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Correlation between peripheral skeletal muscle functions and the stable phase of COPD in older patients

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Abstract. – OBJECTIVE: To establish normal values for detection indexes of peripheral skeletal muscle dysfunction (quadriceps femoris) of healthy older subjects, and investigate the functional status of the peripheral skeletal muscle of patients with stable phase COPD.

PATIENTS AND METHODS: Patients with stable phase COPD and healthy subjects of similar age were included. The assessments of strength and myoelectricity of the quadriceps femoris were recorded. The twitch tension of the quadriceps femoris (TwQ), quadriceps maximum voluntary contraction (QMVC), and endurance time (Tf) were measured. The multiple-parameter malnutrition index (MNI) was used for overall evaluation of the nutritional status of patients. The femoral muscle volume was estimated. All subjects were subjected to a routine pulmonary function test including indexes such as FEV_1, FVC, FEV_1/FVC (%), and PEF. Enzyme-linked immunoassay (ELISA) was used to measure the levels of myostatin, tumor necrosis factor-α, TNF-like apoptosis-inducing factor (TWEAK), surface active protein D (SPD), C-reactive protein (CRP), interleukin (IL)-1β, and IL-6. The cell immunohistochemical method was used to detect the expression of nuclear factor Kappa B (NF-κB).

RESULTS: There were significant differences in body weight, BMI, femoral muscle volume, and physical activity scores between the two groups ($p<0.01$). The MNI of patients in the COPD group was significantly higher than that in the control group ($p<0.01$). The QMVC of 51 male and 16 female patients decreased. All eight tested cytokines increased in the COPD group but there were only significant differences in four cytokines ($p<0.05$).

CONCLUSIONS: Chronic systemic inflammation is a major risk factor of skeletal muscle dysfunction (SMD) in COPD patients. The levels of SPD, myostatin, TWEAK, and TNF-α decreased significantly in COPD patients.

Key Words
Chronic obstructive pulmonary disease, Quadriceps femoris, Maximum active contraction force, Endurance, Maximum twitch tension.

Introduction

Chronic obstructive pulmonary disease (COPD) is a chronic inflammatory disease characterized by partially reversible airway limitation accompanied by multi-systemic damage[1]. It is a preventable and treatable disease, although it causes significant extrapulmonary effects (i.e., systemic effects)[2,3] that may exacerbate the disease. The systemic effects primarily manifest as skeletal muscle wasting (SMW) and dysfunction, loss of body weight, cardiovascular complications, malnutrition, and changes in body composition[4]. Skeletal Muscle Dysfunction (SMD) is particularly significant[5]. As one of the systemic effects of COPD, SMD not only affects the pulmonary functions and daily activities of patients, but also severely affects their quality of life and prognosis. A decline in peripheral skeletal muscle function is one of the major manifestations occurring in the early stage of the disease[6]. SMD is also an important factor affecting the severity of COPD[7].

Scholars[8-15] have proposed several mechanisms of SMD, such as chronic systemic inflammation, malnutrition, muscle wasting, disuse atrophy, and glucocorticoid metabolism. However, each theory is insufficient to explain the occurrence of SMD in patients with COPD completely. Investigating the severity and risk factors of SMD in patients with COPD will help to understand its mecha-

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nism. However, comparisons with normal control groups are required to judge SMD in patients with COPD. The establishment of reference values for peripheral muscle functions of the local normal older population (with the same age range as patients with COPD) will help to understand the occurrence and severity of peripheral muscle dysfunction.

The functions of the quadriceps femoris of patients in the stable phase of COPD were determined and compared with those of local healthy older subjects of similar age. The comparison helps analyze the degree of severity, universality, and occurrence of SMD in patients with COPD. Combined with research on the mechanism of occurrence of SMD in COPD patients, we aimed to identify the potential risk factors involved in the incidence of SMD in patients with COPD, analyze potential related cytokines in the blood of patients, evaluate the nutritional status of patients, estimate the volume of the quadriceps femoris, investigate daily activities, screen for relevant factors, and further explore the mechanism of occurrence of SMD in patients with COPD.

