Relationship between IL-6 and sarcopenia in female patients with hyperthyroidism

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Abstract: To investigate the relationship between IL-6 and sarcopenia in patients with hyperthyroidism. 60 female patients with hyperthyroidism were selected, and 37 healthy female were chosen as control group. There was no significant difference in age between the two groups. The body fat compositions were measured by dual energy X-ray absorptiometry (DXA), to calculate the skeletal muscle mass index (SMI). Moreover, grip strength and walking speed were collected. The FT3, FT4, TSH and IL-6 levels of subjects in the two groups were detected and collected. The correlation analysis on the results was performed and various factors that influence SMI were analyzed by multivariate stepwise regression. A significant negative correlation existed between SMI and serum IL-6 (r=−0.315, P=0.014). The multivariate stepwise regression analysis showed that the serum IL-6 and BMI conformed to the equation: SMI=5.333−0.028× serum IL-6+0.052×BMI. The abnormally elevated serum IL-6 in patients with hyperthyroidism may lead to a reduction in skeletal muscle mass and increase the risk of occurrence of sarcopenia.

Keywords: Sarcopenia; Hyperthyroidism; IL-6

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1. Introduction

In recent years, sarcopenia has attracted more and more attention by researchers. With the decreasing in skeletal muscle mass, patients will have such manifestations as decrease muscle strength, lack of physical strength, easy to fall, etc. Their risks of fracture are higher than ordinary people, seriously affect their quality of life. The sarcopenia mostly occurs in elderly people, and the disease is mainly caused by aging, malnutrition, lack of physical activity, asymptomatic inflammation, abnormal hormone levels. Clinical studies have found that sarcopenia is not unique to the elderly. Many patients with chronic diseases suffer from sarcopenia, and hyperthyroidism is considered to be one of the primary diseases of sarcopenia[2]. Previous studies have shown that patients with hyperthyroidism mainly lose muscles associated with their weight loss[3]. Skeletal muscle is an important tissue for human exercises and physical activity. Therefore, the reduction of skeletal muscle mass has a serious impact on the living standard of patients with hyperthyroidism. Regarding its pathogenesis, some researchers thought that hyperthyroidism can release muscle amino acids. It can promote the decomposition of muscle proteins, result in loss of muscle mass[4]. Some researchers believed that the reduction of muscle mass in patients with hyperthyroidism may be associated with inflammatory reactions caused by abnormal hormone levels[5]. However, the pathogenesis of hyperthyroidism is still unknown. The abnormal IL-6 level has possibly relationship with the occurrence of sarcopenia in patients who have hyperthyroidism. Studies on age-related sarcopenia have shown that IL-6 is associated with the onset of sarcopenia and IL-6 can promote the decomposition of skeletal muscle and lead to a reduction in skeletal muscle mass[6]. Therefore, in this study, we investigated the relationship between IL-6 levels and sarcopenia in 60 female patients with hyperthyroidism, to provide scientific basis for the prevention of sarcopenia in patients with hyperthyroidism.

2. Objects and methods

2.1. Objects

60 female patients with hyperthyroidism were selected in the Endocrinology Department of Linyi People's Hospital from January 2017 to October 2017 as observation group. 37 healthy women were included in the control group. All subjects were excluded from combined disease that would cause sarcopenia or long-term use of hormones and drugs that would influence the muscle mass.

2.2. Diagnostic criteria

The SMI for reduction of female skeletal muscle mass in the Asian Working Group for Sarcopenia's diagnostic criteria was used as reference (AWGS, 2014)[7]: walking speed less than 0.8m/s, grip strength: below 18kg, below 5.40kg/m² for women.

2.3. Methods

Determination of Skeletal Muscle: The fat-free substance without bone mineral content of the whole body was measured by dual energy X-ray absorptiometry (Lunar, GE, USA). The soft tissues of the four limbs removed from fats were collected to calculate the skeletal muscle mass index: SMI = amount of fat-free soft tissues in the four limbs...
Measurement of grip strength and walking speed: Grip strength was measured by a grip dynamometer (WCS-10000, China). Measurements were performed on the left and right sides, twice each side respectively, and the average value was used. The walking speed was measured by a 6-meter walking test. Patients walked a straight-line distance of 6m in a daily walking speed, and the time for walking was recorded by a stopwatch. The walking speed was calculated by the average time of the twice walking.

