Beneficial Effects of Insulin on Glycemic Control and β-Cell Function in Newly Diagnosed Type 2 Diabetes with Severe Hyperglycemia after Short-Term Intensive Insulin Therapy

Harn-Shen Chen, MD, PhD, Tzu-En Wu, MD, Tjin-Shing Jap, MD, Li-Chuan Hsiao, BSC, Shen-Hung Lee, BSC, Hong-Da Lin, MD

Running title: Insulin therapy in type 2 diabetes

Correspondence to: Hong-Da Lin, MD,
Division of Endocrinology and Metabolism, Department of Medicine,
Taipei Veterans General Hospital
Taipei, Taiwan, ROC.
E-mail: chenhs@vghtpe.gov.tw

Clinical trial reg. No NCT00506194, clinicaltrials.gov.

Received 15 January 2008 and accepted 3 June 2008.

Additional information for this article can be found in an online appendix at http://care.diabetesjournals.org.
**Objective**- To evaluate whether treatment with insulin is advantageous compared with oral anti-diabetic agents in newly diagnosed type 2 diabetes with severe hyperglycemia after short-term intensive insulin therapy.

**Research design and methods**- Newly diagnosed type 2 diabetic patients with severe hyperglycemia were hospitalized and treated with intensive insulin injections for 10-14 days. The oral glucose tolerance test (OGTT) was performed after intensive insulin treatment. After discharge, the patients were randomized to receive either insulin injections or oral anti-diabetic drugs (OAD) for further management. The OGTT was repeated 6 months later, and the β–cell function and insulin sensitivity were evaluated again. These subjects were continually followed-up for another 6 months to evaluate their long-term glycemic control.

**Results**- At the 6th month of the study, the A1C level was significantly lower in the insulin group than in the OAD group (6.33±0.70% vs. 7.50±1.50%, p=0.002). During the follow-up visit, the A1C level was still better in the insulin group (6.78±1.21% vs. 7.84±1.74%, p=0.009). All parameters regarding β-cell function measured in the OGTT were improved significantly in both groups after 6 months of treatment. Compared with the OAD group, the HOMA-beta index, insulin AUC and insulinogenic index were better in the insulin group.

**Conclusions**- A 6-month course of insulin therapy, compared with OAD treatment, could more effectively achieve adequate glycemic control and significant improvement of β-cell function in new-onset type 2 diabetic patients with severe hyperglycemia.
Insulin resistance and impaired insulin secretion are the main pathophysiological defects responsible for the development of hyperglycemia in type 2 diabetes (1,2). With the continuous presence of insulin resistance, progressive loss of ß-cell function is the crucial defect. The continuous decline in ß-cell function is affected by glucotoxicity generated by hyperglycemia and lipotoxicity due to lipolysis (3). Impaired ß-cell function appears to be reversible, particularly in the early stage of the disease where the limiting threshold for reversibility of decreased ß-cell mass has probably not been passed (4). So the potential benefits of early, aggressive intervention with insulin treatment to counter both ß-cell dysfunction and insulin resistance must be considered. Several reports have shown that short-term intensive insulin therapy can induce long-term glycemic control in newly diagnosed type 2 diabetic patients with mild to moderate hyperglycemia (5-7). However, more than half of these patients require oral anti-diabetic drug (OAD) therapy within one year to maintain near euglycemia.

When a new-onset type 2 diabetic patient presents with severe hyperglycemia, there are defects in insulin secretion and action, which is optimally treated with aggressive insulin injections (8-9). After the symptoms have been relieved, it may be possible to withdraw insulin and shift to oral agents. We hypothesized that continuous insulin therapy for a few months in new-onset type 2 diabetes with severe hyperglycemia may have a prolonged glycemic control. To address this concept, we designed this 6-month study to evaluate whether treatment with insulin is advantageous compared with OAD in newly diagnosed type 2 diabetes with severe hyperglycemia after short-term intensive insulin therapy.

