. At this stage, patients require escalating doses of sulfonylureas (SU), and later on, would not further respond to these agents (secondary SU failure). The persistence of hyperglycemia, if uncorrected, would be able to inhibit not only glucose-induced insulin secretion but also peripheral insulin action resulting in more hyperglycemia[3]. These abnormalities can be reversed by correction of hyperglycemia, for example, by insulin treatment.

Since the progressive failure to treatment with SU in type 2 diabetic patients occurs in association with the progressive decline of β cell function, it is plausible that the former is the consequence of the latter. However, the studies of β cell function in SU failure patients have inconsistent results. Although most studies reported decreased β cell function in SU failure patients[4-6], it has not been confirmed in some other studies[7,8]. The differences in glycemic control, degree of obesity, duration of diabetes as well as definition of SU failure may in part contribute to the discrepant results. Correction of hyperglycemia by insulin treatment has been shown to ameliorate β cell function and insulin resistance in SU failure patients[7-10], therefore it is possible that the apparent decrease in β cell function is in part the result of hyperglycemia. Furthermore, there appears to have disparate responses between tests of β cell function among these patients. C-peptide responses to meal or glucose were improved after insulin treatment[7,9,10], whereas, those responses to glucagon were reported to be unchanged [9,10], improved[11] or decreased[7,12,13]. The objectives of this study were to determine β cell secretory reserve and insulin sensitivity in Thai type 2 diabetic patients with secondary SU failure compared with those who were SU responsive who had age, duration of diabetes, degree of obesity and glycemic control matched and to examine how different β cells of these two groups responded to glucose and non-glucose stimuli.

SUBJECTS AND METHOD

Eight type 2 diabetic patients, 5 women 3 men, who had a history of secondary failure to treatment with SU and metformin and currently on insulin treatment and 11 patients, 7 women 4 men, who were still responsive to SU (± metformin) were enrolled into the study. Patients of both groups were matched for age, body mass index, waist-hip ratio, duration of diabetes as well as duration of SU treatment (Table 1). Secondary SU failure was defined by a history

of successful treatment with SU for >1 year and current failure to respond to fasting plasma glucose (FPG) persistently elevated >11 mmol/l despite maximum daily dosages of SU (glibenclamide 20 mg, glipizide 30 mg, glicazide 320 mg) and metformin (2,550 mg). Five of 8 patients had been hospitalized for one week for dietary management while on maximum dosages of SU and metformin, 3 denied hospitalization but were given intensive dietary advice. All failed to improve their diabetes control. Therefore, dietary non-compliance was unlikely to be the cause of SU failure in this group of patients. None was positive for glutamic acid decarboxylase antibodies ($GAD_{65}Ab$). Four patients were on insulin alone and the other four were on combined SU and insulin at the time of study. Duration of insulin treatment was 3.8±3.8 (SD) years; range 3 months-11 years. SU responsive patients were those whose FPG levels were ≤7 mmol/l under SU (± metformin) treatment in the last 3 consecutive clinic visits before entering the study, 9 were being treated with combined SU and metformin, 2 were on SU alone. All patients of both groups had normal serum creatinine levels.

