Effect of depression on renal function as well as oxidative stress and inflammatory response in patients with diabetic nephropathy

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Objective: To study the effect of depression on renal function as well as oxidative stress and inflammatory response in patients with diabetic nephropathy. Methods: Patients with type 2 diabetes alone, patients with diabetic nephropathy and patients with diabetic nephropathy and depression treated in our hospital between May 2014 and September 2016 were selected as the research subjects and included in simple diabetes group, diabetic nephropathy group and complicated depression group, and the renal function indexes, oxidative stress indexes and inflammatory response indexes were detected. Results: Scr, BUN, CysC, ROS, MDA, 8-OHdG, IL-6, IL-18, MCP-1, ICAM-1, and TNF-α levels in serum as well as MA and A1M levels in urine of complicated depression group and diabetic nephropathy group were significantly higher than those of simple diabetes group while serum Mn-SOD, CAT, GSH-Px and T-AOC levels were significantly lower than those of simple diabetes group; Scr, BUN, CysC, ROS, MDA, 8-OHdG, IL-6, IL-18, MCP-1, ICAM-1, and TNF-α levels in serum as well as MA and A1M levels in urine of complicated depression group were significantly higher than those of diabetic nephropathy group while serum Mn-SOD, CAT, GSH-Px and T-AOC levels were significantly lower than those of diabetic nephropathy group. HAMD score was positively correlated with Scr, BUN, CysC, ROS, MDA, 8-OHdG, IL-6, IL-18, MCP-1, ICAM-1 and TNF-α levels in serum as well as MA and A1M levels in urine, and negatively correlated with Mn-SOD, CAT, GSH-Px and T-AOC levels in serum. Conclusion: Depression in patients with diabetic nephropathy can aggravate the renal injury and increase oxidative stress and inflammatory response.

1. Introduction

Type 2 diabetes mellitus is the most common chronic metabolic disease in our country, it is mainly characterized by insulin resistance, and macrovascular complications, microvascular complications and a variety of other complications may occur in the progression of disease. Diabetic nephropathy is a common complication in patients with type 2 diabetes, belongs to the category of microvascular complications, and is the most common cause of clinical end-stage kidney diseases. The endothelial injury caused by oxidative stress and inflammatory response activation is the important pathological link in diabetic nephropathy[1]. Oxidative stress response and inflammatory response in patients with type 2 diabetes are associated with the persistent insulin resistance and hyperglycemia, and are also affected by the patients’ mental state and emotional response. In the progression of diabetic nephropathy, adverse emotional response can cause internal environment disturbance and lead to the aggravation of oxidative stress response, inflammatory response and other pathological processes, which will affect the renal function [2,3]. At present, there is no report about the effect of depression on renal function as well as oxidative stress and inflammatory response in patients with diabetic nephropathy. In the following study, the effect of depression on renal function as well as oxidative stress and inflammatory response in patients with diabetic nephropathy was analyzed.
2. Subjects and methods

2.1. Research subjects

The patients with type 2 diabetes mellitus treated in our hospital between May 2014 and September 2016 were selected as the research subjects, patients with microalbuminuria/creatinine < 30 mg/mmol and HAMD score 0-19 points were selected as simple diabetes group, patients with microalbuminuria/creatinine ≥ 30 mg/mmol and HAMD score 0-19 points were selected as diabetic nephropathy group, and patients with microalbuminuria/creatinine ≥ 30 mg/mmol and HAMD score > 20 points were selected as complicated depression group. All patients were informed of the research items and signed the informed consent.

2.2. General information obtaining methods

Patients’ medical records were reviewed to obtain gender, age, BMI and other general data, specifically as follows: simple diabetes group (n=68) included 41 male cases and 27 female cases, they were 42-65 years old and the BMI was (23.2±4.3) kg/m²; diabetic nephropathy group (n=32) included 19 male cases and 13 female cases, they were 39-67 years old and the BMI was (23.2±4.3) kg/m²; complicated depression group (n=28) included 16 male cases and 12 female cases, they were 40-67 years old and the BMI was BMI (24.4±4.2) kg/m².