The evaluation of skeletal muscle function includes the evaluation of contractility and endurance[16,17]. Contractility and endurance are mutually correlated but they also have their own respective characteristics. They play different roles in human body functions. The decline of any single function can influence the overall muscle function. In addition, improving the endurance or contractility can effectively improve the functions of skeletal muscle and benefit patients with declined skeletal muscle function during functional rehabilitation training. Whether there is a balance between the severity of the decline in contractility and the severity of decline of endurance during the occurrence and progression of SMD in patients with COPD remains unclear. Furthermore, it remains to be determined if they are mutually predictable. The traditional method for evaluating skeletal muscle contractility in COPD patients is to observe the maximum active contraction force. However, compared with traditional methods, the advantages and disadvantages of magnetic stimulation as a new means of detection remain unclear.

The aim of the present study was to explore the relevant mechanism of occurrence of SMD in patients with COPD, compare the advantages and disadvantages of three different methods of detection of the function of the quadriceps femoris, and investigate the methodology, so as to provide a method for accurate evaluation of muscle function.

Patients and Methods

Patients

1. Normal control group: we selected healthy older subjects who underwent physical examinations in the Physical Examination Department of the Binzhou People's Hospital. Their age range roughly coincided with the age range of COPD patients. 2. COPD group: All COPD patients were from the Outpatient Department of the Binzhou People's Hospital. Based on the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, pulmonary functions were used as the gold standard to preliminarily screen for patients with chronic bronchitis and/or emphysema. Patients with $FEV_1/FVC < 70\%$ were eligible for preliminary screening after being administered a bronchodilator. In addition, patients were required to meet the following requirements: age $\geq$ 50 years; negative bronchial dilation test result; patients in the stable phase without a history of acute attack within 8 weeks before being included; patients received no oral administration or injection of glucocorticoids within 8 weeks before being included (inhaled corticosteroids were allowed). Exclusion criteria: patients with bronchial asthma; COPD patients accompanied by extremely severe respiratory failure and incapable of undergoing muscular strength tests; patients with severe anoxia or acidosis, or without proper subjective and objective conditions; patients with a history of mental diseases, or alcohol or drug abuse; patients accompanied by cardiovascular diseases, arrhythmia, or heart failure; patients accompanied by rheumatic diseases or immune-related diseases; patients accompanied by neuromuscular diseases; patients who received intravenous injection or oral administration of glucocorticoids within 4 weeks before being included (prednisone > 10 mg/day); patients accompanied by cerebrovascular sequelae; patients complicated with other diseases affecting muscle function. The study was approved by the Ethics Committee of Binzhou People's Hospital.

Evaluation of Nutritional Status

The multiple-parameter malnutrition index (MNI)[18] was used for the overall evaluation of nutritional status of healthy subjects and COPD

patients. The parameters for evaluation primarily comprised biochemical blood indexes and anthropometric indexes. The biochemical blood indexes included: serum albumin (ALB), transferrin receptor (TFR), triglyceride (TRG), and cholesterol (CHO). The anthropometric indexes included: stature, body weight, thickness of subcutaneous fat (TSF) of the musculus triceps brachii, mid-upper arm circumference (MUAC), abdomen circumference, and abdominal subcutaneous fat. Based on TSF and MUAC, the MAMC was calculated, which indirectly reflected the muscular volume of the upper arm. The specific formula for calculation was as follows: MAMC (cm) = MAC (cm) − 0.314 × TSF (mm).

Functional Test of the Quadriceps Femoris

Each subject sat on a special chair with a mobilizable backrest, with knee joints bent at 90°, suspended from the chair end. A nonelastic belt was used to fix the ankle and was connected to a stress measurer (measurement range: 0-0.150 kg) (Thermo Scientific, Waltham, MA, USA). One end of the belt was fixed 1-2 cm above the ankle and perpendicular to the ankle. The other end of the belt was connected to the back of the chair. It was connected to the stress measurer via the load sensor. The known force was used for calibration before each test. Test electrodes were located on the surfaces of the bellies of the vastus lateralis muscle (VL), rectus femoris, and vastus medialis muscle (VM), respectively. The reference electrodes were located at the knee joints. The angles of the knee joints of the subjects were to remain unchanged during the entire test. The belt fixing the ankle and the load sensor were always made to be parallel to the floor. The force and electromyogram generated by the test were recorded and preserved by the Powerlab 8/16S synchronizing signal (Thermo Scientific, Waltham, MA, USA)[19]. The functional test for the quadriceps femoris included the following three parameters: muscular twitch tension (TwQ) induced by magnetic stimulation of the femoral nerve, quadriceps maximum voluntary contraction (QMVC), and endurance time.

