Effect of aerobic exercise training on insulin resistance, lipid metabolism and inflammatory response in patients with AD

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ABSTRACT

Objective: To study the effect of aerobic exercise training on insulin resistance, lipid metabolism and inflammatory response in patients with Alzheimer’s disease (AD).

Methods: A total of 84 patients who were diagnosed with Alzheimer’s disease in the Mental Health Center in Zigong City between June 2014 and December 2016 were selected and randomly divided into aerobic exercise group and normal control group who received aerobic exercise intervention combined with conventional drug therapy and conventional drug therapy respectively. The insulin resistance indexes, blood lipid metabolism indexes and inflammatory response indicators were detected before intervention as well as 3 months and 6 months after intervention.

Results: 3 months and 6 months after intervention, the HOMA-IR levels as well as serum TC, LDL-C, ApoB, TNF-α, MCP-1, MIA-1 and HMGB1 contents of aerobic exercise group were significantly lower than those before intervention while HOMA-β, ISIcomp and MBCI levels as well as serum HDL-C and ApoAI contents were significantly higher than those before intervention; the HOMA-IR, HOMA-β, ISIcomp and MBCI levels as well as serum TC, LDL-C, HDL-C, ApoAI, ApoB, TNF-α, MCP-1, MIA-1 and HMGB1 contents of normal control group were not statistically different from those before intervention.

Conclusion: Aerobic exercise training can improve insulin resistance and blood lipid metabolism, and inhibit inflammatory response in patients with AD.

1. Introduction

Alzheimer's disease (AD) is a common clinical neurodegenerative disease, which is mainly characterized by cognitive dysfunction and impaired memory function, and still without effective treatment. The incidence of Alzheimer's disease is increasing year by year, which causes a serious effect on the normal life of the elderly and increases the burden on family and society[1,2]. At present, the pathogenesis of Alzheimer's disease has not been clarified, insulin resistance is a pathological link closely associated with Alzheimer's disease in recent years, and it can cause cognitive impairment through affecting the energy metabolism of central nervous system, causing β -amyloid and Tau protein deposition, and other ways[3]; lipid metabolism disorder and abnormal inflammatory response activation play an important role in the production of insulin resistance[4]. Aerobic exercise is an effective intervention to improve insulin resistance and regulate blood lipid metabolism, but the effect of this intervention on Alzheimer's disease has not been reported. In the following studies, we specifically analyzed the effects of aerobic exercise training on insulin resistance, lipid metabolism and inflammatory response in AD patients.

2. Case information and research methods

2.1 General case information

A total of 84 patients who were diagnosed with Alzheimer’s disease in the Mental Health Center in Zigong City between June 2014 and December 2016 were selected, and all patients met the diagnostic criteria for Alzheimer-type dementia, were with MMSE score 10-24 points and could complete aerobic training independently or in the company of the nursing staff. Patients with vascular dementia, patients combined with severe depression and...
schizophrenia, and patients with long-term use of psychotropic drugs were excluded. Random number table was used to divide the 84 patients into aerobic exercise group and normal control group, 42 cases in each group. Aerobic exercise group included 18 men and 24 women that were 59-71 years old; control group included 20 men and 22 women that were 57-69 years old. There was no statistically significant difference in general information between the two groups (P>0.05).

2.2 Clinical intervention

The two groups of patients received memantine or donepezil therapy according to the condition, the memantine dose was 10 mg/d and donepezil dose was 5 mg/d, and both were taken continuously for more than six months. Aerobic exercise group, on the basis of conventional drug treatment, received aerobic training, and the method was as follows: riding bicycle was selected, exercise intensity was set to 70% of maximum heart rate, the training time is 25-30 min and the load was 0.5 kg·M in the first week, the training time increased to 40 min and the load was 1.0 kg M after 1 week, and the exercise was conducted three times a week for total six months.

2.3 Clinical index detection

Before intervention as well as 3 months and 6 months after intervention, oral glucose tolerance test was conducted respectively, fasting venous blood as well as the venous blood 1 h and 2 h after the oral glucose was collected, fasting blood glucose, insulin, TC, LDL-C, HDL-C, ApoAI, ApoB/TNF-α, MIP-1, MIP-1 and HMGBl as well as blood glucose contents 1 h and 2 h after the oral glucose were detected, and insulin resistance index (HOMA-IR), islet β cell function index (HOMA-β), insulin sensitivity index composite (ISIcomp) and islet β cell function index (MBCI) were calculated.