METHODS

Subjects: Consecutive newly diagnosed type 2 diabetic patients with severe hyperglycemia (fasting plasma glucose >300 mg/dL or random plasma glucose >400 mg/dL) were recruited between October 2005 and December 2006. All patients were admitted to the hospital and received intensive insulin therapy. The excluding criteria included active liver disease, serum creatinine concentration >2.0 mg/dL after 5-10 days of therapy, proliferative diabetic retinopathy, definite coronary artery disease, malignancy and pregnancy. The patients with peak C-peptide levels during the oral glucose tolerance test (OGTT) less than 2.0 ng/mL were also excluded to rule out type 1 diabetes and latent autoimmune diabetes in adults. The study was approved by the Institutional Review Board of the Taipei Veterans General Hospital, and written informed consent was given before the OGTT.

During the hospitalization: The basal and pre-meal insulin doses were adjusted according to the preprandial and bedtime capillary blood glucose levels. The target glucose levels were preprandial blood glucose 90-130 mg/dL and bedtime blood glucose 100-160 mg/dL. After 10-14 days of intensive insulin treatment with their fasting blood glucose levels between 100 and 140 mg/dL, subjects received a 75-g OGTT after discontinuing regular insulin for about 12 hr and NPH insulin for about 24 hr. Baseline blood samples were drawn for A1C, cholesterol, triglyceride, glucose, insulin, C-peptide and other biochemicals. Blood samples were further collected for glucose and insulin at 30, 60, 90 and 120 minutes, and C-peptide at 120 minutes.

Outpatient clinic follow-up: All subjects were discharged after 10-14 days of intensive insulin therapy, and then randomized into two groups: continuing with insulin treatment or shifting to OAD. Subjects were then followed-up as outpatients and
Insulin therapy in type 2 diabetes

visited our clinic every two weeks during the first two months and then every four weeks for another 4 months.

In the insulin therapy group, subjects were instructed in the techniques for NPH insulin (Insulatard, Norvo Nordisk, Denmark) injection and home capillary glucose monitoring. Two thirds of the daily dose was administrated before breakfast and the other was administrated at bedtime. Insulin doses were titrated every three days to achieve target fasting plasma glucose (FPG) values between 90 and 130 mg/dl. The titration of OAD in our protocol was modified from Steno-2 study published in 2003 (10). As the initial step, overweight or obese patients (defined as body mass index above 25) received metformin (submaximal dose, 500 mg three times a day) and lean patients received a sulfonylurea, gliclazide-MR (submaximal dose, 90 mg per day). The dosage was titrated based on the FPG on the visiting day to achieve target values between 90 and 130 mg/dl. As the second step, metformin was added to the lean patients and gliclazide-MR to overweight or obese patients. As the third step, gliclazide-MR should be up-titrated to a maximum dose of 120 mg per day and metformin to 2550 mg per day with a splitting dose.

Clinical examination: A1C measurements were further performed at three and six months, and the OGTT was repeated after six months of randomization. We stopped pharmacological treatment for about 12 hr (metformin after the evening dose) and 24 hr (gliclazide-MR and insulatard after the morning dose) before performing the OGTT. Areas under the glucose and insulin curves (AUCs) during the OGTT were calculated by the trapezoid rule. Early-phase insulin secretion (insulogenic index) was calculated as the ratio between the incremental areas under the insulin and glucose curves during the OGTT \([\Delta G(AUC)/\Delta I(AUC)]\). The Matsuda index was calculated for insulin resistance as previously reported (11). Homeostasis model assessment was used to estimate insulin resistance (HOMA-IR) and \(\beta\)-cell function (HOMA-B) (12).

Follow-up examination: After the six months of intervention, patients in the insulin group also shifted to OAD for further management. All of these subjects were continually followed-up in our clinics for another six months to evaluate their long-term glycemic control.