Intravenous glucagon and oral glucose tolerance tests (OGTT) as well as short intravenous insulin tolerance test (ITT) were randomly performed in each patient on separate occasions, not greater than one month apart, to assess β cell secretory function and insulin sensitivity, respectively. Patients came to our research unit in the morning after an overnight fast and all medications were withheld. FPG and HbA1c were measured on the day of each test in all patients. The test was performed unless FPG was >10 mmol/l, otherwise it would be postponed until FPG criteria was met. Glucagon test was performed by administration of 1 mg glucagon (Glucagon®, Novo Nordisk, Denmark) intravenously, blood samples were drawn at before and 6 minutes after glucagon administration for the measurement of serum c-peptide levels. OGTT was performed with 75 g oral glucose, blood samples were drawn at before and 30, 60, 120 minutes after glucose ingestion for the measurement of plasma glucose and serum c-peptide levels. Patients were instructed to stay on their usual diet and activities at least 3 days prior to the test. ITT was performed by intravenous bolus insulin injection using regular insulin (Actrapid HM®, Novo Nordisk, Denmark) 0.1 U/kg. Arterialized venous blood samples were taken from the dorsal hand vein kept in a thermoregulated box maintaining a temperature at ~50-55°C[14,15]. Blood samples were drawn at before and 3, 5, 7, 9, 11, 13 and 15 minutes after insulin injection for determination of plasma glucose and insulin levels. Plasma glucose was measured in duplication at each time point, the mean value was used to represent the plasma glucose level at that time point. Insulin sensitivity was indicated by the glucose disappearance rate (K_{ITT}) estimated from the slope of the regression line of log-transformed plasma glucose against time during the 3-15 minutes of the test[16]. All blood samples were drawn *via* catheters which were retained for at least 15 minutes before the tests. The analysis of plasma glucose was made immediately after the test. Sera for c-peptide and insulin levels was kept frozen at -80°C until analysis.

The study was approved by the hospital ethic committee and all patients gave written informed consent before beginning the study.

Laboratory analysis

Plasma glucose was measured by the glucose oxidase method with automated machine Hitachi model 717 (Boehringer Mannheim, Germany). Interassay CV of the test for plasma glucose ranging from 6.1-13.9 mmol/l were 0.92-2.29 per cent. HbA1c was measured by immunoturbidimetric assay (Boehringer Mannheim, Germany) with a normal range of 4.4-6.2 per cent. Insulin and c-peptide levels were measured by double antibody radioimmunoassay (RIA) (Diagnostic Products Coporation, Los Angeles, USA) with respective intra-assay CV of 0.9-4.7 and 0.9-7.1 per cent. $GAD_{65}Ab$ was also measured by RIA (CIS, France).

Statistical methods

Differences of means between and within the groups were tested with unpaired and paired *t*-test, respectively. Incremental changes of plasma glucose and serum c-peptide levels after oral glucose load were analysed using one-way analysis of variance for repeated measurements. Areas under the curves were calculated by the trapezoidal rule. Relationships between different variables were examined by linear regression analysis and Pearson product-moment correlation coefficient. All data analysis were performed using the statistical program SPSS 9.0 for windows. Data were presented as mean ±SEM unless indicated otherwise. $P < 0.05$ was considered to be statistically significantly different.

RESULTS

Glycemic control of SU failure and SU responsive patients were not significantly different on the day of each test (Table 1). As shown in Fig. 1, serum c-peptide levels were significantly increased after glucagon administration in both groups ($p< 0.0001$). Basal as well as stimulated c-peptide levels were significantly lower in SU failure patients ($p= 0.02$ and 0.007, respectively). Although the incremental changes over basal were less in SU failure patients, they were not different from the SU responsive group (0.29 ± 0.06 *vs* 0.37 ± 0.09 nmol/l). There was a strong positive relationship between basal and stimulated c-peptide responses to glucagon ($r=0.818$; 95%CI 0.371-1.211; $p=0.002$) in SU responsive patients. However, such a relationship was less strong in SU failure patients ($r=0.682$; 95%CI-0.028-0.816; $p=0.062$).

With regards to OGTT, plasma glucose and serum c-peptide levels in response to oral glucose load were significantly increased in both groups. Similar to the glucagon test, basal and maximal c-peptide responses to glucose (Fig. 2) were significantly lower in SU failure patients ($p=0.046$ and 0.021, respectively) despite comparable plasma glucose before (8.8 ± 0.7 *vs* 7.3 ± 0.6 mmol/l) and 30 minutes (15.3 ± 1.0 *vs* 14.4 ± 0.9 mmol/l), 60 minutes (18.9 ± 0.7 *vs* 18.5 ± 0.7 mmol/l) and 120 minutes (20.6 ± 0.7 *vs* 19.2 ± 1.0 mmol/l) after glucose ingestion. AUC of plasma glucose (507.4 ± 46.0 *vs* 536.3 ± 30.8 mmol/l/h) and serum c-peptide (36.9 ± 7.6 *vs* 47.9 ± 4.5 nmol/l/h) were also not different between both groups. For SU responsive patients, there was not only a strong positive relationship between basal and maximal c-peptide responses to oral glucose ($r=0.85$; 95%CI 0.324-0.891; $p=0.001$) but the latter also correlated well with stimulated c-peptide responses to glucagon ($r=0.853$; $p=0.001$). Nevertheless, these positive relationships could not be demonstrated in SU failure patients ($r=0.41$; 95%CI-0.16-0.423; p=NS and $r=-0.692$; $p=0.057$, respectively).

