Original Article
Effects of intensive insulin therapy upon pancreatic β cell function in patients newly diagnosed with type II diabetes

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Abstract: Objective: This study was designed to evaluate the clinical efficacy of intensive insulin therapy for patients newly diagnosed with type 2 diabetes. Methods: A total of 219 patients newly diagnosed with type 2 diabetes were randomly assigned into insulin group (n = 55), gliclazide group (n = 52), metformin group (n = 55) and pioglitazone group (n = 57). On the basis of diet and physical interventions, patients in the insulin group received intensive insulin therapy. Those in other three groups were given oral intake of medication. All treatment schemes endured for 12 weeks. A variety of indexes including fasting blood-glucose (FPG), FPG at 2 h after diet (FPG 2 h), hemoglobin A1c (HbAlc), area under the curve (AUC) for insulin (insulin AUC) after glucose load, C-peptide AUC after glucose load (C-peptide AUC), changes in insulin secretion index (Homa-β) and insulin resistance index (Homa-IR) were accurately measured and statistically among different groups. Results: The insulin AUC at 0-30 min, C-peptide AUC at 0-30 min and Homa-β in the insulin group were equally significantly higher compared with those levels in the other three groups. In addition, the level of Homa-IR in the insulin, metformin and pioglitazone groups were all significantly reduced compared with the values prior to respective treatment (all P < 0.05). Conclusion: Compared with oral administration of hypoglycemic drugs, intensive insulin therapy is able to better improve pancreatic β cell function and insulin resistance for newly-diagnosed type 2 diabetes patients.

Keywords: Diabetes, noninsulin-dependent, insulin, pancreatic β cell

Introduction
The pathogenesis of type 2 diabetes mainly ascribes to insulin resistance and pancreatic β cell function defects. With continuous presence of insulin resistance, progressive loss of β-cell function is the crucial defect [1-3]. The subjects who were newly-diagnosed with type 2 diabetes between March 2011 and April 2014 were enrolled in this clinical trial and randomly divided into different groups: some receiving intensive insulin therapy and others were given oral administration of hypoglycemic drugs. The clinical effects of these interventions upon alleviating pancreatic β cell function defects and insulin resistance were assessed and compared. Herein the outcomes were reported as follows.

Materials and methods
Clinical data
A total of 219 patients who were newly-diagnosed with type 2 diabetes were included, 108 males and 111 females, aged (48 ± 11.34) years on average. Inclusion criteria: this study complies with 1999 WHO diagnostic criteria for diabetes mellitus. FPG ≥ 11.1 mmol/L, no cardiocerebral vascular complications and capillary nervous lesions, no history of oral intake of hypoglycemic drugs or hypolipidemic drugs and had no history of insulin treatment. All enrolled subjects were randomly divided into insulin group (n = 55), gliclazide group (n = 52), metformin group (n = 55) and pioglitazone group (n = 57). The indexes including age, gender and
body-mass index (BMI) were comparable among the four groups. This study has been approved by the Ethics Committee of Hebei Provincial People’s Hospital and that it conforms to the provisions of the Declaration of Helsinki.

Treatment methods

All patients were subject to diet and physical activity interventions. In the insulin group, patients received subcutaneous injection of 8 U novolin R (Novolin R, Novo, Copenhagen) at 30 min prior to breakfast, lunch and dinner, triple times daily and were subject to subcutaneous injection of 8U novolin N (Novolin N, Novo, Copenhagen) at 22:00 p.m. In the gliclazide group, the subjects were delivered with oral administration of 80 mg gliclazide at 30 min before breakfast and dinner, twice daily. In the metformin group, patients received oral intake of 500 mg metformin before three meals daily. In the pioglitazone group, the subjects were given 30 mg pioglitazone once daily. In each group, the dosage of drugs was adjusted according to blood glucose levels. FPG was maintained below 7.0 mmol/L, FPG 2 h < 10 mmol/L, HbA1c < 7%. The course of treatment lasted for 12 weeks.

Pancreatic β cell function test

Function test of pancreatic β cell was performed before and after treatment: The subjects were delivered with oral administration of 75 g glucose within 5 min. The concentrations of blood glucose, insulin and C-peptide were measured at 30, 60, 120 and 180 min after drug administration, respectively. The level of blood glucose was measured by using glucose oxidase, insulin, C-peptide and HbA1c levels were determined by radioimmunoassay. Insulin AUC after glucose load = (0.5 × Finsulin + insulin30 + insulin60 + insulin120 + 0.5 × insuli

### Table 1. Changes in Homa-β and Homa-IR before and after treatment (mean ± s)

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Homa-β Before treatment</th>
<th>Homa-β After treatment</th>
<th>Homa-IR Before treatment</th>
<th>Homa-IR After treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin group</td>
<td>55</td>
<td>3.42 ± 0.43</td>
<td>5.68 ± 0.34*</td>
<td>1.79 ± 0.55</td>
<td>1.34 ± 0.36*</td>
</tr>
<tr>
<td>Gliclazide group</td>
<td>52</td>
<td>3.57 ± 0.34</td>
<td>4.51 ± 0.26*</td>
<td>1.82 ± 0.39</td>
<td>1.79 ± 0.35*</td>
</tr>
<tr>
<td>Metformin group</td>
<td>55</td>
<td>3.48 ± 0.41</td>
<td>4.53 ± 0.37*</td>
<td>1.79 ± 0.33</td>
<td>1.34 ± 0.24*</td>
</tr>
<tr>
<td>Pioglitazone group</td>
<td>57</td>
<td>3.57 ± 0.33</td>
<td>4.41 ± 0.28*</td>
<td>1.77 ± 0.29</td>
<td>1.38 ± 0.27*</td>
</tr>
</tbody>
</table>

Note: *denotes \( P < 0.05 \) compared with other three groups.
Homa-β and Homa-IR in all groups were illustrated in Table 1.