Analytical methods: Plasma insulin levels were assayed using direct chemiluminescent technology with a two-site sandwich immunoassay (ADVIA Centaur, Bayer Corporation, Japan). The A1C was measured using high performance liquid chromatography (HPLC) instruments (HLC-723 GHB IIIs, Tosoh, Japan) with a reference range of 4.5% - 6.2%.

Outcomes: The primary outcome was the comparison of A1C change and the proportion of subjects who reached the treatment target (A1C ≤7.0% or ≤6.5% at 6 and 12 months, respectively). The secondary outcome was the \(\beta\)-cell function and insulin sensitivity calculated from the OGTT, hypoglycemic rate and weight change.

Statistical Analyses: The Statistical Package for the Social Sciences (SPSS) program for Windows, version 15.0, was used for data analysis. The paired Student’s t-test was used to analyze the difference from baseline to the end point, and the independent Student’s t-test was used to compare differences between the management programs. Changes from baseline in A1C, mean SMBG, insulin dose, OAD dose, body weight, and hypoglycemic events were analyzed using one-way ANOVA. Data are presented as mean±SD unless otherwise
stated, and a p value of less than 0.05 was taken to indicate a significant difference.

RESULTS

Study design: This study was a randomized, open label, parallel trial (Appendix Figure). Randomization was performed after 10-14 days of intensive insulin treatment. Because we suspected that some patients would refuse insulin therapy after randomization, we attempted to minimize patient drop-out, by randomizing in a 2:1 fashion between OADs and insulin. There were 60 patients with type 2 diabetes who were assessed for eligibility, and 50 subjects were randomized. Thirty patients were randomly assigned to receive insulin therapy and 20 patients to undergo OADs treatment.

Baseline characteristics: The baseline clinical characteristics and biochemical status of the patients in the insulin and OAD groups are shown in Table 1. The data presented in Table 1 were obtained after 10-14 days of intensive insulin therapy, except for peak fasting and random plasma glucose levels. The two treatment groups did not differ significantly in baseline clinical features.

Insulin and OAD dosage: During the study period, the insulin dose was decreased from 26.4±10.5 IU/day to 16.8±11.0 IU/day. Eleven patients started with gliclazide-MR and eight with metformin. The OAD dosage was increased gradually and titrated to 54.5±22.5 mg/day of gliclazide-MR and 884±416 mg/day of metformin at the end of the intervention. There were 4 patients who only used gliclazide-MR (mean dose, 45 mg) and 4 patients who only used metformin (mean dose, 750 mg), and 6 of them reached the target A1C (<7.0%). There were 10 patients who combined both drugs (mean dose, gliclazide-MR 60 mg and metformin 1200 mg).

Glycemic control: Figure 1A shows the FPG concentration in both groups in the study period. The FPG level was stable in the insulin group, while it increased in week two and week four and then decreased gradually in the OAD group. Figure 1B reveals the A1C changes in both groups during the study period and follow-up visits. At the end of the intervention, the A1C level was significantly lower in the insulin group than in the OAD group (6.33±0.70% vs. 7.50±1.50%, p=0.002). During the follow-up visits, the A1C level was still better in the insulin group (6.78±1.21% vs. 7.84±1.74%, p=0.009). Figure 1C shows the proportion with an A1C level less than 6.5% or 7.0% at six months and one year. The proportions of patients with A1C levels reaching these targets at six months and one year were significantly greater in the insulin group (p<0.001).

β-cell function and insulin resistance: Since the patients in the OAD group did not achieve the same glycemic target as the insulin group, we therefore only chose those with A1C level less than 7% to assess β-cell function and insulin resistance. There was no difference between the two subgroups of the OAD group at the baseline (Appendix Table). Table 2 reveals the changes in biochemical measurements over the course of the study, and the plasma glucose and insulin excursions at each OGTT are illustrated in Figure 2. All parameters regarding β-cell function measured in the OGTT were improved significantly in both groups after six months of intensive treatment. Compared with the OAD group, the HOMA-beta index, insulin AUC and insulinogenic index were significantly improved in the insulin group. The HOMA-IR and Matsuda index for insulin resistance showed no significantly change from baseline to the end of the intervention and without differences between the two groups.

