Effection of saxagliptin therapy on elderly patients with type 2 diabetes on pancreatic $\beta$-cell function and micro-inflammatory state

Jin-Ying Zhao\textsuperscript{1}\textsuperscript{*}, Bo Chen\textsuperscript{2}, Xiao-Dong Peng\textsuperscript{3}

\textsuperscript{1}Department of Endocrinology, Lanzhou General Hospital of Lanzhou Military Area Command, Lanzhou 730050, China
\textsuperscript{2}Department of emergency, Lanzhou General Hospital of Lanzhou Military Area Command, Lanzhou 730050, China
\textsuperscript{3}Department of Pharmacology, Ningxia Medical University, Yinchuan 750004, China

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Saxagliptin
Elderly patients
Type 2 diabetes mellitus
Islet $\beta$-cell function
Micro inflammation

ABSTRACT

Objective: To explore the effection of saxagliptin therapy on elderly patients with type 2 diabetes on pancreatic $\beta$-cell function and micro-inflammatory state. Methods: A total of 150 cases of elderly patients with type 2 diabetes were randomly divided into A, B, C three groups, and each 50 cases. A group received metformin treatment, B group given saxagliptin treatment, C group given saxagliptin and metformin treatment, observed three groups of patients islet $\beta$-cell function index and microinflammation improvement situation after three months of treatment. Results: (1) After three months of treatment, FPG, P2hPG, HbA1c levels in three groups were significantly lower than before treatment, The levels of FPG, P2hPG, HbA1c in group C lower than group A and group B after treatment, and group B were lower than that of group A. All the above differences were statistically significant; (2) After three months of treatment, FIns, HOMA-B levels in groups of B and C were higher than before treatment and group A, which were significant differences; (3) After three months of treatment, the serum of CRP, IL-6, LPS levels in the three groups were significantly reduced than before treatment, After treatment, the serum of CRP, IL-6, LPS levels in group C were lower than group A and group B, and group B were lower than that of group A. All the above differences were statistically significant. Conclusion: Saxagliptin treatment of elderly patients with type 2 diabetes to improve the function and micro aspects of islet $\beta$-cell inflammation than metformin, combine with metformin the treatment better.

1. Introduction

In elderly patients with type 2 diabetes mellitus (T2DM), micro inflammation exists in different degrees, which can promote a variety of complications\textsuperscript{[1,2]}. At present, there are many drugs for T2DM treatment, mainly to promote insulin secretion and increase the sensitivity of peripheral tissues to insulin. In recent years, the research of new drugs which can improve the function of islet cells and reduce the micro inflammatory state for the treatment of T2DM has become a hot spot\textsuperscript{[3]}. Saxagliptin is the two peptide based-4 (DPP-4) inhibitor, as a novel hypoglycemic drug, it has been widely used in clinical. Our study found that it has a significant effect on improving the function of islet beta cells and micro inflammatory state, and the reports as follows.

2. Objects and methods

2.1 General information

A total of 150 cases of elderly patients with type 2 diabetes admitted to the Department of endocrinology of Lanzhou General Hospital from January 2014 to June 2015 were randomly divided into A, B, C three groups, and each 50 cases. A group: male 31 cases, female 19 cases; age from 61-69 years old with an average (64.19±3.33) years; body weight from 55 to 76 kg with an average (63.65±6.75) kg; Fasting blood glucose (FPG) from 7.21 to 10.20 mmol/L with an average (8.45±1.22) mmol/L; glycosylated hemoglobin (HbA1c) from 6.16% to 8.72% with an
average (7.59±1.23)%. B group: male 30 cases, female 20 cases; age from 61 to 70 years old with an average (64.35±4.41) years; body weight from 54 to 77 kg with an average (63.26±6.49) kg; Fasting blood glucose (FPG) from 7.22 to 10.26 mmol/L with an average (8.47±1.36) mmol/L; glycosylated hemoglobin (HbA1c) from 6.09% to 8.53% with an average (7.54±1.18)%. C group: male 28 cases, female 22 cases; age from 60-70 years old with an average (64.72±3.58) years; body weight from 53 to 78.5 kg with an average (64.16±6.62) kg; Fasting blood glucose (FPG) from 7.19 to 10.34 mmol/L with an average (8.51±1.38) mmol/L; glycosylated hemoglobin (HbA1c) from 6.12% to 8.45% with an average (7.51±1.05)%. There were no significant differences in gender, age, body weight, FPG, HbA1c and other general data between the three groups (P>0.05).