2.4 Statistical methods

SPSS 21.0 software was used to input and analyze data, measurement data between two groups was by t test, and P<0.05 indicated statistical difference in test results.

3. Results

3.1 Insulin resistance before and after intervention

Before intervention as well as 3 months and 6 months after intervention, analysis of insulin resistance indexes HOMA-IR index, HOMA-β index, ISIcomp and MBCI was as follows: before intervention, HOMA-IR index, HOMA-β index, ISIcomp and MBCI levels were not statistically different between two groups of patients (P>0.05); 3 months and 6 months after intervention, the HOMA-IR index of aerobic exercise group were significantly lower than those before intervention while HOMA-β index, ISIcomp and MBCI levels were significantly higher than those before intervention (P<0.05); the HOMA-IR index, HOMA-β index, ISIcomp and MBCI levels of normal control group were not statistically different from those before intervention (P>0.05).

3.2 Blood lipid metabolism indexes before and after intervention

Before intervention as well as 3 months and 6 months after intervention, analysis of blood lipid metabolism indexes TC, LDL-C, HDL-C, ApoAI and ApoB was as follows: before intervention, serum TC, LDL-C, HDL-C, ApoAI and ApoB contents were not

Table 1.

Comparison of insulin resistance before and after intervention.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Time</th>
<th>HOMA-IR</th>
<th>HOMA-β</th>
<th>ISIcomp</th>
<th>MBCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aerobic exercise</td>
<td>39</td>
<td>Before intervention</td>
<td>3.05±0.47</td>
<td>149.7±20.4</td>
<td>71.3±9.6</td>
<td>6.87±0.82</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 months after intervention</td>
<td>2.31±0.38</td>
<td>192.2±23.5</td>
<td>88.4±9.3</td>
<td>8.02±0.95</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6 months after intervention</td>
<td>1.97±0.25</td>
<td>225.8±25.2</td>
<td>95.2±11.3</td>
<td>8.95±1.15</td>
</tr>
<tr>
<td>Normal control group</td>
<td>39</td>
<td>Before intervention</td>
<td>3.03±0.47</td>
<td>155.12±17.74</td>
<td>70.8±9.3</td>
<td>6.81±0.78</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 months after intervention</td>
<td>2.98±0.42</td>
<td>159.3±15.35</td>
<td>71.4±8.7</td>
<td>6.92±0.83</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6 months after intervention</td>
<td>3.01±0.38</td>
<td>160.24±22.57</td>
<td>71.2±9.1</td>
<td>6.84±0.72</td>
</tr>
</tbody>
</table>

*: comparison between aerobic exercise group and normal control group, P<0.01; †*: compared with same group before intervention, P<0.01; ‡*: compared with same group 3 months after intervention, P<0.01.

Table 2.

Comparison of blood lipid metabolism indexes before and after intervention.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Time</th>
<th>TC</th>
<th>LDL-C</th>
<th>HDL-C</th>
<th>ApoAI</th>
<th>ApoB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aerobic exercise</td>
<td>39</td>
<td>Before intervention</td>
<td>4.98±0.75</td>
<td>2.98±0.41</td>
<td>0.92±0.11</td>
<td>1.22±0.15</td>
<td>1.02±0.14</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 months after intervention</td>
<td>4.13±0.58</td>
<td>2.25±0.32</td>
<td>1.15±0.18</td>
<td>1.53±0.18</td>
<td>0.84±0.11</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6 months after intervention</td>
<td>3.98±0.45</td>
<td>2.04±0.29</td>
<td>1.18±0.15</td>
<td>1.59±0.20</td>
<td>0.71±0.09</td>
</tr>
<tr>
<td>Normal control group</td>
<td>39</td>
<td>Before intervention</td>
<td>5.02±0.77</td>
<td>2.95±0.38</td>
<td>0.91±0.12</td>
<td>1.18±0.14</td>
<td>0.76±0.09</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 months after intervention</td>
<td>4.98±0.71</td>
<td>2.98±0.41</td>
<td>0.94±0.10</td>
<td>1.22±0.16</td>
<td>0.71±0.08</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6 months after intervention</td>
<td>5.03±0.69</td>
<td>2.91±0.34</td>
<td>0.92±0.13</td>
<td>1.24±0.18</td>
<td>0.73±0.10</td>
</tr>
</tbody>
</table>