Adverse events: No severe hypoglycemia occurred in either group. The
overall rate of minor hypoglycemia showed no significant difference between the two groups (1.39±1.16 vs. 2.30±1.87 episodes, p=0.082). There was a small increase in body weight from baseline to the end point in the insulin group (from 71.4±10.6 to 73.1±11.6 kg, p=0.028) and the OAD group (from 71.7±21.3 to 72.5±18.8 kg, p=0.021), but there was no significant difference between the two groups.

CONCLUSIONS
The study showed that desired glycemic control was successfully achieved by intensive insulin therapy for 10-14 days in cases of newly diagnosed type 2 diabetes with severe hyperglycemia. However, most of these subjects required pharmacological therapy to maintain near euglycemia in our study period. A six month course of further insulin therapy, compared with OAD treatment, could more effectively achieve a near-normal A1C level. We also found that parameters of the β-cell function were better improved in the insulin-treated than in the OAD-treated patients.

There has emerged evidence that short-term intensive insulin therapy in newly diagnosed type 2 diabetes could improve glycemic control associated with improved insulin secretion (5-7). Ryan et al. recently reported that, in 16 newly diagnosed type 2 diabetes cases with moderate hyperglycemia (mean fasting blood glucose of 239 mg/dL), a two to three week course of intensive insulin therapy was able to maintain good glycemic control at one year in seven of the subjects (6). In a similar study (7), 138 newly diagnosed type 2 diabetic patients with fasting blood glucose greater than 200 mg/dL (mean fasting blood glucose of 268 mg/dL, peak blood glucose of 390 mg/dL) were hospitalized and treated with continuous subcutaneous insulin infusion for two weeks. Optimal glycemic control was achieved within 6.3±3.9 days in 126 patients. The remission rate at the 12th month was 47.1%. In patients with moderate hyperglycemia, a two week course of intensive insulin therapy achieving near euglycemia might induce long-term glycemic control. This result may not be suitable in patients with severe hyperglycemia, such as our subjects with mean initial fasting blood glucose of 338 mg/dL, peak blood glucose of 508 mg/dL. All of our study subjects had received 10-14 days of intensive insulin therapy in hospital to make sure the glycemic control was optimal. After randomization, almost all of the patients were unable to maintain euglycemia without medication. Our data revealed that 10-14 days of intensive insulin treatment with near-normoglycemia can not maintain good glycemic control lasting for a long period. We suggest that short-term intensive insulin therapy may induce long-term glycemic control in newly diagnosed type 2 diabetes with moderate hyperglycemia, but not in patients with severe hyperglycemia. Further treatment with insulin for at least 1 year was necessary to maintain the euglycemia and improve β-cell function.

The favorable effect of insulin treatment on endogenous insulin secretion in our study could be due to better glycemic control. Glucose toxicity has been demonstrated clinically and has been investigated extensively in the laboratory (13). Defects in insulin secretion have been documented and directly related to hyperglycemia, and are correctable with the establishment of euglycemia (14-15). Thus, the shorter the period of antecedent glucotoxicity, the more likely the full recovery of β-cell function. Our results do support the concept that correction of hyperglycemia can improve insulin secretion. Another possibility is that β-cell secretory capacity may have been restored by “rested” β-cells induced by insulin injection (16). In our study, most of the subjects required pharmacological therapy to maintain near euglycemia after discontinuing insulin
therapy. In the insulin-treated subjects, the fasting blood glucose levels were maintained between 90-130 mg/dL with the insulin dose decreased from 26.4 IU per day to 16.8 IU per day, which means endogenous insulin secretion was increased. In the OAD-treated patients, however, the OAD doses were up titrated in the following six months to reach our glycemic target. Our data provide evidence that a short-term intensive insulin therapy can shorten the period of glucotoxicity and another six months of insulin therapy can further improve endogenous insulin secretion.