Pulmonary Function Test

All healthy subjects were subjected to routine pulmonary function tests (ABI PE-Applied Biosystems, Foster City, CA, USA), including pulmonary functional indexes such as FEV_1, FVC, FEV_1/FVC (%), and PEF. The pulmonary function indexes of COPD patients were compared before and after inhalation of the bronchodilator. The numerical values after inhalation of the bronchodilator were selected when asthma was excluded.

Routine Activity Scores

The subjects were evaluated according to a questionnaire survey involving five major parameters: occupation, routine activities, physical exercise, hobbies, and leisure-time activities excluding sleep and exercise. All questionnaires have been verified. They comprised 19 sub-items; each sub-item was rated on the basis of intensity and frequency. Finally, the total score was calculated.

ELISA

Serum inflammatory cytokines were measured by enzyme-linked immunosorbent assay (ELISA; Gibco BRL, Life Technologies Inc., NY, USA), including: C-reactive protein (CRP), myostatin, interleukin (IL)-1β, IL-6, tumor necrosis factors (TNF)-α, TNF-like apoptosis-inducing factor (TWEAK), and surface active protein D (SPD). Each cytokine was measured in strict accordance with the instructions of the kit. A total of 50-100 μl of quality control, sample, and standard were pipetted in the appropriate wells, and incubated for 2 h on a shaking table at room temperature (the specific antigens were linked to solid phase carriers to form solid phase antigens). The wells were washed three times with an automatic microplate washer. Only specific antibodies were left on the solid phase carrier. The biotinylated antibody was then added to each well. The wells were blocked and incubated for 2 h on the shaking table at room temperature. The wells were washed three times with the automatic microplate washer. They were blocked and incubated for 30-60 min on the shaking table at room temperature after addition of horseradish peroxidase-chain avidin binding buffer. The wells were washed three times with the automatic microplate washer. After 50-100 μl of TMB substrate developing solution was added to each well, the samples were blocked and incubated for 15-30 min at room temperature in the dark. The specific time for termination was determined on the basis of the shade and gradient of the standard. A total of 50 μl of sulfuric acid stop buffer was added to each well. Samples were read at 450 nm with a microplate reader. The reference wavelength was 630 nm.

Cell Immunochemical Detection

The cell immunochemical (ICC) method was used to detect the expression of NF-κB in monocytes and neutrophils from peripheral blood. The sections were washed three times for 5 min with phosphate-buffered saline (PBS) at room temperature. Each section was incubated for 5-10 min at room temperature following the dropwise addition of 3% H_2O_2 to each section. Samples were washed three times for 5 min with PBS. The cellular surface permeation reagent (Invitrogen, Carlsbad, CA, USA) was then added dropwise to each section, and incubated for 15 min at room temperature. Samples were washed three times for 5 min with PBS. Samples were then incubated for 15 min at room temperature after one drop of ready-to-use normal goat serum operating solution was added (Bio-Oss Biology Co., Ltd., Beijing, China). The ready-to-use primary antibody (Abcam, Cambridge, MA, USA) was added dropwise after the serum was discarded and incubated overnight in a refrigerator at 4°C. The samples were washed three times for 5 min with PBS. Each section was incubated for 30 min at 37°C after one drop of ready-to-use biotinylated second antibody operating solution was added (Bio-Oss Biology Co., Ltd., Beijing, China). Samples were washed three times for 5 min with PBS. Each section was incubated for 30 min in an incubator at 37°C after one drop of ready-to-use horseradish peroxidase-labeled streptavidin operating solution was added (Bio-Oss Biology Co., Ltd., Beijing, China). Samples were washed three times for 5 min with PBS. Each section was observed for staining under a microscope after one drop of freshly prepared diaminobenzidine (DAB) solution (Boster Bioengineering Co., Ltd., Wuhan, China) was added. Samples were washed with tap water, counterstained with hematoxylin, subjected to color separation with alcoholic hydrochloric acid, and blued with tap water after 5-10 min. Samples were dehydrated for 5 min with gradient ethanol, clarified with xylene, and mounted with neutral balsam.