Detection of thyroid function and IL-6 level: For all subjects, fasting blood samples were taken in the early morning. The FT3, FT4, and TSH levels were detected in the Biochemistry Laboratory of the hospital. At the same time, IL-6 levels were measured by enzyme-linked immunosorbent assay (ELISA) (BIOSH, China).

2.4. Statistical analysis
Statistical analysis was performed by the SSPS 21.0 statistical software. For comparison between groups, t-test was used. For non-normal data, SQR transformation or non-parametric test was used. Pearson correlation analysis was used for linear relationship between two variables. Spearman correlation analysis was used for non-normal data. Various factors influencing SMI were analyzed by multivariate stepwise regression method.

3. Results
3.1. Basic data of patients in the two groups
There was no significant differences in age, grip strength, and BMI between the two groups (P>0.05). A significant difference in the incidence of sarcopenia existed between the two groups (P=0.010). The sarcopenia-related indexes such as SMI and muscle mass in the experimental group were significantly different from those in the control group (P<0.05). For the thyroid function indexes and serum IL-6 levels, the FT3, FT4, IL-6 levels in the observation group were significantly higher than those in the control group (P<0.001), while TSH in the observation group was significantly lower than that in the control group (P<0.001) (Table 1).

3.2. Results of SMI and factor correlation analysis in the observation group
In the observation group, the serum IL-6 levels in female patients with sarcopenia and hyperthyroidism were significantly higher than those without sarcopenia (P<0.05), and the FT4 level in female patients with sarcopenia and hyperthyroidism were significantly higher than those without sarcopenia (P<0.05), but there was no significant differences in FT3 and TSH levels between them (P>0.05).

### Table 1. Initial values of indexes of patients in the two groups (x ± s)

<table>
<thead>
<tr>
<th></th>
<th>Observation group</th>
<th>Control group</th>
<th>t or χ²</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>49.92±11.53</td>
<td>51.68±12.39</td>
<td>-0.718</td>
<td>0.474</td>
</tr>
<tr>
<td>SMI(Kg/m²)</td>
<td>5.74±0.80*</td>
<td>6.07±0.65</td>
<td>-2.040</td>
<td>0.044</td>
</tr>
<tr>
<td>Muscle mass (kg)</td>
<td>34.11±3.56*</td>
<td>36.31±4.98</td>
<td>-2.541</td>
<td>0.013</td>
</tr>
<tr>
<td>Grip strength(kg)</td>
<td>19.85±9.24*</td>
<td>23.55±8.92</td>
<td>-1.959</td>
<td>0.053</td>
</tr>
<tr>
<td>IL-6(pg/ml)</td>
<td>27.75±9.01*</td>
<td>11.79±7.22</td>
<td>9.198</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FT3(Pmol/l)</td>
<td>21.28±11.40*</td>
<td>4.54±1.37</td>
<td>8.994</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FT4(Pmol/l)</td>
<td>51.03±25.41*</td>
<td>17.72±4.02</td>
<td>8.005</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TSH(mul/l)</td>
<td>0.007±0.003*</td>
<td>3.00±1.05</td>
<td>-22.132</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI(Kg/m²)</td>
<td>22.94±4.57</td>
<td>23.61±3.36</td>
<td>-0.782</td>
<td>0.436</td>
</tr>
<tr>
<td>Subjects with sarcopenia</td>
<td>22(36.67%)</td>
<td>5(13.51%)</td>
<td>7.182</td>
<td>0.010</td>
</tr>
</tbody>
</table>