Some reports have shown that induction of normoglycemia in type 2 diabetes results in improved insulin resistance (17-19). In our present study, the insulin resistance measured by HOMA-IR and Matsuda index showed no significant change from baseline to the end of the intervention in both groups, and without significant difference between the two groups. The insulin resistance measured during the OGTT in our study was performed after intensive insulin therapy for 10-14 days. Some degree of insulin resistance might have been corrected in the 10-14 days of intensive insulin therapy. Both intensive therapy, either with OAD or insulin, could not further increase insulin sensitivity by improving glycemic control in the following six months. This should be confirmed by further study.

One limitation of our study is that some subjects in the OAD group were treated with different orders of gliclazide-MR and metformin. Sulphonylureas and metformin have different actions on the insulin sensitivity and secretion in type 2 diabetic patients. Our titration protocol was also inadequate to fully treat the patients randomized to OAD. It might have been more effective to use a modern OAD protocol utilizing self blood glucose monitoring and more frequent titration to rapidly achieve full dose and get more optimal glycemic control. Further studies will be required to intensively treat patients with insulin or one OAD to achieve the same glycemic control and then compare the β-cell function. Another limitation is that the numbers in this study were small and used indirect methods for assessing beta cell function and insulin sensitivity. The results need to confirm with a larger study and a better methodology before being considered as a routine clinical option.

In conclusion, our data demonstrated that intensive insulin therapy for 10-14 days can achieve optimal glycemic control in newly diagnosed type 2 diabetes with severe hyperglycemia, but cannot induce a long-term glycemic control. A six-month course of further insulin therapy, compared with OAD treatment, could more effectively maintain adequate glycemic control accompanied with significant improvement of β-cell function. Therefore, in the management of newly diagnosed type 2 diabetic patients with severe hyperglycemia, strong consideration should be given to early, aggressive insulin therapy for a rapid and sustained effect on glycemic control and beta cell function.
REFERENCES
1. Saad MF, Knowler WC, Pettitt DJ, Nelson RG, Charles MA, Bennett PH: A two-step model for development of non-insulin-dependent diabetes. *Am J Med* 90:229–235, 1991
2. Nathan DM: Clinical practice. Initial management of glycemia in type 2 diabetes mellitus. *N Engl J Med* 347:1342-1349, 2002
3. Robertson RP, Harmon J, Tran PO, Poitout V: β-Cell glucotoxicity, lipotoxicity, and chronic oxidative stress in type 2 diabetes. *Diabetes* 53(Suppl. 1):S119–S124, 2004
4. Wajchenberg BL: Beta-cell failure in diabetes and preservation by clinical treatment. *Endocr Rev* 28: 187-218, 2007
5. Alvarsson M, Sundkvist G, Lager I, Henricsson M, Berntorp K, Fernqvist-Forbes E, Steen L, Westermark G, Westermark P, Orn T, Grill V: Beneficial effects of insulin versus sulphonylurea on insulin secretion and metabolic control in recently diagnosed type 2 diabetic patients. *Diabetes Care* 26:2231-2237, 2003
6. Ryan EA, Imes S, Wallace C: Short-term intensive insulin therapy in newly diagnosed type 2 diabetes. *Diabetes Care* 27:1028–1032, 2004
7. Li Y, Xu W, Liao Z, Yao B, Chen X, Huang Z, Hu G, Weng J: Induction of long-term glycemic control in newly diagnosed type 2 diabetic patients is associated with improvement of beta-cell function. *Diabetes Care* 27:2597-2602, 2004
8. Nathan DM, Buse JB, Davidson MB, Heine RJ, Holman RR, Sherwin R, Zinman B: Management of hyperglycemia in type 2 diabetes: A consensus algorithm for the initiation and adjustment of therapy: a consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 29:1963-1972, 2006
9. Bloomgarden ZT: Exploring Treatment Strategies for Type 2 Diabetes. *Diabetes Care* 30:2737-2745, 2007
10. Gaede P, Vedel P, Larsen N, Jensen GV, Parving HH, Pedersen O: Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med* 348: 383-393, 2003
11. Matsuda M, DeFronzo RA: Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic glucose clamp. *Diabetes Care* 22:1462–1470, 1999
12. Matthews D, Hosker J, Rudenski A, Naylor B, Treacher D, Turner R: Homeostasis model assessment: insulin resistance and beta cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 28:412–419, 1985
13. Yki-Järvinen H: Toxicity of hyperglycaemia in type 2 diabetes. *Diabetes Metab Rev* 14:S45–S50, 1998
14. Hidaka H, Nagulesparan M, Klimses I, Clark R, Sasaki H, Aronoff SL, Vasquez B, Rubensteiin AH, Unger RH: Improvement of insulin secretion but not insulin resistance after short term control of plasma glucose in obese type II diabetics. *J Clin Endocrinol Metab* 54:217–222, 1982
15. Garvey WT, Olefsky JM, Griffin J, Hamman RF, Kolterman OG: The effect of insulin treatment on insulin secretion and insulin action in type II diabetes mellitus. *Diabetes* 34:222-234, 1985
16. Kilpatrick ED, Robertson RP: Differentiation between glucose-induced desensitization of insulin secretion and β-cell exhaustion in the HIT-T15 cell line. *Diabetes* 47:606–611, 1998
17. Samanta A, Burden AC, Jones GR, Clarkson L: The effect of short-term intensive insulin therapy in non-insulin-dependent diabetes who had failed on sulphonylurea therapy. *Diabetes Res* 3:269–271, 1986
18. Yki-Järvinen H, Esko N, Eero H, Taskmo MR: Clinical benefits and mechanisms of sustained response to intermittent insulin therapy in type 2 diabetic patients with secondary drug failure. *Am J Med* 84:185–192, 1988
19. Glaser B, Leibovich G, Nesher R, Hartling S, Binder C, Cerasi E: Improved beta-cell function after intensive insulin treatment in severe non-insulin-dependent diabetes. *Acta Endocrinol* 118:365–373, 1988
### Table 1. Baseline demographic and clinical characteristics in the two treatment groups