Insulin sensitivity was not different between both groups. K_{ITT} of SU failure patients was 0.068 ± 0.004 mmol/l/min, whereas, it was 0.072 ± 0.002 mmol/l/min in SU responsive patients. Insulin levels as determined by AUC were not different between these two groups (4222.02 ± 366.04 *vs* 3454.22 ± 150.34 pmol/l/min; $p=0.088$).

DISCUSSION

Secondary failure to treatment with SU is common, perhaps inevitable, in type 2 diabetic patients. The decline in β cell function appears to be a major culprit although other factors, for instance, poor dietary compliance, lack of physical exercise, stress or latent autoimmune diabetes are also in-

Table 1. Clinical characteristics and glycemic control of sulfonylurea failure and sulfonylurea responsive type 2 diabetic patients.

	Sulfonylurea failure (n=8)	Sulfonylurea responsive (n=11)	P
Age (yr)	60.5 ± 6.9	65.9 ± 5.6	NS
BMI (kg/m^2)	26.8 ± 4.9	25.3 ± 2.6	NS
Waist/ hip	0.93 ± 0.07	0.96 ± 0.07	NS
Duration of DM (yr)	15.8 ± 5.4	13.9 ± 5.3	NS
Duration of sulfonylurea treatment (yr)	12.0 ± 7.1	13.9 ± 5.3	NS
Glycemic control on test day			
Glucagon test			
FPG (mmol/l)	7.6 ± 2.3	6.6 ± 1.3	NS
HbA1c (%)	8.5 ± 1.1	7.7 ± 1.0	NS
OGTT			
FPG (mmol/l)	8.8 ± 2.0	7.3 ± 2.0	NS
HbA1c (%)	8.2 ± 1.1	7.3 ± 1.0	NS
ITT			
FPG (mmol/l)	6.4 ± 1.7	6.9 ± 1.7	NS
HbA1c (%)	7.1 ± 2.8	7.0 ± 1.7	NS

Data are expressed as mean ± SD. BMI = body mass index; FPG = fasting plasma glucose; OGTT = oral glucose tolerance test; ITT = insulin tolerance test; NS = not significant