2.3. Clinical index detection methods

Peripheral blood samples were collected from three groups of patients and centrifuged to get serum, then automatic biochemical analyzer was used to determine serum creatinine (Scr) and blood urea nitrogen (BUN) levels, enzyme-linked immunosorbent assay kits were used to detect cystatin C (CysC), 8-hydroxy-2-deoxyguanosine (8-OHdG), interleukin-6 (IL-6), IL-18, monocyte chemoattractant protein-1 (MCP-1), intercellular adhesion molecule-1 (ICAM-1) and tumor necrosis factor-α (TNF-α) levels and radioimmunoprecipitation kits were used to detect reactive oxygen species (ROS), malondialdehyde (MDA), manganese-superoxide dismutase (Mn-SOD), catalase (CAT) and glutathione peroxidase (GSH-Px) levels as well as total antioxidant capacity (T-AOC); urine samples were collected from three groups of patients to detect microalbuminuria (MA) and urine α1-microglobulin (A1M) levels.

2.4. Statistical methods

SPSS 17.0 software was used to input and analyze data, measurement data analysis among three groups was by variance analysis, pair-wise comparison was by LSD-τ and P<0.05 indicated statistical significance in differences.

3. Results

3.1. Renal function indexes of three groups of patients

Analysis of renal function indexes Scr (μmol/L), BUN (mmol/L) and CysC (μg/mL) in serum as well as renal function indexes MA (mg/g.Cr) and A1M (mg/g.Cr) in urine among three groups of patients was as follows: Scr, BUN and CysC levels in serum as well as MA and A1M levels in urine of complicated depression group and diabetic nephropathy group were significantly higher than those of simple diabetes group; Scr, BUN and CysC levels in serum as well as MA and A1M levels in urine of complicated depression group were significantly higher than those of diabetic nephropathy group. Differences in pair-wise comparison of Scr, BUN and CysC levels in serum as well as MA and A1M levels in urine was statistically significant among three groups of patients (P<0.05). Pearson correlation analysis showed that HAMD score was positively correlated with Scr, BUN and CysC levels in serum as well as MA and A1M levels in urine.

3.2. Serum oxidative stress indexes of three groups of patients

Analysis of serum oxidative stress products ROS (nmol/L), MDA (nmol/L) and 8-OHdG (ng/mL) among three groups of patients was shown in Table 2: serum ROS, MDA and 8-OHdG levels of complicated depression group and diabetic nephropathy group were significantly higher than those of simple diabetes group, and serum ROS, MDA and 8-OHdG levels of complicated depression group were significantly higher than those of diabetic nephropathy group; analysis of serum anti-oxidation indexes Mn-SOD (U/mL), CAT (U/mL), GSH-Px (U/mL) and T-AOC (mmol/mL) was shown in Table 3: serum Mn-SOD, CAT, GSH-Px and T-AOC levels of complicated depression group and diabetic nephropathy group were significantly lower than those of simple diabetes group, and serum Mn-SOD, CAT, GSH-Px and T-AOC levels of complicated depression group

Table 1

Comparison of renal function indexes in serum and urine among three groups of patients.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Serum samples</th>
<th>Urine samples</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Scr</td>
<td>BUN</td>
</tr>
<tr>
<td>Simple diabetes</td>
<td>68</td>
<td>62.3±7.86</td>
<td>5.25±0.67</td>
</tr>
<tr>
<td>Diabetic nephropathy</td>
<td>32</td>
<td>77.65±9.25</td>
<td>7.02±0.79</td>
</tr>
<tr>
<td>Complicated depression</td>
<td>28</td>
<td>109.31±13.25</td>
<td>8.71±0.92</td>
</tr>
</tbody>
</table>

*: compared with simple diabetes group, P<0.05; **: compared with diabetic nephropathy group, P<0.05.
were significantly lower than those of diabetic nephropathy group. Differences in pair-wise comparison of serum ROS, MDA, 8-OHdG, Mn-SOD, CAT, GSH-Px and T-AOC levels were statistically significant among three groups of patients ($P<0.05$). Pearson correlation analysis showed that HAMD score was positively correlated with serum ROS, MDA and 8-OHdG levels, and was negatively correlated with serum Mn-SOD, CAT, GSH-Px and T-AOC levels.

