Effect on T cell subsets and function of islet β cells of levemir combined with acarbose in elder patients with early-onset type 2 Diabetes Mellitus

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Objective: To discuss the effect of the combined therapy of levemir and acarbose on T cell subsets and function of islet β cells in elder patients with early-onset type 2 Diabetes Mellitus.

Methods: According to the number parity of entry sequence, 100 cases of elder patients with early-onset type 2 Diabetes Mellitus are divided into the control group and the observation group of 50 cases. The control group was treated with novolin and acarbose, the observation group was given subcutaneous injection of levemir and acarbose treatment. Compare the T cell subsets and function of islet β cells in two group of patients before the treatment (T0), treatment for 4 weeks (T1), treatment for 8 weeks (T2).

Results: (1) The levels of T0, T1, T2CD3+, CD4+, CD4+/CD8+ were increased in both groups, and CD8+ decreased. Among them, the levels of T1, T2CD3+, CD4+, CD4+/CD8+ of the observation group were obviously higher than the control group, the level of CD8+ was lowly than the control group, the difference was statistically significant; (2) In the stage of T0, T1, T2, the levels of FPG, HbA1c, HOMA-IR were showed a downward trend, the levels of FIns, HOMA-B were increased. In these two groups, the levels of T1, T2FPG, HbA1c, HOMA-IR of the observation group were lower than the control group, and the levels of FIns, HOMA-B were higher than the control group, the difference was statistically significant; (3) In the control group occurred 3 cases of hypoglycemia, and the incidence of adverse reactions was 6%. However, in the observation group no occurred adverse reactions, the difference was statistically significant. Conclusions: The combined therapy of levemir and acarbose in elder patients with early-onset type 2 Diabetes Mellitus, It helps to improve immune function, protect the islet β-cell function.

1. Introduction

With the aging process of society, also is affected by the habit of diet, the incidence of type 2 Diabetes Mellitus in elder patient(T2DM) obviously present a trend of increasing, and the Diabetes has a destructive effect on immune function, at the same time, also is the predisposing factor of a variety of disease[1]. In the past for the elder patient with diabetes, we mainly taken oral hypoglycemic therapy. Though the long term clinical study we found that, although oral drugs can control glycemia level, but the compliance rate is low, also there is no help to function of system immune and the islet β-cell[2]. In recent years, scholar from everywhere of the world recommend that in connection with early on-set T2DM patients to provide early insulin therapy[2,3]. Since 2015, the author began to use the combined therapy of levemir and acarbose in elder patient with T2DM, and achieved good results.

2. Materials and methods

2.1 Study population

According to the number parity of entry sequence, 100 cases of elder patients with early-onset type 2 Diabetes Mellitus are divided into the control group and the observation group of 50 cases. In
the observation group, 26 cases of male, 24 of female, aged at 60 to 68, average in (64.45±3.45) years, Fasting blood glucose (FBG): 22.36-28.62 kg/m², average in (25.75±2.44) kg/m²; Body Mass Index (BMI): 22.36-28.62 kg/m², average in (25.75±2.44) kg/m². In the control group, 25 cases of male, 25 of female, aged at 61 to 70, average in (65.15±3.25) years, FBG: 10.21-13.12 mmol/L, average in (11.75±1.26) mmol/L, BMI: 22.12-28.29 kg/m², average in (25.42±2.47) kg/m². There were no statistically significant differences in sex, age, blood glucose, BMI and other clinical data between the two group (P>0.05), comparable.

2.2 Inclusion and exclusion criteria

Inclusion criteria: (1) Clinical symptoms and laboratory indicators in line with the relevant diagnostic criteria of “Chinese type 2 diabetes prevention and treatment guide”[4]; (2) Age in 60 and over; (3) First diagnosed T2DM, simple oral drug poorly controlled the level of glycemia; (4) FBG>10.0 mmol/L; (5) The protein uria negative; (6) Compliance with good behavior, and coordinate with this experimental study.

Exclusion criteria: (1) Non-diabetic-induced hyperglycemia; (2) Within a month treat with immune agents, glucocorticoids and other drugs; (3) Combined infection, malignancy, and other serious endocrine diseases.