* Compared with female patients of hyperthyroidism without sarcopenia, P<0.05.
The effect of hyperthyroidism on skeletal muscle mass may be mediated by IL-6, that is, IL-6 may promote the onset of sarcopenia in patients with hyperthyroidism. Previous studies have concluded that aging is the most important factor in the reduction of skeletal muscle mass. The mechanism of age-related reduction of skeletal muscle may be related to abnormal levels of IL-6 which was caused by the increasing age[9,10]. The existing studies showed that IL-6 is associated with sarcopenia from the following two aspects: first, IL is involved in the decomposition of skeletal muscles, resulting in the loss of skeletal muscle mass; second, IL-6 is related to low muscle strength. Studies have shown that IL-6 can disrupt the synthesis of skeletal muscle proteins and it is directly involved in protein decomposition in skeletal muscle, leading to a reduction in skeletal muscle mass. IL-6 also inhibits the promotion of muscle tissue by the insulin-like growth factor-I (IGF-1)[6]. Furthermore, studies have shown that sustained activation of the transcription factor NF-κB can cause muscle damage and decrease. However, the intermittent rhythmic activation of NF-κB has the completely opposite functions. IL-6, as a target gene of NF-κB, may inherit NF-κB signals and involve in the continuous activation of NF-κB. It may influence the occurrence of sarcopenia induced by skeletal muscle injury and the remission process of sarcopenia and by NF-κB intermittent rhythmic activation[11]. In addition, IL-6 can lead to insulin resistance, indirectly involved in the occurrence of sarcopenia[12]. IL-6 further exerts an influence on muscle strength. Study by Pereira[13] have shown that IL-6 has effects on the strength of upper and lower extremities. The elevated serum IL-6 levels may result in decreased muscle strength. Park[14] found that IL-6 levels were negatively correlated with grip strength in menopausal women, further studies found that, the grip strength was negatively correlated with IL-6 gene expression levels[15]. In addition, walking speed, as an evaluation standard of physical strength, is also one of the reference indexes for the diagnosis of sarcopenia. Verghese[16] found that the walking speed was also negatively correlated with IL-6 level. In summary, IL-6 is an important factor influencing the loss of skeletal muscle mass and reduction of muscle strength, and has an important association with sarcopenia. Therefore, we speculate that the immune disorders that occur in hyperthyroidism may cause the upregulation of abnormal secretion of IL-6, resulting in a chronic inflammatory environment in the chronic diseases.

### 3.3. Relationship Between SMI and Various Factors By Multivariate Stepwise Regression in the Observation Group

Using the SMI as a dependent variable and the age, BMI, FT3, FT4, TSH, and IL-6 as independent variables, multivariate stepwise regression analysis was performed. The results of IL-6 and BMI were selected into the equation. The regression equation was SMI=5.333-0.028*serum IL-6+0.052*BMI, (R²=0.186, adjusted R²=0.158), (Table 2).

### 4. Discussion

In this study, we found that the SMI and muscle mass of female patients with hyperthyroidism were significantly lower than those of healthy females in the control group. The incidence of sarcopenia was significantly higher than that of healthy females in the control group. Sarcopenia may occur in female patients with hyperthyroidism. Those with hyperthyroidism are prone to sarcopenia compared with healthy females.

Patients with hyperthyroidism have high IL-6 levels[8]. Our study also showed that serum levels of IL-6 in female patients with hyperthyroidism in the observation group were significantly higher than those in healthy controls (P<0.05). IL-6 may be involved in the onset of hyperthyroidism. Furthermore, in this study, we observed that there was a significant negative correlation between SMI and IL-6 in the observation group. Further multivariate stepwise regression analysis showed that IL-6 was negatively correlated with SMI. Female patients with hyperthyroidism and sarcopenia the level of IL-6 significantly were higher than those without sarcopenia.

![Figure 2. Correlation between BMI and SMI.](image)

<table>
<thead>
<tr>
<th>variable</th>
<th>regression coefficient(β)</th>
<th>standard error(SEB)</th>
<th>standardized regression coefficient(β)</th>
<th>t</th>
<th>P</th>
</tr>
</thead>
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<tr>
<td>constant term</td>
<td>5.333</td>
<td>0.572</td>
<td></td>
<td>9.315</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IL-6</td>
<td>-0.028</td>
<td>0.011</td>
<td>-0.313</td>
<td>-2.621</td>
<td>0.011</td>
</tr>
<tr>
<td>BMI</td>
<td>0.052</td>
<td>0.021</td>
<td>0.295</td>
<td>2.446</td>
<td>0.017</td>
</tr>
</tbody>
</table>

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patients with hyperthyroidism. In this state, a long-term elevated IL-6 level may further lead to the decrease in muscle mass and muscle strength, thereby lead to the occurrence of sarcopenia in patients with hyperthyroidism.

5. Conclusion

In summary, the abnormally elevated serum IL-6 in patients with hyperthyroidism may lead to a reduction in skeletal muscle mass and decrease in muscle strength, and increase the risk of occurrence of sarcopenia. Therefore, studies on IL-6 inhibition can be carried out in the future, to play a role in the prevention and treatment of sarcopenia in patients with hyperthyroidism.

References