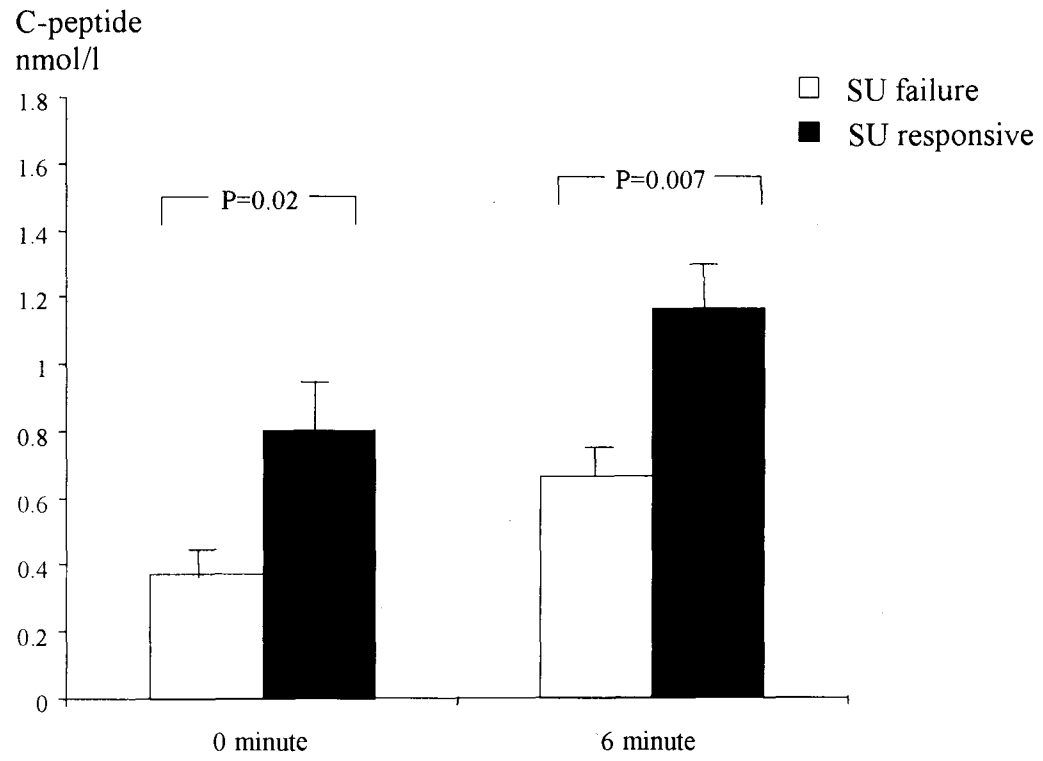

Fig. 1 Serum c-peptide levels at before and 6 minutes after 1 mg glucagon intravenous injection in SU responsive (■) and SU failure (□) type 2 diabetic patients.

volved[17]. The United Kingdom Prospective Diabetes Study (UKPDS) demonstrated the progressive deterioration of β cell function, but not insulin resistance, with time in patients with type 2 diabetes accompanied by worsening of glycemic control[2]. However, details of β cell function of patients with and without SU failure have not been reported. Groop, et al[17] reported lower basal and stimulated c-peptide responses to intravenous glucagon in type 2 diabetic patients who failed to respond to SU treatment. However, it appeared that a significant proportion of their secondary SU failure patients were, in fact, type 1 diabetic patients since islet cell antibodies (ICA) were positive in about one-fourth of these patients. They subsequently repeated the study but this time using mixed meal as a test for β cell function and excluding ICA positive patients and reported that patients with SU failure had lower insulin and c-peptide responses to a mixed meal as well as higher hepatic and peripheral insulin resistance[4]. The similar lower c-peptide responses to a mixed meal in secondary SU failure patients were also reported by other investigators[6,18]. Nevertheless, given the poorer glycemic control in SU failure patients of the previous studies, it is uncertain whether these changes indicated an irreversible decline in β cell function or were the consequences of the reversible, detrimental effect of chronic hyperglycemia[3]. Since c-peptide responses to mixed meal has been shown to improve after correction of hyperglycemia by insulin treatment in type 2 diabetic patients with SU failure[9,11], therefore it is conceivable that the apparent decreases in β cell function reported from those studies were in part due to the glucose toxicity effect. This study was designed to control factors that one way or the other can have effects on tests of β cell function as well as insulin sensitivity. SU failure and SU responsive patients in this study were matched for age, degree of obesity, duration of diabetes and glycemic con-