2.3 Method of treatment

Two group of patients based on BMI, activity, glycemia level and personal physical condition, create a prescription of diet and an exercise program, quite e cigarete and alcohol, processing a training of self - management ability. While the patient of observation group treated with the combined therapy of novolin and acarbose, the usage and dosage are as follows: Novolin 30IR (Isophane Protamine Biosynthetic Human Insulin Injection, made by Novo Nordisk Company of Denmark, Chinese medicine accurate characters J20030082) subcutaneous injection 30 min before meals, The initial dose of 0.3 U/times, 3 times/d; level of glycemia poorly controlled, alter the dosage to 0.5 U/times. Acarbose (produced by Bayer Healthcare limited company, Chinese medicine accurate characters H19990205) oral take before meals, the initial dose of 50 mg/times, 3 times/d; Gradually increased to each time 0.1 g/times, 3 times/ d. The control group treated with the combined therapy of levmir and acarbose, the usage and dosage are as follows: Lenvemir (Insulin Detemir Injection, made by Novo Nordisk Company of Denmark, Chinese medicine accurate characters J20090100) subcutaneous injection, the initial dose of 0.2 U/times, 1 times/d, Injection time is 22:00 daily, level of glycemia poorly controlled, alter the dosage to 2 times/d, Injection time is 11:00 and 22:00 daily. The usage and dosage of acarbose are the same to the observation group. During the treatment of the patient of two group, we must monitor closely the level of glycemia, observe adverse reactions, and timely adjust the method of treatment, 4 weeks as a course of treatment.

The patient of two group were treated for two consecutive courses.

2.4 Description of the variables

(1) Compare the FBG, Fasting insulin (Fins), glycosylated hemoglobin (HbA1c), Insulin resistance index (HOMA-IR) in two group of patients before the treatment (T0), treatment for 4 weeks (T1), treatment for 8 weeks (T2). Among them, the glycemia is detected by hexokinase method, HbA1c test used the affinity chromatography micro-column method, the insulin test processed the luminescence immunoassay method, HOMA-IR=FBG FINS/22.5; HOMA-B=20×FINS/(FBG-3.5). (2) Compare the change of T cell subsets in two group of patients before the treatment (T0), treatment for 1 month (T1), treatment for 3 months (T2). Specifically included: CD3+, CD4+, CD8+, CD4+/CD8+, the test results was detected by the flow cytometer of Belhai City People ´s Hospital; (3) The incidence of adverse reactions was compared between the two groups.

2.5 Statistical analysis

Statistical analysis were performed using SPSS for windows version 17.0, measured data expressed with, submitted the normal distribution, One-way repeated and t test measures were used for analysis of variance. The comparison data used the χ² test, P<0.05 indicates that the difference was statistically significant.

3. Results

3.1The comparison of levels of T lymphocyte subsets between the two groups

In the stage T0, there was no significant difference in CD3+, CD4+, CD8+, CD4+/CD8+ levels between the two groups (P>0.05); in the stage T1, T2, CD3+, CD4+, CD4+/CD8+ levels were increased, CD8+ showed a downward trend, no significant difference between the two groups (P>0.05). However, the observation group compared with the control group, in the stage T1, T2, CD3+, CD4+, CD4+/CD8+ levels were significantly higher, CD8+ was lower, the comparison was significantly different (P<0.05). See Table 1.

3.2 The comparison of the indexes of islet β – cell function between two groups

The levels of FPG, HbA1c, FIns, HOMA-IR, HOMA-B in the stage T0 present no significant difference between those two groups (P>0.05), FPG, HbA1c and HOMA-IR levels decreased at T1 and T2, and the levels of FIns and HOMA-B were increased, there was significant difference in all time points (P>0.05), but the levels of FPG, HbA1c and HOMA-IR in observation group were significantly lower than those in control group at T1 and T2, FIns and HOMA-B were higher than those in the control group. At T1 and T2 when the two groups were significantly different (P<0.05). See table 2.
Ps: compared with the observation group:

### Table 1
The comparison of T lymphocyte subsets between the two groups (n=50).

<table>
<thead>
<tr>
<th>Group</th>
<th>T0</th>
<th>T1</th>
<th>T2</th>
<th>Value F</th>
<th>Value P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Observation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD3 (%)</td>
<td>51.21±7.02</td>
<td>52.75±6.55</td>
<td>58.09±6.55</td>
<td>13.485</td>
<td>0.018</td>
</tr>
<tr>
<td>CD4 (%)</td>
<td>34.57±7.24</td>
<td>35.09±7.81</td>
<td>36.44±7.38</td>
<td>11.327</td>
<td>0.022</td>
</tr>
<tr>
<td>CD8 (%)</td>
<td>21.84±2.15</td>
<td>19.25±3.38</td>
<td>17.77±3.22</td>
<td>9.181</td>
<td>0.026</td>
</tr>
<tr>
<td>CD4+/CD8+</td>
<td>1.77±0.22</td>
<td>1.85±0.19</td>
<td>2.01±0.22</td>
<td>6.385</td>
<td>0.034</td>
</tr>
<tr>
<td><strong>Control</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD3 (%)</td>
<td>51.28±7.15</td>
<td>52.36±6.19</td>
<td>54.11±6.85</td>
<td>11.787</td>
<td>0.021</td>
</tr>
<tr>
<td>CD4 (%)</td>
<td>34.72±7.27</td>
<td>33.96±7.53</td>
<td>35.72±5.72</td>
<td>10.452</td>
<td>0.030</td>
</tr>
<tr>
<td>CD8 (%)</td>
<td>21.91±2.23</td>
<td>20.46±3.46</td>
<td>19.09±2.32</td>
<td>8.176</td>
<td>0.029</td>
</tr>
<tr>
<td>CD4+/CD8+</td>
<td>1.76±0.21</td>
<td>1.81±0.16</td>
<td>1.89±0.19</td>
<td>5.378</td>
<td>0.039</td>
</tr>
</tbody>
</table>

Ps: compared with the observation group: *P*<0.05.

### Table 2
The comparison of the indexes of islet β-cell function between two groups (n=50).

<table>
<thead>
<tr>
<th>Group</th>
<th>Indicator</th>
<th>T0</th>
<th>T1</th>
<th>T2</th>
<th>Value F</th>
<th>Value P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Observation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FPG (mmol/L)</td>
<td>11.75±1.26</td>
<td>6.50±0.63</td>
<td>6.01±0.42</td>
<td>16.325</td>
<td>0.008</td>
<td></td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>7.95±1.23</td>
<td>6.82±1.05</td>
<td>6.21±0.84</td>
<td>9.526</td>
<td>0.025</td>
<td></td>
</tr>
<tr>
<td>Fins (mIU/L)</td>
<td>7.38±0.85</td>
<td>9.15±1.62</td>
<td>10.55±1.67</td>
<td>13.457</td>
<td>0.016</td>
<td></td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>4.62±0.52</td>
<td>3.75±0.45</td>
<td>3.06±0.38</td>
<td>8.372</td>
<td>0.028</td>
<td></td>
</tr>
<tr>
<td>HOMA-B</td>
<td>32.52±12.86</td>
<td>51.65±14.32</td>
<td>60.11±16.37</td>
<td>58.257</td>
<td>0.000</td>
<td></td>
</tr>
<tr>
<td><strong>Control</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FPG (mmol/L)</td>
<td>11.71±1.22</td>
<td>7.15±1.35</td>
<td>6.72±0.43</td>
<td>12.157</td>
<td>0.019</td>
<td></td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>7.58±1.21</td>
<td>7.11±1.05</td>
<td>6.77±0.92</td>
<td>8.325</td>
<td>0.028</td>
<td></td>
</tr>
<tr>
<td>Fins (mIU/L)</td>
<td>7.26±0.91</td>
<td>8.67±0.95</td>
<td>9.44±1.13</td>
<td>11.652</td>
<td>0.021</td>
<td></td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>4.64±0.62</td>
<td>4.25±0.64</td>
<td>4.02±0.71</td>
<td>7.257</td>
<td>0.032</td>
<td></td>
</tr>
<tr>
<td>HOMA-B</td>
<td>32.41±11.31</td>
<td>37.73±12.12</td>
<td>53.87±12.46</td>
<td>37.157</td>
<td>0.000</td>
<td></td>
</tr>
</tbody>
</table>

Ps: compared with the observation group: *P*<0.05.

### 3.3 Comparison of adverse reaction between two groups

In the control group occurred 3 cases of hypoglycemia, and the incidence of adverse reactions was 6%. There were no adverse reactions in the observation group, the difference was statistically significant (*P*<0.05).