Statistical Analysis

SPSS 19.0 software (IBM Corp., IBM SPSS Statistics for Windows, Armonk, NY, USA) was used for data analysis. Quantitative data are presented as $\bar{x}\pm s$. The categorical variables are presented as percentage (%). $p<0.05$ was considered statistically significant. Comparisons between the COPD group and normal group were carried out by a non-paired *t*-test and χ^2-test. Comparisons of the degrees of variation in the subjective and objective testing methods were carried out by the following two methods: 1. In terms of the degree of variation in individuals, the variation coefficient was used for evaluation as follows: [CV = (standard deviation/mean) × 100%]; 2. In term of the degree of variation in repeated measures data, the variation rate of three repeated measures data was used for evaluation, with variation rate = [(maximum − minimum)/(maximum + minimum) × 100%]. The relationships between the three indexes of the functional test for the quadriceps femoris of the two groups and their related factors were evaluated by stepwise regression analysis. The relationships between contractility and endurance and active and passive contractility in the functional test of the quadriceps femoris were evaluated by simple linear correlation analyses.

Results

General Condition of Patients

None of the subjects participated in any rehabilitation or physical training or received nutritional support treatment. The general conditions of the two groups of subjects are shown in Table I. There were no differences in age or stature between the two groups. However, there were significant differences in sex ratio between the two groups. There were 60 subjects in the normal control group including 23 males and 37 females. There were 71 patients in the COPD group including 56 males and 15 females ($p<0.01$). In addition, there were significant differences in body weight, BMI, femoral muscle volume, and Physical Activity (PA) scores between the two groups ($p<0.01$). The results of the calculation of muscle volume indicated that the average value of MTMC in COPD patients decreased significantly compared with that in the normal control group. There were significant differences between the two groups (as shown in Table I). This indicated that femoral muscle atrophy and decreased routine activities occurred in COPD patients. Compared with the normal control group, the PA score of the COPD patients decreased significantly. There were significant differences between the two groups (Table I).

Results of the Pulmonary Function Test

The comparison of FEV_1%pred and FEV_1/FVC between the two groups is shown in Table II. The results of the pulmonary ventilation function

Table I. General conditions of the two groups ($\bar{x}$±s).

	Normal control group	COPD group	*t*	*p*
Sex, M (%)	23 (38.33%)	56 (78.87%)	21.58*	0.000*
Age (years)	65.45±5.34	66.67±6.54	1.12	2.16
Stature (cm)	155.45±7.80	158.92±7.41	0.87	0.27
Body weight (kg)	58.45±8.67	51.34±8.36	5.13	0.000*
BMI (kg/m^2)	21.35±2.17	19.34±3.21	7.44	0.000*
FEV1%pred (%)	96.35±8.65	36.76±13.27	26.54	0.000*
FEV_1/FVC (%)	87.34±8.34	43.58±11.14	23.79	0.000*
MTMC	43.19±3.55	36.58±3.56	8.34	0.000*
PA score	7.97±1.21	5.17±1.12	11.16	0.000*

Legend: *p<0.05 indicates a statistically significant difference.

Table II. Classification of pulmonary functions in COPD patients ($\bar{x}$±s).

Male			Female		
Classification	Number of Cases	FEV_1% pred (%)	Classification	Number of Cases	FEV_1% pred (%)
Class II	8	64.38±6.45	Class II	3	58.65±3.17
Class III	23	40.32±7.19	Class III	7	37.56±2.32
Class IV	22	24.45±5.43	Class IV	8	26.62±3.36

test indicated that the various indexes of subjects in the control group were within the normal ranges. However, declined pulmonary ventilation function and significant limitation of expiratory air current were observed in COPD patients. There were significant differences between the two groups (p<0.01). Based on the GOLD guidelines, the severity of limitation of the expiratory air current was rated as the percentage of forced expiration volume in the first second in the predicted value (FEV_1%pred) (Table II).

Rating of Nutritional Indexes

The specific results of the two groups are shown in Table III. Multiple nutritional indexes of the COPD patients declined, while the majority of indexes of subjects in the normal control group were within the normal ranges. The MNI of patients in the COPD group was significantly higher than that in the control group (p<0.01).