*: comparison between aerobic exercise group and normal control group, P<0.01; †*: compared with same group before intervention, P<0.01; ‡*: compared with same group 3 months after intervention, P<0.01.
with same group 3 months after intervention, the main pathological characteristics in patients with AD deposit and Tau protein aggregation into neurofibrillary tangle are system function, and diffuse cerebral cortical atrophy, clinical feature is the progressive degenerative change of nervous system function, and diffuse cerebral cortical atrophy. Under physiological conditions, insulin can make the Tau protein in normal stable state of phosphorylation through MAPK/CDK5 downstream signaling pathways, while β amyloid protein is in the stable soluble form under the action of the biological effects of insulin; when insulin sensitivity decreases, Tau protein will experience hyperphosphorylation, accumulate in neurons and gradually form fiber tangle, and β amyloid will be continuously transported to the cell membrane, form the insoluble form in cytoplasm, gradually deposit and become the age pigment[8,9]. That Tau protein forms fibrous tangles and β-amyloid deposits and forms age pigment can cause neurological damage and lead to cognitive hypofunction and other clinical symptoms.

Insulin resistance in patients with AD is characterized by the decreased peripheral tissue sensitivity to insulin as well as the decreased effective concentrations and bioavailability of insulin, and the compensatory hyperinsulinemia and relatively insufficient insulin secretion appear in the body[10,11]. Aerobic exercise is a common clinical intervention method to improve insulin resistance, which can promote the glucose uptake of peripheral tissue and increase insulin sensitivity. Studies have reported that aerobic exercise is able to improve the cognitive function and viability of Alzheimer’s patients, but there is no report about whether aerobic exercise can improve the insulin resistance as well as the related lipid metabolism disorder and inflammatory reaction activation in Alzheimer’s patients. In the above study, the change of insulin resistance before and after the treatment were analyzed at first, and the results showed that the HOMA-IR levels of aerobic exercise group after intervention were significantly lower while HOMA-β, ISIcomp and MBCI levels were significantly higher than those before intervention; the HOMA-IR, HOMA-β, ISIcomp and MBCI levels of normal control group didn’t change significantly before and after intervention. This suggests that aerobic exercise can significantly reduce insulin resistance and increase insulin sensitivity in Alzheimer’s patients.

The decrease of insulin sensitivity and the presence of insulin resistance can affect lipid metabolism in the body, and the close relationship between lipid metabolism disorder and insulin resistance has received more and more attention[12,13]. Cholesterol is an important lipid composition in the body, LDL-C and its major apolipoprotein ApoB can promote the synthesis and deposition of cholesterol, and HDL-C and its major apolipoprotein ApoAI can promote cholesterol metabolism and degradation. Insulin resistance in AD patients can affect blood lipid metabolism and lead to higher levels of TC and LDL-C, and abnormally increased cholesterol and LDL-C can promote the deposition of β amyloid protein[14]. In the study, the analysis of the blood lipid metabolism before and after treatment in patients with AD showed that serum TC, LDL-C and ApoB contents of aerobic exercise group significantly decreased statistically different between two groups of patients (P>0.05); 3 months and 6 months after intervention, serum TC, LDL-C and ApoB contents of aerobic exercise group were significantly lower than those before intervention while HDL-C and ApoAI contents were significantly higher than those before intervention (P<0.05); serum TC, LDL-C, HDL-C, ApoAI and ApoB contents of normal control group were not statistically different from those before intervention (P>0.05).

3.3 Serum inflammatory response indexes before and after intervention

Before intervention as well as 3 months and 6 months after intervention, analysis of serum inflammatory response indexes TNF-α (ng/mL), MCP-1 (pg/mL), MIP-1 (pg/mL) and HMGB1 (pg/mL) was as follows: before intervention, serum TNF-α, MCP-1, MIA-1 and HMGB1 contents were not statistically different between two groups of patients (P>0.05); 3 months and 6 months after intervention, serum TNF-α, MCP-1, MIA-1 and HMGB1 contents of aerobic exercise group were significantly lower than those before intervention (P<0.05); serum TNF-α, MCP-1, MIA-1 and HMGB1 contents of normal control group were not statistically different from those before intervention (P>0.05).