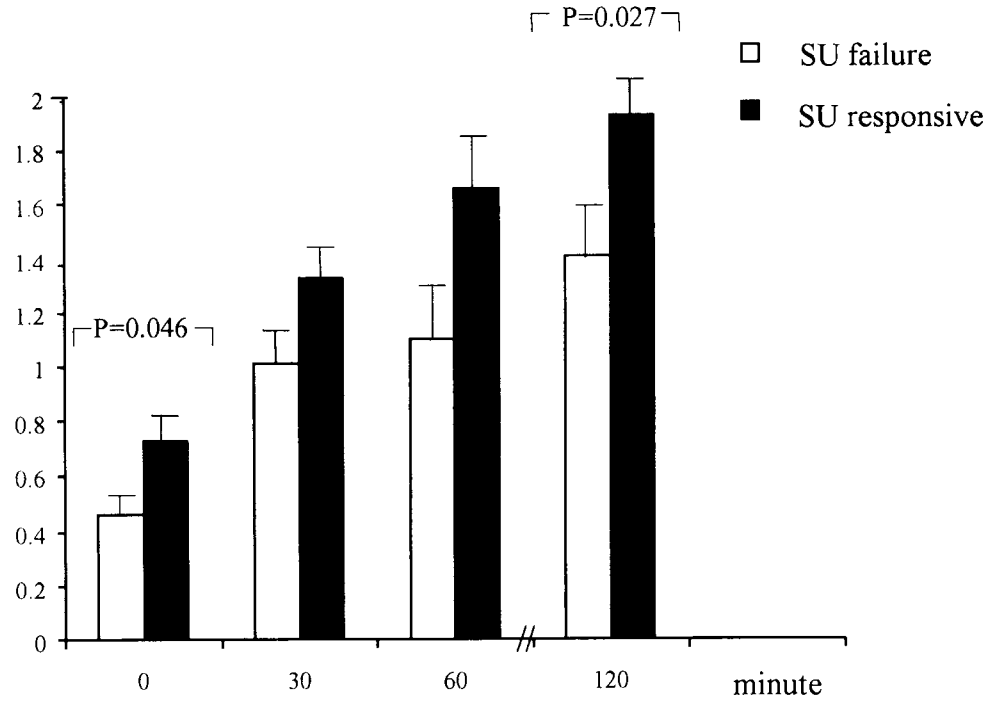

Fig. 2. The basal and stimulated c-peptide levels after ingestion of 75 g glucose in SU responsive (■) and SU failure (□) type 2 diabetic patients.

trol. Poor dietary compliance, an important factor contributing to SU failure, was excluded in this study. The possibility of latent autoimmune type 1 diabetes was also excluded given negative $GAD_{65}Ab$ in all of these patients.

The authors evaluated β cell secretory reserve with two different stimuli including glucose and glucagon since it appears that β cells of type 2 diabetes respond differently to these two stimuli. Whereas, β cell responses to glucagon have been shown to be positively correlated with degree of glycemic control in some studies[5,9,12], β cell responses to glucose are in the opposite direction[5, 9,19]. Therefore, comparable glycemic control is crucial if β cell secretory reserves need to be determined in different patient groups. Our study showed that with comparable HbA1c levels, there was no disagreement between β cell responses to oral glucose and glucagon in either SU failure or SU responsive patients. Although insulin treatment in SU failure patients in this study may theoretically suppress c-peptide responses by negative feedback mechanism, it seems to be due to the effect of better glycemic control rather than the effect of insulin itself[13]. The present study showed that although the basal and maximal c-peptide responses to glucagon and oral glucose were lower in SU failure patients, the stimulated c-peptide responses over basal, both in glucagon and oral glucose tolerance tests, were not significantly different suggesting a similar degree of stimulability of β cells in both groups. With regards to OGTT, not only were the AUC of c-peptide responses similar but the AUC of plasma glucose as well as plasma glucose levels at each time point during the test were also not different. These unanticipated findings of lower basal but not stimulated c-peptide secretion in SU failure patients warrant further comment. Firstly, the results of this study were not against the findings from UKPDS or other studies, in which only fasting