|                      | Insulin group (Intention-to-treat) | OAD group (Intention-to-treat) | Insulin group (A1C <7.0%) | OAD group (A1C <7.0%) |
|----------------------|------------------------------------|--------------------------------|---------------------------|-----------------------|
| Number               | 25                                 | 19                             | 22                        | 8                     |
| Age (years)          | 57.9±8.5                           | 59.6±12.6                      | 58.7±16.0                 | 56.5±15.9             |
| Sex (male : female)  | 19 : 6                             | 13 : 6                         | 17 : 5                    | 5 : 3                 |
| Body weight (kg)     | 71.4±10.6                          | 71.7±21.3                      | 71.2±10.3                 | 71.8 ± 23.6           |
| BMI (kg/m²)          | 27.55±4.20                         | 28.31±6.20                     | 27.69±6.58                | 26.64±8.01            |
| *Peak fasting plasma glucose (mg/dL)* | 345.0±82.2              | 329.2±24.0                     | 338.6±66.4                | 311.3±94.0            |
| *Peak plasma glucose (mg/dL)*    | 527.3±163.8                       | 483.7±217.2                    | 557.4±160.9               | 487.6±142.1           |
| A1C (%)              | 11.89±1.91                         | 11.33±1.57                     | 11.73±1.94                | 11.29±1.46            |
| Systolic BP (mmHg)   | 125.4±13.4                         | 130.7±12.9                     | 129.2±12.4                | 130.0±15.7            |
| Diastolic BP (mmHg)  | 74.2±10.6                          | 78.5±8.1                       | 76.1±10.0                 | 79.7±11.3             |
| Total cholesterol (mg/dL) | 193.1±54.8                   | 184.7±39.5                     | 202.3±56.9                | 197.2±25.0            |
| HDL cholesterol (mg/dL) | 45.9±15.1                      | 45.7±12.7                      | 44.4±14.2                 | 45.7±16.0             |
| Triglyceride (mg/dL) | 135 (52, 1234)                     | 131 (34, 1074)                 | 135 (52, 1234)            | 92 (34, 794)          |
| Urine albumin-to-creatinine ratio (mg/g) | 14.1 (3.2, 293.9)             | 17.3 (4.2, 626.2)              | 15.4 (3.2, 293.9)         | 17.9 (6.7, 418.0)     |