Discussion

Previous studies indicated that early level of insulin secretion serves as the major factor reflecting the function of pancreatic β cells [4-6]. After oral administration of glucose, patients with type 2 diabetes presented with relatively flat level of insulin AUC (0-30 min) and insignificant and delayed peak, hinting that the early secretion function was damaged. Previous studies [7-9] reported that type 2 diabetes patients with loss of the first-phase insulin secretion received intensive insulin therapy for two weeks on the basis of diet and physical activity interventions and then were given intravenous administration of glucose, which induced significant secretion phase of insulin and C-peptide and greatly increased the insulin and C-peptide AUCs, suggesting the recovery of first-phase insulin secretion. In this clinical trial, a sudden rise was noted in insulin and C-peptide AUCs at 0-30 min after intensive insulin therapy, indicating that intensive insulin therapy could recover the first-phase insulin secretion for patients who were newly-diagnosed with type 2 diabetes. The underlying mechanism probably ascribes to eliminating the toxic effects of hyperglycemia upon β cells [10, 11].

The insulin AUC (0-180 min) could reflect the overall level of insulin secretion. Previous investigations demonstrated that intensive insulin therapy exerted a significant effect upon improving the second-phase insulin secretion of pancreatic β cells in patients with type 2 diabetes, which has a higher clinical efficacy compared with diet control therapy and administration of sulfonylurea compounds [12]. In current investigation, the outcomes proved that both insulin and C-peptide AUCs were significantly elevated by 17.62% and 19.96% at 0-180 min after intensive insulin therapy, suggesting that intensive insulin therapy could improve the second-phase insulin secretion in patients with newly-diagnosed type 2 diabetes.

A variety of studies have been conducted to assess the role of intensive insulin therapy in improving insulin resistance. Scholars [13] analyzed 10 type 2 diabetes patients with insulin resistance and conducted insulin treatment for consecutive 40 weeks. The clinical outcomes indicated that the requirement of insulin decreased from (1.46 ± 0.43) U/(kg.d) to (1.19 ± 0.42) U/(kg.d), a mild loss of body weight and a significant reduction of HbAlc were also observed after 40-week treatment. These results demonstrated that intensive insulin therapy could effectively ease insulin resistance without the need to increase the dosage of insulin. It has been found [14-16] that the required dosage of insulin gradually decreased over the proceeding of intensive insulin therapy, hinting that intensive insulin therapy could exert certain effects on improving insulin resistance. In this clinical trial, all patients presented with Homa-IR reduction following intensive insulin therapy. The underlying mechanism is probably that intensive insulin therapy could mimic the physiological mode of insulin secretion, directly enhance the sensitivity of insulin, inhibit steatolysis and alleviate the toxic effects of lipids. Moreover, it could keep pancreatic β cells in a resting status, ease the burdens of β cells, accelerate the repairing of β cells and suppress the influence of fatty acids upon the insulin secretion of β cells [17].

It has been widely accepted that sulfaurea drugs could stimulate the secretion of insulin and improve the function of β cell secretion. The function indexes of β cell secretion were significantly enhanced after 12-week gliclazide treatment in newly-diagnosed type 2 diabetes patients [18]. Albeit gliclazide had small effects on early secretion of insulin, it could exert a strong impact upon the second-phase insulin secretion, which allows for a slow rise in insulin secretion after glucose load and delays the incidence of peak level of insulin secretion. The underlying mechanism of metformin effect is probably that it augments the sensitivity of peripheral tissues towards insulin, inhibits hepatic gluconeogenesis, decreases glycogen release and enhances the anaerobic glycolysis of glucose. Pioglitazone is able to bind with peroxisome proliferator-activated receptor γ to play a vital role in maintaining the stability of lipid levels, cell differentiation of adipocytes and insulin secretion. In addition, pioglitazone could enhance insulin sensitivity and improve insulin resistance.

In this investigation, patients from all groups had an increasing tendency in terms of insulin and C-peptide AUCs at 0-30 min after treat-
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However, no statistical significance was noted before and after treatment. In three groups, insulin and C-peptide AUCs at 0-180 min after treatment were significantly increased with the highest elevation in the gliclazide group. Homa-β function indexes were equally raised. In the metformin and pioglitazone, patients had a decrease in Homa-IR, whereas no significant changes were observed in the gliclazide group. These outcomes collectively demonstrated that gliclazide, metformin and pioglitazone could enhance the second-phase insulin secretion and improve pancreatic β cell function, while exert no significant effects on improvement of the first-phase insulin secretion. Both metformin and pioglitazone could improve insulin resistance, whereas gliclazide has no apparent effects.

Taken together, intensive insulin therapy could significantly improve the islet cell function in newly-diagnosed type 2 diabetes patients and ease insulin resistance, which is more efficacious compared with oral administration of three conventional medications.

Disclosure of conflict of interest

None.

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