### Table 2
Comparison of serum oxidative stress products among three groups of patients.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>ROS</th>
<th>MDA</th>
<th>8-OHdG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple diabetes</td>
<td>68</td>
<td>6.84±0.93</td>
<td>3.41±0.45</td>
<td>13.21±1.52</td>
</tr>
<tr>
<td>Diabetic nephropathy</td>
<td>32</td>
<td>9.25±1.18</td>
<td>5.52±0.67</td>
<td>19.46±2.46</td>
</tr>
<tr>
<td>Complicated depression</td>
<td>28</td>
<td>14.62±1.92</td>
<td>9.25±1.12</td>
<td>32.69±4.41</td>
</tr>
</tbody>
</table>

*: compared with simple diabetes group, $P<0.05$; #: compared with diabetic nephropathy group, $P<0.05$.

### Table 3
Comparison of serum anti-oxidation indexes among three groups of patients.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Mn-SOD</th>
<th>CAT</th>
<th>GSH-Px</th>
<th>T-AOC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple diabetes</td>
<td>68</td>
<td>72.32±9.35</td>
<td>55.28±6.26</td>
<td>83.85±10.25</td>
<td>49.54±6.13</td>
</tr>
<tr>
<td>Diabetic nephropathy</td>
<td>32</td>
<td>53.46±6.71</td>
<td>39.18±4.95</td>
<td>62.11±7.68</td>
<td>30.25±4.66</td>
</tr>
<tr>
<td>Complicated depression</td>
<td>28</td>
<td>37.65±4.46</td>
<td>25.22±3.41</td>
<td>44.26±6.32</td>
<td>18.61±2.08</td>
</tr>
</tbody>
</table>

*: compared with simple diabetes group, $P<0.05$; #: compared with diabetic nephropathy group, $P<0.05$.

### 3.3. Serum inflammation indexes of three groups of patients

Analysis of serum inflammation indexes IL-6 (ng/mL), IL-18 (pg/mL), MCP-1 (pg/mL), ICAM-1 (ng/mL) and TNF-α (ng/mL) among three groups of patients was as follows: serum IL-6, IL-18, MCP-1, ICAM-1, and TNF-α levels of complicated depression group and diabetic nephropathy group were significantly higher than those of simple diabetes group; serum IL-6, IL-18, MCP-1, ICAM-1, and TNF-α levels of complicated depression group were significantly higher than those of diabetic nephropathy group. Differences in pair-wise comparison of serum IL-6, IL-18, MCP-1, ICAM-1 and TNF-α levels were statistically significant among three groups of patients ($P<0.05$) (Table 4). Pearson correlation analysis showed that HAMD score was positively correlated with serum IL-6, IL-18, MCP-1, ICAM-1 and TNF-α levels.

### Table 4
Comparison of serum inflammation indexes among three groups of patients.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>IL-6</th>
<th>IL-18</th>
<th>MCP-1</th>
<th>ICAM-1</th>
<th>TNF-α</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple diabetes</td>
<td>68</td>
<td>25.92±3.51</td>
<td>103.45±12.31</td>
<td>176.58±20.34</td>
<td>13.41±1.68</td>
<td>9.25±1.03</td>
</tr>
<tr>
<td>Diabetic nephropathy</td>
<td>32</td>
<td>41.29±5.67</td>
<td>176.58±22.15</td>
<td>267.65±33.26</td>
<td>20.28±3.32</td>
<td>16.48±2.24</td>
</tr>
<tr>
<td>Complicated depression</td>
<td>28</td>
<td>77.45±9.25</td>
<td>289.35±33.58</td>
<td>413.26±56.75</td>
<td>34.25±4.65</td>
<td>29.46±3.51</td>
</tr>
</tbody>
</table>

*: compared with simple diabetes group, $P<0.05$; #: compared with diabetic nephropathy group, $P<0.05$.