*Peak fasting plasma glucose and plasma glucose indicate the peak glucose level before randomization. OAD = oral anti-diabetic drug; BMI = body mass index; FPG = fasting plasma glucose; A1C = glycated hemoglobin A1C; BP = blood pressure; HDL = high-density lipoprotein. The 2 right columns revealed those subjects whose A1C level was less than 7.0%. Since the patients in the OAD group did not achieve the same glycemic target as the insulin group, we therefore only chose those with A1C level less than 7% to assess β-cell function and insulin resistance. (*p<0.05 compared with baseline; ¶p<0.05 between groups)
Table 2. Measures of glycemia and insulin secretion during OGTT before and after intensive treatment

|                          | Start of study period | End of intervention period |
|--------------------------|-----------------------|---------------------------|
|                          | Insulin group         | OAD group                 | Insulin group         | OAD group                 |
| N                        | 22                    | 8                         | 22                    | 8                         |
| Sex (male : female)      | 17 : 5                | 5 : 3                     | 17 : 5                | 5 : 3                     |
| A1C (%)                  | 11.73±1.94            | 11.29±1.46                | 6.15±0.51*            | 6.40±0.39*                |
| HOMA-IR                  | 3.81±1.48             | 4.33±1.42                 | 4.39±2.85             | 3.95±3.23                 |
| HOMA-Beta (%)            | 49.7±19.7             | 67.0±31.0                 | 111.2±66.7*¶          | 69.1±33.5                 |
| Glucose AUC (mg·hr·dL⁻¹) | 639.1±102.7           | 586.5±120.8               | 457.5±87.5*           | 498.1±107.8*              |
| Insulin AUC (µU·hr·mL⁻¹) | 58.3±18.7             | 66.1±16.9                 | 158.0±71.9*¶          | 93.04±44.7*               |
| Insulin0-30/Glucose0-30 (µU·mg⁻¹) | 1.30±0.85         | 1.39±1.22                 | 6.48±5.05*¶          | 2.78±1.78                 |
| Matsuda index            | 114.9±31.4            | 108.4±14.2                | 86.0±25.5             | 104.3±22.4                |
| ΔInsulinAUC/ΔGlucoseAUC (µU·mg⁻¹) | 1.17±0.71         | 1.17±0.71                 | 6.52±4.20*¶          | 3.33±2.11*                |

OAD = oral anti-diabetic drug; A1C = glycated hemoglobin A1C; AUC = area under curve.
*, p<0.05 compared with baseline; ¶, p<0.05 between each group at the end of the study.

We only chose those patients with A1C level less than 7.0% to assess β-cell function and insulin sensitivity.
**Figure Legends**

Figure 1. Glycemic control in the insulin-treatment group and OAD-treatment group.

(A) Fasting plasma glucose concentration (Mean±SE) in both groups in the study period. -2 weeks means pre-randomization.

(B) The A1C changes (Mean±SE) in both groups during the study period and follow-up visit.
(C) The proportion with A1C level less than 6.5% or 7.0% at six months and one year.
(*p<0.05 between groups).
Figure 2. Mean±SE for plasma glucose (A) and insulin (B) concentration during the OGTT at baseline and six months later in both groups. (*p<0.05 between groups; #p<0.05 baseline vs. after treatment)