Evaluation of insulin secretion by glucagon stimulation test predicts long-term glycemic control in type 2 diabetes

Daisuke Ikeda, Hiroaki Koiwa, Tsuyoshi Takeuchi

Department of Cardiovascular, Chitose City Hospital, Chitose, Japan.

Background

Type 2 diabetes is a heterogeneous disease characterized insulin secretion and insulin resistance. Insulin secretion is one of important factors determining glycemic control of patients with diabetes. Glucagon stimulation test is one of older methods evaluating insulin secretion and is common in Japan.¹⁻⁴⁾ Glucagon stimulation test is well known experimentally but does not be reported so much to keep glycemic control good for the long term. In recent years, dipeptidyl peptidase 4 (DPP4) inhibitor, glucagon like peptide 1 (GLP1) agonist and inhibitor of sodium glucose cotransporter 2 (SGLT2) have been launched. These medicines make glycemic control in patients with type 2 diabetes easier.

Aim

We aim to know whether we can still predict glycemic control for the long term by insulin secretion evaluated by glucagon stimulation test.

Method

Japanese type 2 diabetes patients without medication with HbA1c >8.0 were evaluated for β-cell function by increments of C-peptide immunoreactivity in glucagon stimulation test (GST-ΔCPR) within 3 months from first visit. We retrospectively examined 101 patients in the first visit from April 2012 to Dec 2016. They were divided into quartiles by GST-ΔCPR (Q1:4.3±0.7, Q2:2.8±0.3, Q3:1.8±0.2, Q4:1.1±0.1, Table1).

Results

At baseline, HbA1c and BMI had no significant change among each quartile (Table1). HbA1c of highest quartile of GST-ΔCPR (Q1) tended to be better than lowest quartile (Q4) after 6-18 month from first visit (6M 6.4±1.1%, 7.1±1.0%, p<0.07, 12M 6.4±1.0%, 7.1±1.1%, p<0.07, 18M 6.6±1.0%, 7.3±1.1%, p<0.09, Figure 1). Numbers of categories of drugs taken in highest quartile of GST-ΔCPR were more than lowest quartile after 12 month (1.7±0.8, 2.4±1.2, p<0.05, Figure 2). After 12 month, patients whose GST-ΔCPR was low (Q4) had worse HbA1c and more numbers of categories of drugs taken than that whose GST-ΔCPR was high (Q1). After 24 month, it might have poor statistical power that HbA1c and number of categories of drugs taken did not significantly change among quartiles.

Many type2 diabetes patients took metformin and DPP4 inhibitors in all quartiles. Few patients used insulin, GLP-1 analog or sulfonylurea in highest quartiles (Q1). On the contrary, patients used insulin, GLP-1 analog or sulfonylurea increased, as GST-ΔCPR was decreased from Q2 to Q4 (Table 2).

Discussion

Our recent study shows that type 2 diabetes patients with poor insulin secretion in first visit tend to become poor glycemic control for 2 years. We evaluated β-cell function by GST-ΔCPR of type 2 diabetes patients without medication within 3 months from first visit. Its results were reflected in their treatment. We tended to use metformin and DPP4 inhibitors, not sulfonylurea to avoid hypoglycemia, especially for patients with good insulin secretion. SGLT2 inhibitors were used for few patients because SGLT2 inhibitors were recently launched in Japan in April 2014. Use of insulin, GLP1 analogs and sulfonylurea tended to increase as GST-ΔCPR was low. Previous studies reported indices related to insulin secretion including GST-ΔCPR as predictors for insulin,^{5,6)} and as predictor changing from insulin to liraglutide.⁷⁾ Averages of quartile of highest HbA1c were never poor from 7.1 to 7.3. This fact may mean that we optimized their drugs by checking insulin secretion used GST-ΔCPR. Nevertheless quartile of lowest GST-ΔCPR (Q4) was poorest glycemic control.

We did not evaluate dose of other drugs than metformin. We simply counted insulin or GLP-1 analog as one category. For example, GLP1 analogs are stronger than DPP4 inhibitors. But GLP1 analogs are counted as same one category as DPP4 inhibitors. Nevertheless we thought that numbers of categories of drugs reflects strength of medications, although not accurate. The medical care cost including drugs, although not evaluated in recent study, may be associated to gain as numbers of categories of drugs increase.

Conclusion

Evaluation of insulin secretion by glucagon stimulation test contributes not only to choosing appropriate therapeutic medicine but also predicting glycemic control for the long term. Glucagon stimulation test is one of valuable tools by which we know insulin secretion of patients with type 2 diabetes.

Reference

- 1) Diabetes 1977; 26: 605
- 2) Diabetologia 1977; 13: 65
- 3) Diabetes Care 1987; 10: 487
- 4) Endocrinol Jpn 1979; 26: 65
- 5) Acta Med Scand 1981; 210: 153
- 6) J Diabetes Invest 2011; 2: 297
- 7) J Diabetes Invest 2013; 4: 585

	Quartile 1 (n=28)	Quartile 2 (n=26)	Quartile 3 (n=23)	Quartile 4 (n=24)	
Age (years)	54±17	52±12	56±15	58±11	n.s.
Male	15 (54%)	16 (62%)	17 (73%)	13 (54%)	n.s.
Early Admission	16 (57%)	13 (50%)	16 (70%)	14 (58%)	n.s.
BMI (kg/m ²)	27.6±5.9	27.1±5.9	26.1±6.2	24.7±4.9	n.s.
HbA1c (%)	11.0±1.5	10.8±1.7	11.6±2.1	11.3±2.4	n.s.
ΔCPR (ng/ml)	4.3±0.7	2.8±0.3	1.8±0.2	1.1±0.4	p<0.001
Pre CPR (ng/ml)	3.2-6.1	2.1-3.1	1.5-2.0	0.3-1.4	
Post CPR (ng/ml)	2.9±1.1	2.7±1.3	2.1±1.1	1.9±1.2	p<0.01
	7.2±1.4	5.5±1.3	3.9±1.1	3.0±1.2	p<0.01

Table 1 : Characteristics of the patients

Figure 1 : BS control of the patients

Figure 2 : Total numbers of categories of drugs

Quartile 1			Quartile 2			Quartile 3			Quartile 4		
3M	12M	24M	3M	12M	24M	3M	12M	24M	3M	12M	24M
n=28	n=20	n=14	n=26	n=22	n=9	n=23	n=16	n=9	n=24	n=19	n=14
20(71)	14(70)	10(71)	20(77)	16(73)	7(78)	14(61)	9(56)	7(78)	14(58)	14(74)	12(86)
1138	964	1025	1103	1016	1125	1179	1083	1179	1143	1214	1167
16(57)	15(75)	13(92)	20(77)	16(73)	6(67)	15(65)	12(75)	8(89)	15(63)	15(79)	11(78)
0	2	1	2	2	1	0	0	1	1	2	2
1/0	1/0	1/0	3/0	2/1	2/0	2/0	1/1	1/1	2/1	3/3	5/0
1/1	1/0	1/0	1/0	0/0	0/0	1/1	0/3	0/2	1/3	2/3	2/1
0	1	0	0	0	0	3	2	1	5	2	1
1	0	0	2	2	1	3	2	1	2	1	1

Table 2 : Each numbers of Categories of drugs