TwQmax Test Results for Muscle Functions

Sixty subjects achieved TwQmax under average magnetic stimulation intensity of 80%. A total of 121 subjects achieved TwQmax and the maximum CMAP under average magnetic stimulation intensity of 90%. No TwQmax was detected in 10 cases. The average value of TwQ (TwQ100%) induced three times by magnetic

Table III. Nutritional indexes scores of the two groups ($\bar{x}$±s).

	Normal control group	COPD group	*t*	*p*
Body weight, % predicted value for IBW (%)	101.57±10.53	85.82±13.16	10.55	0.000*
Albumin (g/L)	41.34±2.55	35.43±2.87	7.56	0.000*
Transferrin (μg/ml)	2.16±0.42	1.73±0.33	3.87	0.000*
TSF% pred (%)	10.09±5.85	71.45±15.32	6.15	0.000*
MAMC% pred (%)	101.53±6.54	86.88±7.53	4.23	0.000*
Cholesterol (pg/ml)	5.53±1.42	5.41±0.43	0.44	0.96
Triglyceride (pg/ml)	1.18±0.78	1.12±0.42	1.53	0.12
MNI (scores)	1.21±0.88	7.66±3.67	13.97	0.000*

Legend: Comparison with the normal control group, p<0.01.

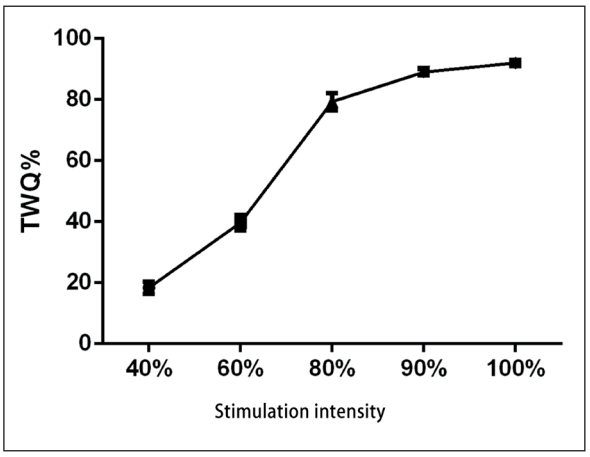

Figure 1. TwQmax test results of muscle functions. With the increase of magnetic stimulation intensity, the appropriate TwQ increased gradually and was maintained at a stable level when magnetic stimulation with about 90% intensity occurred. The degree of variation of TwQ induced by magnetic stimulation with non-maximum intensity was significantly higher than TwQ 100%. With the increase of the intensity of magnetic stimulation, the degree of variation of TwQ values of the quadriceps femoris induced by magnetic stimulation decreased.

stimulation under 100% intensity was used as the final TwQmax. Each subject underwent magnetic stimulation with four different non-maximum intensities in ascending sequence: 40%, 60%, 80%, and 90%. More magnetic stimulations with intensity ranging from 90-100% were applied to subjects who achieved no TwQmax under magnetic stimulation with 90% intensity. TwQ100% of each subject was used as the baseline value to standardize the TwQ under different stimulation intensities (TwQ: TwQ100%) and observe the degree of variation of TwQ in individuals induced by the non-maximum stimulation intensity. Figure 1 shows TwQ: TwQ100% induced by magnetic stimulation with different intensities in 55 COPD patients.

QMVC and Tf Testing Results for Muscle Function

The results of the functional test of the quadriceps femoris of the two groups are shown in Table IV. The results indicated that QMVC of 51 male patients and 16 female patients decreased. Declined active contraction functions occurred in 94% of patients. The Tf values of 38 male patients and 11 female patients decreased. Declined endurance occurred in 69% of patients. A total of 94% of COPD patients experienced a decline in any single function of the quadriceps femoris, while 56% of COPD patients experienced a decline in both QMVC and Tf. Furthermore, compared with the healthy male subjects, on average, the male COPD patients experienced a 45% decline in QMVC and 35% decline in endurance time (Tf). Compared with the healthy female subjects, on average, the female COPD patients experienced a 42% decline in QMVC and 37% decline in Tf.