insulin levels were measured, and that poor β cell function was the major cause of secondary SU failure in type 2 diabetic patients. However, the lower basal c-peptide levels of SU failure patients in this study are less likely to be due to the greater reduction in functioning β cell mass given a similar degree of stimulability by glucagon and glucose in SU failure and SU responsive patients. Nevertheless, this does not exclude the importance of β cell mass as the contributing cause of SU failure. Secondly, the similar c-peptide responses to oral glucose between SU failure and SU responsive patients in the present study was in contrast with the studies of Prando et al[6] and Gjessing et al[18] who reported lower c-peptide responses to mixed meal in SU failure patients. The poorer glycemic control in SU failure patients of the latter studies may in part explain this discrepant result. However, although the magnitude of responses to glucagon and glucose between these two groups were not different, the weaker relationships between basal and maximal responses to glucagon and glucose in SU failure patients possibly indicated the marginal reserve of and the heterogeneity in functioning β cell mass among this group of patients. It is conceivable that if a larger number of patients were studied, the lower β cell responses to such stimuli as well as stronger relationships between basal and maximal responses in SU failure patients could be demonstrated. Nevertheless, concerning the progressive deterioration of basal and glucose stimulated insulin secretion in type 2 diabetes, this study implied that diminished basal insulin secretion was the major factor associated with secondary SU failure. Diminished glucose-stimulated insulin secretion possibly also contributed but played a minor role, at least in the early years of failure. Why only basal but not stimulated β cell function was lower in secondary SU failure patients is unknown, the defect in basal insulin secretion may be in part responsible. Thirdly, since the criteria of secondary SU failure depends on FPG level, not postprandial glucose, therefore, the finding of diminished basal insulin secretion is reasonable. The authors speculated that, with a comparable long duration of diabetes, stimulated plasma glucose levels particularly postprandial plasma glucose were similarly impaired between SU responsive and SU failure patients.

Although the short intravenous insulin tolerance test, a method used for evaluation of insulin sensitivity in this study, appeared to be less standardized than the standard hyperinsulinemic euglycemic clamp technique, it has been shown to be reproducible[20] and correlated well with the clamp study in both diabetic and nondiabetic patients particularly when using arterialized venous blood[16, 21]. Eventhough the present study did not demonstrate a difference in insulin sensitivity between patients with and without SU failure, it could not exclude small differences given the limitation of the test. However, if such a difference existed, it should not play a major role in the development of secondary SU failure. One may speculate that the lower c-peptide levels in the face of equivalent levels of plasma glucose by OGTT was suggestive of lower insulin resistance in SU failure patients, the authors don't think this would be the case given the impaired insulin secretion independent of insulin resistance in type 2 diabetic patients.

In conclusion, the present study demonstrated that diminished basal, but not stimulated, insulin secretion might be a major factor associated with secondary SU failure in type 2 diabetic patients. With comparable glycemic control, there were no disparate β cell responses to glucose and glucagon in either SU responsive or SU failure patients.

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บทบาทของเบตาเซลล์ที่ลดลงและการดื้ออินสุลินในการหยุดตอบสนองต่อซัลโฟนิลยูเรียของโรคเบาหวานชนิดที่สอง

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บทนำ : การลดระดับน้ำตาลในเลือดด้วยการฉีดอินสุลินในผู้ป่วยเบาหวานชนิดที่สองที่หยุดตอบสนองต่อซัลโฟนิลยูเรียสามารถทำให้การทำงานของเบตาเซลล์ดีขึ้นได้ ดังนั้นจึงเป็นไปได้ว่าการทำงานของเบตาเซลล์ที่ลดลงในภาวะดังกล่าวส่วนหนึ่งเป็นผลจากระดับน้ำตาลในเลือดสูง นอกจากนั้นการทดสอบที่ใช้ประเมินการทำงานของเบตาเซลล์ก็ให้ผลแตกต่างกัน วัตถุประสงค์ของการศึกษาเพื่อประเมินความสามารถในการหลั่งอินสุลินของเบตาเซลล์และการดื้ออินสุลิน (insulin resistance) ในผู้ป่วยเบาหวานชนิดที่สองเปรียบเทียบระหว่างผู้ป่วยที่ไม่ตอบสนองและผู้ป่วยที่ตอบสนองต่อซัลโฟนิลยูเรีย และศึกษาความแตกต่างของการตอบสนองของเบตาเซลล์ต่อกลูโคสและตัวกระตุ้นที่ไม่ใช่กลูโคส