2.2 Inclusion and exclusion criteria

Inclusion criteria: (1) type 2 diabetes mellitus diagnosis criteria were in line with the guidelines for the prevention and treatment of type 2 diabetes in China (2010 Edition) [4]; Fasting blood glucose (FPG) over 7 mmol/L or random blood glucose over 11.1 mmol/L; Oral glucose tolerance test (OGTT) 2 h blood glucose (2hPBG) over 11.1 mmol/L. (2) Age over 60 years old; (3) HbA1C<9%; (4) The initial diagnosis, without the use of hypoglycemic drugs. Exclusion criteria: (1) Type 1 diabetes mellitus or other causes of hyperglycemia; (2) Combined with metformin or/and Saxagliptin contraindication; (3) Combined liver and kidney dysfunction, cardiovascular diseases, malignant tumor; (4) The use of corticosteroids within 6 months.

2.3 Treatment methods

All the three groups patients were given diabetes diet prescription control, and make individual exercise programs, health education and other basic treatment. Group A was given metformin treatment (Yongkang Beijings Pharmaceutical Co., Ltd. Chinese medicine quasi word H11020596, batch number 2013011520140520), with the initial 0.25 g/times, 2-3 times/d, then gradually increase according to the effect to the general 1.0-1.5 g/d. Group B was given saxagliptin treatment (Sino American Shanghai Squibb pharmaceuticals company, Chinese medicine quasi word J20110028, batch number 2012112520140613), with 5 mg/ times, 1 times/d. Group C was given saxagliptin combined with metformin treatment, the specific usage and dosage was same as group A and B.

2.4 Observation indexes

Compare the levels of FPG, 2hPBG, HbA1c, insulin (FIns) and insulin secretion index (HOMA-B) of the three groups patients before and 3 months after treatment. Used Glucose oxidase method to detect the blood glucose level, the content of insulin was detected by radioimmunoassay and the level of HbA1c was detected by chromatography, HOMA-B=20×FINS/(FPG-3.5). Compare the levels of C reactive protein (CRP), interleukin 6 (IL-6) and lipopolysaccharide (LPS) of the three groups patients before and 3 months after treatment. The level of serum CRP was detected by immune turbidity method, the serum IL-6 and LPS levels were detected by Enzyme linked immunosorbent assay (ELISA).

2.5 Statistical methods

Using SPSS 19.0 software for statistical analysis, the measurement data were expressed by Mean ± SD, using T test for groups comparison, P<0.05 was considered the difference to be statistically significant.

3. Results

3.1 Comparison the levels of FPG, 2hPBG and HbA1c between the three groups before and after treatment

All the three groups patients had no obvious complications during the treatment and no patients quit the study. There were no significant differences in FPG, 2hPBG and HbA1c between the three groups before treatment (P>0.05). After 3 months treatment, the levels of FPG, 2hPBG and HbA1c in the three groups were lower than those before treatment, the levels of FPG, P2hPG, HbA1c in group C were lower than those in group A and group B , and those in group B were lower than in group A, the differences were statistically significant (P<0.05). See table 1.

3.2 Comparison the levels of FIns and HOMA–B between the three groups before and after treatment

There were no significant differences in FIns and HOMA–B between the three groups before treatment (P>0.05). After 3 months treatment, the levels of FIns and HOMA-B in group B and group C were significantly higher than those before treatment, and the differences were statistically significant (P<0.05). FIns and HOMA-B levels had no significant differences in group A compared