4. Discussion

Diabetic nephropathy is the most common microvascular complication in patients with type 2 diabetes mellitus, and the activation of oxidative stress response and inflammatory response is the key pathological link of renal injury in patients with type 2 diabetes. In the renal impairment process of patients with diabetic nephropathy, in vivo metabolites creatinine, urea nitrogen and CysC will be difficult to be discharged and accumulate in the blood circulation, proteins leak out from the glomeruli constantly and it leads to proteinuria[4,5]. In the study, analysis of the above renal function indexes in serum and urine of patients with diabetic nephropathy and patients with simple diabetes showed that Scr, BUN and CysC levels in serum as well as MA and A1M levels in urine of complicated depression group and diabetic nephropathy group were significantly higher than those of simple diabetes group. This means that there is the accumulation of metabolites in blood circulation as well as the protein leakage in urine in patients with diabetic nephropathy. Studies on diabetic nephropathy in recent years have shown that in the pathological process of renal impairment, the activation of oxidative stress response and inflammatory response is closely associated with renal injury, and the changes in patients’ psychological status and emotional response may also affect the renal function[6,7]. In order to define the effect of depression on renal function of patients with diabetic nephropathy, the renal function indexes of diabetic nephropathy patients with and without depression were analyzed in the study, and the results showed that Scr, BUN and CysC levels in serum as well as MA and A1M levels in urine of complicated depression group were significantly higher than those of diabetic nephropathy group and positively correlated with HAMD score. This means that the depression in patients with diabetic nephropathy is correlated with renal function, and depression can aggravate the renal injury degree, and increase the accumulation of metabolites in blood circulation as well as the protein leakage in urine of patients with diabetic nephropathy.

Oxidative stress response is an important pathological link of renal injury in patients with type 2 diabetes[8,9]. In the disease progression in patients with type 2 diabetes, the persistent insulin resistance and high glucose environment will interfere with the oxidation respiration process of mitochondrial respiratory chain, the reactive oxygen species (ROS) are massively produced in the process and then lead to endothelial cell function and basement membrane structure damage in glomeruli, which result in the reduced glomerular filtration rate, side metabolite excretion disorder as well as protein leakage through urine[10]. In the process of glomerular damage and function injury caused by ROS, the lipid peroxidation in local tissue will generate MDA, and nucleic acid peroxidation will...
generate 8-OHdG. In the study, analysis of the serum levels of above oxidative stress products in diabetic nephropathy patients with and without depression showed that serum ROS, MDA and 8-OHdG levels of complicated depression group were significantly higher than those of diabetic nephropathy group and positively correlated with HAMD score. There are Mn-SOD, CAT, GSH-Px and many other antioxidant enzymes in local kidney, and the antioxidant enzymes are constantly consumed during the massive production of ROS and characterized by the reduced content of antioxidant enzymes and the weakened total antioxidant capacity. In the study, analysis of these serum anti-oxidation indexes in diabetic nephropathy patients with and without depression showed that serum Mn-SOD, CAT, GSH-Px and T-AOC levels of complicated depression group were significantly lower than those of diabetic nephropathy group and negatively correlated with HAMD score. This means that the depression in patients with diabetic nephropathy is associated with oxidative stress response degree, and depression will increase ROS generation, aggravate oxidative stress damage, excessively consume antioxidant enzymes and weaken the total antioxidant capacity.

Excessive ROS generation can not only cause oxidative stress injury, but will also activate inflammation cascade amplification and promote the release of IL-6, IL-18, MCP-1, ICAM-1, TNF-α and a variety of other inflammatory factors, which lead to the inflammatory glomerular structure and function damage. IL-6 and IL-18 are the members of interleukins family that have regulating the weakened total antioxidant capacity. In the study, analysis of these serum anti-oxidation indexes in diabetic nephropathy patients with and without depression showed that serum Mn-SOD, CAT, GSH-Px and T-AOC levels of complicated depression group were significantly lower than those of diabetic nephropathy group and negatively correlated with HAMD score.

To sum up, it shows that depression can aggravate the renal injury in patients with diabetic nephropathy, and also increase the oxidative stress and inflammatory response during disease progress.

References