4. Discussion

Alzheimer’s disease (AD) is a common cause of dementia, the main clinical feature is the progressive degenerative change of nervous system function, and diffuse cerebral cortical atrophy. β amyloid deposit and Tau protein aggregation into neurofibrillary tangle are the main pathological characteristics in patients with AD[5-7], but the mechanism causing the pathological characteristics is still not clear. The incidence of AD has been increasing in recent years, and the resulting cognitive hypofunction can be a great burden on both the patient and the family. Insulin resistance is the newly discovered pathological link associated with AD pathogenesis, and the aggravation of insulin resistance is believed to be closely related to the β amyloid deposit and Tau protein aggregation tangle. In the above study, the change of insulin resistance before and after the treatment were analyzed at first, and the results showed that the HOMA-IR levels of aerobic exercise group after intervention were significantly lower while HOMA-β, ISIcomp and MBCI levels were significantly higher than those before intervention; the HOMA-IR, HOMA-β, ISIcomp and MBCI levels of normal control group didn’t change significantly before and after intervention. This suggests that aerobic exercise can significantly reduce insulin resistance and increase insulin sensitivity in Alzheimer’s patients.

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<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Time</th>
<th>TNF-α (ng/mL)</th>
<th>MCP-1 (pg/mL)</th>
<th>MIP-1 (pg/mL)</th>
<th>HMGB1 (pg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aerobic exercise group</td>
<td>39</td>
<td>Before intervention</td>
<td>18.52±2.31</td>
<td>264.5±33.6</td>
<td>38.65±4.88</td>
<td>54.24±7.83</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 months after intervention</td>
<td>11.43±1.54</td>
<td>178.4±20.4</td>
<td>20.25±3.15</td>
<td>32.15±4.52</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6 months after intervention</td>
<td>9.36±0.05</td>
<td>135.5±15.6</td>
<td>14.54±1.89</td>
<td>26.74±3.48</td>
</tr>
<tr>
<td>Normal control group</td>
<td>39</td>
<td>Before intervention</td>
<td>18.27±2.16</td>
<td>263.8±29.7</td>
<td>39.11±4.98</td>
<td>55.10±2.72</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 months after intervention</td>
<td>18.81±2.35</td>
<td>265.1±33.2</td>
<td>38.87±4.56</td>
<td>54.75±7.51</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6 months after intervention</td>
<td>18.44±1.98</td>
<td>264.7±31.7</td>
<td>38.29±5.03</td>
<td>54.03±6.57</td>
</tr>
</tbody>
</table>

*: comparison between aerobic exercise group and normal control group, P<0.01; **: compared with same group before intervention, P<0.01; ***: compared with same group 3 months after intervention, P<0.01.
while HDL-C and ApoAI contents significantly increased after intervention; serum TC, LDL-C, HDL-C, ApoAI and ApoB contents of normal control group didn't change significantly before and after intervention. This suggests that aerobic exercise can significantly improve blood lipid metabolism and reduce cholesterol levels in Alzheimer's patients.

In recent years, study on AD pathogenesis shows that chronic neuroinflammation is the secondary change caused by β amyloid deposition, and the inflammatory cells infiltrating in the brain and the inflammatory mediators released by them can cause neurodegenerative disease[15]. TNF-α is the first cytokine that changes in the process of inflammatory response, which can not only mediate the cascade amplification of inflammatory reactions, but also cause inflammatory damage of the nerve tissue[16]; MCP-1 and MIP-1 are cytokines that have monocyte and macrophage chemotaxis effect, which can promote the aggregation of monocytes and macrophages in inflammatory sites and amplify inflammatory responses[17,18]; HMGB1 is a class of late inflammatory mediator that can stimulate the activation of mononuclear macrophages and activate inflammatory response in the process of inflammatory response. In the study, analysis of the inflammatory response in patients with AD before and after treatment showed that serum TNF-α, MCP-1, MIA-1 and HMGB1 contents of aerobic exercise group after intervention were significantly lower than those before intervention; serum TNF-α, MCP-1, MIA-1 and HMGB1 contents of normal control group didn't change significantly before and after intervention. It indicates that aerobic exercise can significantly inhibit the activation of inflammatory response and reduce the synthesis and secretion of inflammatory mediators in Alzheimer's patients.

Aerobic exercise training for Alzheimer's disease can effectively improve the insulin resistance and increase insulin sensitivity, and can also regulate blood lipid metabolism, reduce blood lipid levels and suppress the activation of the inflammatory response.

References