### 4. Discussion

In recent years, the incidence of diabetes in China has been increasing year by year, according to the International Diabetes Federation(IDF) published in 2013 diabetes map shows that the number of people with diabetes in China is the world’s first, of which more than 90% are the T2DM[5,6]. Although clinical T2DM shows a trend of younger, but T2DM is still present a significant harm on the elderly patients[7]. Because of elderly patients with more complications, acarbose is the first line for clinical treatment, it is α-glucosidase inhibitor, its functioning mainly by inhibiting the α-glucosidase, reducing the decomposition of polysaccharides into glucose, slowing the absorption of glucose, and achieve the goal of reducing PBG, especially for carbohydrate-based Chinese elderly patients with T2DM[8]. In this respect, this study selected acarbose as the preferred oral drug.

Some elderly patients are often found T2DM when treated with complications, such early onset T2DM patient, glycemia levels are often high, laboratory tests show more severe loss of islet β cell function, insufficient secretion of endogenous insulin, simple oral medication is difficult to control this situation[9]. Some scholars recommend the insulin intervention for the patient with uncontrol glycemia levels or patient with severe complications[10,11]. In addition, a large number of clinical studies have shown that T2DM have a larger devastating on the immune function, in which changes in T lymphocyte subsets are more sensitive, the condition of T lymphocyte improvement is related to the control of diabetes[12]. This study shows that elderly patients with T2DM T lymphocytes have a certain inhibition phenomenon.

Currently, there is no standard for the selection of insulin type in early onset of type 2 diabetes, in the past, mainly to take novolin as the representative of the short-acting insulin subcutaneous injection with oral drug therapy. However, in recent years, levemir (insulin detemir) as the long-acting insulin began to be applied to clinical, its efficacy and safety are fully affirmed.

Yang Yongmei, et al[13] found the combination of acarbose and levemir in the treatment of T2DM in elderly patients confirmed that it can help control glycemia levels, reduce HbA1c, reduce the incidence of adverse reactions such as hypoglycemia, glycemia level compliance rate is higher, the clinical effect is better than Novolin N. Guo xiaofang, et al[14] have been reported that the combination of acarbose and insulin detemir failed in the treatment of oral hypoglycemic agents in elderly patients with T2DM, the levels of HbA1c, FC-P and 2 h C-P were improved, Clinical effect is superior to Novolin 30R. This study shows that the combination of acarbose and levemir in the treatment of early onset T2DM, T cell subsets CD3+, CD4+, CD4+/CD8+ levels, CD8− decreased significantly better than Novolin 30R treatment, suggesting that the levemir can improve the immune function and effect significantly. Further observed the situation of islet β-cell, the levels of FPG, HbA1c, HOMA-IR...
were decreased, and Flns and HOMA-B were increased, which were significant better than patient treated with novolin 30R. Therefore, the study suggested that the levemir to improve the function of islet β-cell is more favorable, and the results are basically the same as Yang Yongmei, Guo Xiaofang and other research results. Besides, therapy levemir in patients treated for 8 weeks without adverse reactions occurred, and therapy novlin bring the incidence of hypoglycemia in rate of 6%, expressing levemir is more secure.

Analysis of the reasons, on the one hand, Levemir is a new long-acting insulin analogues, the pharmacokinetic curve is more moderate, after injection no significant peak effect, and it functioned smoothly. Help to avoid the inhibition of islet β-cell function caused by the peak concentration which produced by short-acting and intermediate-acting insulin and analogs, so the improvement of islet β-cell function is more obvious[3,15]. On the other hand, levemir can provide extended, replicable hypoglycemic effect, in inflammatory effect. Wang Zhenyu reports levemir can inhibit the release of inflammatory mediators, play an anti-inflammatory effect. The application of insulin to strictly control glycemia levels, also cell subsets are always in a relatively constant ratio, CD3+ and CD8+ cell function.

In summary, the combination of levemir and acarbose in the treatment of elderly patients with early T2DM can improve the indicators of T lymphocyte, enhance immune function, and play an important role in the protection of islet β-cell function, worthy of clinical application.

References


[17] Yki-Järvinen H, Bergenstal R, Ziemen M. New insulin glargine 300 units/mL versus glargine 100 units/mL in people with type 2 diabetes using oral agents and basal insulin: glucose control and hypoglycemia in a 6-month randomized controlled trial (EDITON 2). Diabetes Care 2014; 37(12): 3235-3243.