วิธีการศึกษา : ศึกษาในผู้ป่วยเบาหวานชนิดที่สองจำนวน 19 ราย 8 รายเป็นผู้ป่วยที่หยุดตอบสนองต่อยาซัลโฟนิลยูเรียและได้รับการฉีดอินซูลิน 11 รายเป็นผู้ป่วยที่ยังตอบสนองต่อซัลโฟนิลยูเรีย โดยผู้ป่วยทั้งสองกลุ่มมีอายุ ดัชนีมวลร่างกาย (body mass index) ระยะเวลาการเป็นเบาหวานและระดับ HbA1c ไม่แตกต่างกัน ผู้ป่วยทุกรายจะได้รับการฉีดกลูคากอน (glucagon) และรับประทานน้ำตาลกลูโคสเพื่อทดสอบความสามารถในการหลั่งอินสุลิน และได้รับการทดสอบความไวต่ออินสุลินโดยวิธี short intravenous insulin tolerance

ผลการศึกษา : ผู้ป่วยที่หยุดตอบสนองต่อซัลโฟนิลยูเรียมีระดับ c-peptide ก่อน (0.37±0.05 (SE) *vs* 0.80±0.14 นาโนโมล/ลิตร ; p=0.02) และหลังการกระตุ้นด้วยกลูคากอน (0.66±0.08 *vs* 1.16±0.14 นาโนโมล/ลิตร; p=0.007) และระดับ c-peptide ก่อน (0.46±0.06 *vs* 0.73±0.10 นาโนโมล/ลิตร; p=0.046) และระดับ c-peptide สูงสุดหลังรับประทานกลูโคส (1.41±0.14 *vs* 1.97±0.14 นาโนโมล/ลิตร; p=0.021) ต่ำกว่าผู้ป่วยที่ตอบสนองต่อซัลโฟนิลยูเรีย อย่างไรก็ตามปริมาณ c-peptide ที่เพิ่มขึ้นหลังการกระตุ้นด้วยกลูคากอน (0.29±0.06 *vs* 0.37+0.09 นาโนโมล/ลิตร) และกลูโคส (พื้นที่ใต้กราฟ : 36.9±7.6 *vs* 47.9±4.5 นาโนโมล/ลิตร/ชั่วโมง) ไม่แตกต่างกันในผู้ป่วยทั้งสองกลุ่ม ระดับ basal c-peptide มีความสัมพันธ์โดยตรงกับระดับ stimulated c-peptide หลังการกระตุ้นด้วยกลูคากอน (r=0.818; p=0.002) และกลูโคส (r=0.85; p=0.001) ในผู้ป่วยที่ยังตอบสนองต่อซัลโฟนิลยูเรีย แต่ความสัมพันธ์ดังกล่าวลดน้อยลงในผู้ป่วยที่หยุดตอบสนองต่อซัลโฟนิลยูเรีย (r=0.682; p=0.062 และ r=0.41; p=NS ตามลำดับ) ความไวต่ออินสุลินไม่แตกต่างกันในระหว่างผู้ป่วยทั้งสองกลุ่ม

สรุป : การศึกษานี้แสดงให้เห็นว่า การหยุดตอบสนองต่อซัลโฟนิลยูเรียในผู้ป่วยเบาหวานชนิดที่สองมีความสัมพันธ์กับการลดลงของการหลั่งอินสุลินระยะ basal มากกว่าการหลั่งอินสุลินหลังการกระตุ้น ไม่มีความแตกต่างในการตอบสนองของเบตาเซลล์ต่อกลูคากอนและกลูโคสในผู้ป่วยทั้งสองกลุ่ม

คำสำคัญ : การทดสอบกลูคากอน, การทดสอบความทนต่อกลูโคส, การดื้ออินสุลิน, การทดสอบ insulin tolerance, การหยุดตอบสนองต่อซัลโฟนิลยูเรีย, เบาหวานชนิดที่สอง

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