### Table 1.

<table>
<thead>
<tr>
<th>Group</th>
<th>Time</th>
<th>FPG (mmol/L)</th>
<th>2hPBG (mmol/L)</th>
<th>HbA1c (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>Before treatment</td>
<td>8.45±1.22</td>
<td>12.46±2.29</td>
<td>7.59±1.23</td>
</tr>
<tr>
<td></td>
<td>After treatment</td>
<td>6.90±0.66</td>
<td>9.09±0.67</td>
<td>6.82±1.06</td>
</tr>
<tr>
<td>Group B</td>
<td>Before treatment</td>
<td>8.47±1.36</td>
<td>12.51±2.21</td>
<td>7.54±1.18</td>
</tr>
<tr>
<td></td>
<td>After treatment</td>
<td>6.73±0.42</td>
<td>8.86±0.62</td>
<td>6.77±1.15c</td>
</tr>
<tr>
<td>Group C</td>
<td>Before treatment</td>
<td>8.51±1.38</td>
<td>12.49±2.31</td>
<td>7.51±1.05</td>
</tr>
<tr>
<td></td>
<td>After treatment</td>
<td>6.08±0.45abc</td>
<td>8.15±0.66abc</td>
<td>6.23±1.09abc</td>
</tr>
</tbody>
</table>

Ps: Compared with before treatment, *P<0.05; Compared with group A, **P<0.05; Compared with group B, ***P<0.05
with before treatment ($P>0.05$). Fins and HOMA-B levels in group B and C were higher than those in group A, and the differences were statistically significant ($P<0.05$), while it had no significant differences between the B and C group ($P>0.05$). See table 2.

3.3 Comparison the levels of CRP, IL-6 and LPS between the three groups before and after treatment

There were no significant differences in serum CRP, IL-6 and LPS levels between the three groups before treatment ($P>0.05$). After 3 months treatment, the levels of serum CRP, IL-6 and LPS in the three groups were lower than those before treatment, and the differences were statistically significant ($P<0.05$). The levels of CRP, IL-6 and LPS in group C were lower than those in group A and group B, and those in group B were lower than in group A, the differences were statistically significant ($P<0.05$). See table 3.

Table 2
Comparison the levels of Fins and HOMA-B between the three groups before and after treatment ($P=50$).

<table>
<thead>
<tr>
<th>Group</th>
<th>Time</th>
<th>Fins (mIU/L)</th>
<th>HOMA-B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>Before treatment</td>
<td>7.26±0.91</td>
<td>32.52±12.86</td>
</tr>
<tr>
<td>Group B</td>
<td>After treatment</td>
<td>7.61±1.02</td>
<td>33.72±12.98</td>
</tr>
<tr>
<td>Group C</td>
<td>Before treatment</td>
<td>7.38±0.85</td>
<td>32.45±11.39</td>
</tr>
<tr>
<td></td>
<td>After treatment</td>
<td>12.16±1.67</td>
<td>58.65±14.32a</td>
</tr>
</tbody>
</table>

Ps: Compared with before treatment, "$P<0.05$; Compared with group A, "$P<0.05".

Table 3
Comparison the levels of CRP, IL-6 and LPS between the three groups before and after treatment (n=50).

<table>
<thead>
<tr>
<th>Group</th>
<th>Time</th>
<th>CRP (mg/L)</th>
<th>IL-6 (ng/mL)</th>
<th>LPS (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>Before treatment</td>
<td>18.65±5.32</td>
<td>3.52±0.45</td>
<td>6.19±1.81</td>
</tr>
<tr>
<td></td>
<td>After treatment</td>
<td>15.38±3.22</td>
<td>3.06±0.41</td>
<td>5.71±1.28</td>
</tr>
<tr>
<td>Group B</td>
<td>Before treatment</td>
<td>19.05±5.86</td>
<td>3.46±0.46</td>
<td>6.11±1.87</td>
</tr>
<tr>
<td></td>
<td>After treatment</td>
<td>12.92±2.45ab</td>
<td>2.55±0.36a</td>
<td>5.32±1.09ab</td>
</tr>
<tr>
<td>Group C</td>
<td>Before treatment</td>
<td>18.92±5.52</td>
<td>3.58±0.47</td>
<td>6.21±1.86</td>
</tr>
<tr>
<td></td>
<td>After treatment</td>
<td>11.82±2.26abc</td>
<td>2.23±0.37abc</td>
<td>4.87±1.11abc</td>
</tr>
</tbody>
</table>

Ps: Compared with before treatment, "$P<0.05$; Compared with group A, "$P<0.05".

