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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 decr easing in skeletal muscle mass, patients will hav e such manifestations as decrease muscle strength, lack of physical strength, easy to fall, etc. Thei r risks of fracture are higher than ordinary peopl e, seriously affect their quality of life[1].The sarc openia mostly occurs in elderly people, and the disease be mainly caused by aging, malnutrition, lack of physical activity, asymptomatic inflamm ation, abnormal hormone levels. Clinical studies have found that sarcopenia is not unique to the elderly. Many patients with chronic diseases suffe r from sarcopenia, and hyperthyroidism is consid ered to be one of the primary diseases of sarcop enia[2]. Previous studies have shown that patient s with hyperthyroidism mainly lose muscles asso ciated with their weight loss[3]. Skeletal muscle is an important tissue for human exercises and p hysical activity.Therefore, the reduction of skeleta l muscle mass has a serious impact on the livin g standard of patients with hyperthyroidism. Reg arding 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 a ssociated with inflammatory reactions caused by abnormal hormone levels[5].However, the pathoge nesis of hyperthyroidism is still unknown. The a bnormal IL-6 level has possibly relationship with the occurrence of sarcopenia in patients who ha s hyperthyroidism. Studies on age-related sarcope nia have shown that IL-6 is associated with the onset of sarcopenia and IL-6 can promote the de composition of skeletal muscle and lead to a red uction in skeletal muscle mass[6]. Therefore, in t his study, we investigated the relationship betwee n IL-6 levels and sarcopenia in 60 female patien ts with hyperthyroidism, to provide scientific basi s for the prevention of sarcopenia in patients wit h 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/m^2 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

(AMM)/ body length (m^2).

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, SQRT transformation or non-parametric test was used. Pearson correlation analysis was used for linear relationship between two variables. Speamran 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, and all indexes in the observation group were lower than 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).

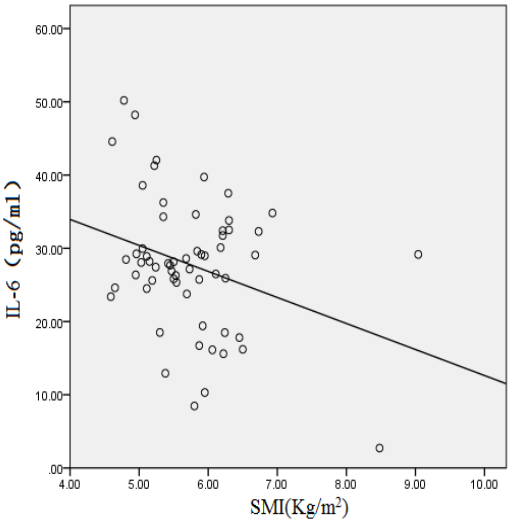

Figure 1. Correlation between IL-6 and SMI.

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).

3.2. Results of SMI and factor correlation analysis in the observation group

The SMI has negatively correlation with IL-6 level (r=-0.315, P=0.014), and has positively correlation with BMI (r=0.297, P=0.021).But it has not correlated with FT3, FT4, TSH.

Table 1. Initial values of indexes of patients in the two groups ($\bar{x}$ ±s)

	Observation group	Control group	*tor* x^2	*P*
Age (year)	49.92±11.53	51.68±12.39	-0.718	0.474
SMI(Kg/m^2)	5.74±0.80*	6.07±0.65	-2.040	0.044
Muscle mass (kg)	34.11±3.56*	36.31±4.98	-2.541	0.013
Grip strength(kg)	19.85±9.24*	23.55±8.92	-1.959	0.053
IL-6(pg/ml)	27.75±9.01*	11.79±7.22	9.198	<0.001
FT3(Pmol/l)	21.28±11.40*	4.54±1.37	8.994	<0.001
FT4(Pmol/l)	51.03±25.41*	17.72±4.02	8.005	<0.001
TSH(mul/l)	0.007±0.003*	3.00±1.05	-22.132	<0.001
BMI(Kg/m^2)	22.94±4.57	23.61±3.36	-0.782	0.436
Subjects with sarcopenia	22(36.67%)	5(13.51%)	7.182	0.010

* Compared with female patients of hyperthyroidism without sarcopenia, P<0.05.

Table 2. Multivariate stepwise regression analysis of SMI and various indexes

variable	regression coefficient(β)	standard error(SEB)	standardized regression coefficient(β)	*t*	*P*
constant term	5.333	0.572		9.315	<0.001
IL-6	-0.028	0.011	-0.313	-2.621	0.011
BMI	0.052	0.021	0.295	2.446	0.017

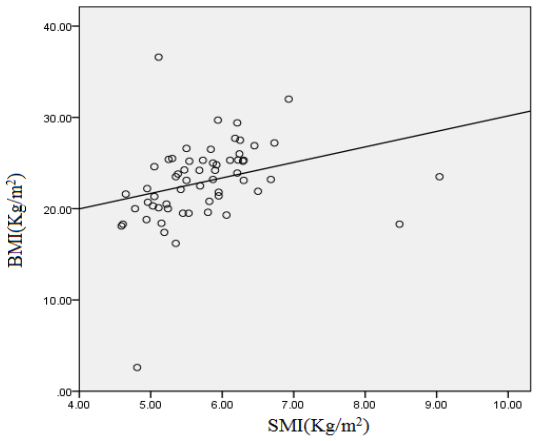

Figure 2. Correlation between BMI and SMI.

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. (R^2=0.186, adjusted R^2=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.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-I)[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, result in a chronic inflammatory environment in

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.

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