4. Discussions

In recent years, with the rapid development of China’s aging population and the influence of people’s life style change, the incidence of diabetes has increased significantly and has become one of the main diseases threatening human health and life quality[5,6]. Especially for elderly patients, it’s very easy to cause a variety of complications and even cause death. Foreign studies have confirmed that T2DM patients mainly exist three shortcomings: insulin resistance, beta cell dysfunction and liver glycogen excessive decomposition[7], and confirmed the existence of micro inflammatory state in T2DM patients, even some scholars believe that T2DM itself is a kind of persistent low level inflammation[8,9]. At present, how to restore the insulin secretion function of islet beta cells and improve its chronic inflammation has become a new target in the field of diabetes research. Two peptide based peptide-4 (DPP-4) inhibitors, new drugs for T2DM treatment, has a certain effect in the control of T2DM blood glucose levels, improve the function of beta cells and reduce the body micro inflammatory reaction, which provide a new way for delaying the progression of T2DM disease in the elderly[10,11].

Abdul-Ghani[12] had confirmed that DPP-4 representative drug saxagliptin could effectively reduce the blood glucose level and stabilize it at a low level, it had significant effect in reducing insulin resistance and increasing insulin secretion in T2DM patients. Our study found that the application of saxagliptin and metformin could reduce the levels of FPG, 2hPBG and HbA1c in elderly patients with T2DM, the indicators improved better in patients treated with saxagliptin than in patients treated with metformin. The effect of the combined application of the two drugs in improving the blood sugar indexes was better than one drug alone. Observation the islet beta cell function indexes, we found that in patients treated with saxagliptin, the levels of Fins and HOMA-B were significantly higher than those before treatment ($P<0.05$), while there was no significant improvement in Fins and HOMA-B levels in patients treated with metformin alone, which indicated that saxagliptin and metformin have a high effective synergy in controlling blood glucose level in the elderly T2DM, the effect of saxagliptin was significant in improving islet beta cell function. The reasons may be that metformin mainly through the inhibition of gluconeogenesis and glycogenolysis, reducing sugar output, and the promotion of peripheral tissue to improve the utilization rate of peripheral blood glucose and achieve the effect of reducing blood sugar. However, with the progress of the disease, its sensitivity is reduced, and the simple application of the drug is not enough to make the blood sugar levels up to the standard[13,14]. And saxagliptin, on the one hand, directly through the inhibition of DPP-4 to delay intestinal insulin inactivation, stimulate glucose mediated insulin release and reduce postprandial glucagon release, so as to improve postprandial beta cell sensitivity to glucose and reduce the blood glucose level[15]. On the other hand, saxagliptin can promote intestinal cell secretion of pancreatic glucagon, inhibit glucose dependent insulin releasing polypeptide (GIP) degradation and promote islet beta cell insulin secretion[16], combined with metformin, through different mechanisms to control blood sugar levels.

Observation the effect of saxagliptin on the micro inflammatory state in elderly patients with T2DM, we found that the level of inflammatory factors increased in different degrees, especially for CRP, IL-6 and LPS, the levels of three inflammatory factors were positively correlated with the inflammatory status of the body[17]. The levels of CRP, IL-6 and LPS were significantly lower in patients treated with saxagliptin than that in patients treated with metformin, and were decreased more obviously in patients treated with the combined drug. The reasons may be that, on the one hand, the improvement of blood glucose level has a significant effect on improving the immunity of the body, reducing the infection and the inflammatory reaction[18,19]; On the other hand, clinical study found that saxagliptin has certain influence on intestinal flora, the trend of the patient’s flora imbalance was obviously improved after the use of the drug. The decreased levels of inflammatory factors may be
associated with the improved intestinal flora imbalance [20].

In summary, saxagliptin has a significant effect in improving islet beta cell function and reducing the body micro inflammatory reaction in the treatment of elderly patients with T2DM. Combined with metformin, the treatment effect is better.

References