Surface Myoelectric Signals

Comparison of the root-mean-square (RMS) of the surface myoelectricity (SEMG) of the quadriceps femoris in QMVC and CAMP tests is shown in Table V. The RMS of SEMG of the VL, RF, and VM muscle and CMAP amplitude under magnetic stimulation decreased significantly in COPD patients ($p<0.05$). Therefore, the surface myoelectric signals decreased in COPD patients.

The Expression of Cytokines in Serum and Peripheral Hemocytes

Comparison of the expression of cytokines in serum and peripheral hemocytes between the two groups is shown in Table VI. The expression of eight cytokines increased in the COPD group, although there were only statistically significant differences in the levels of four cytokines ($p<0.05$), including SPD, TWEAK, myostatin, and TNF-α.

Table IV. Test of muscle functions in the two groups ($\bar{x}\pm s$).

	Sex	Normal control group	COPD patients group	*t*	*p*
QWVC (kg)	Male	41.33±7.58	21.27±5.34	11.34	0.000*
	Female	28.34±4.37	13.45±4.19	10.34	0.000*
Tf (S)	Male	82.34±21.66	52.45±17.76	5.65	0.000*
	Female	84.58±22.19	55.43±16.67	5.16	0.000*

Legend: *Compared with healthy subjects, the COPD patients experienced a significant decline in QMVC and Tf, $p<0.01$.

Table V. SEMG ($\bar{x}$±s) of the two groups in QMVC and CAMP tests.

	Class	Sex	Normal control group	COPD group	t	p
QMVC	VL-RMS (mv)	Male	406.33±81.53	295.76±87.38	4.56	0.000
		Female	305.77±62.19	220.56±47.34	5.07	0.000
	RF-RMS (mv)	Male	333.58±101.27	238.23±88.31	3.56	0.000
		Female	251.56±55.67	172.49±72.35	4.68	0.000
	VR-RMS (mv)	Male	344.56±66.56	273.54±81.98	3.69	0.001
		Female	283.56±74.33	188.45±53.51	4.34	0.000
CAMP	VL-M (mv)	Male	8.05±3.38	3.13±1.56	8.87	0.000
		Female	3.55±1.33	2.68±0.83	5.56	0.000
	RF-M (mv)	Male	5.36±1.63	3.16±1.26	2.21	0.003
		Female	3.38±1.35	2.28±1.35	2.29	0.028
	VR-M (mv)	Male	5.33±2.18	3.29±1.85	2.24	0.035
		Female	3.25±1.38	2.19±0.88	3.67	0.001

VL: vastus lateralis muscle; RF: rectus femoris; VMI: vastus medialis muscle.

Correlation Analysis

The stepwise regression analysis indicated that in normal subjects, the QMVC detection value was associated with sex (0.425), PA score (0.269), and body weight (0.281) (R2=0.55, p<0.001). The endurance time was associated with PA score (0.543), MTMC (0.342), body weight (0.477), and sex (−0.659) (R2=0.53, p<0.001). TwQmax was associated with height (0.68) and PA score (0.257) (R2=0.53, p<0.001). The measured values of the three indexes of muscle function in COPD patients were used as the dependent variables, and the related factors were used as the independent variables for multivariate stepwise regression analysis. The results of the specific regression analysis of QMVC are shown in Table VII. The measured values of endurance time were associated with FEV1%pred and TNF-α (R2=0.24, p<0.001). The TwQmax induced by magnetic stimulation of the femoral nerves was subjected to multivariate regression analysis. The results indicated that the TwQmax of the quadriceps femoris of COPD patients was not associated with the above screening factors.

Discussion

The results of this study show that, compared with healthy subjects, single quadriceps function declines in patients with COPD. This result was consistent with those frequently reported in the literatures[20-22], i.e., a decline in peripheral skeletal muscle function is common in COPD patients. Even patients with FEV_1%pred > 50% experienced a decline in function of the quadriceps. The decline in peripheral skeletal muscle function, as one of the main manifestations of the systemic effects of COPD, often begins from the early stage of the disease. The stepwise

Table VI. The expression of NF-κB and and cytokines in serum peripheral hemocytes in the two groups ($\bar{x}$±s).

Cytokines	Normal control group	COPD patients group	t	p
SPD (ng/ml)	31.45±5.42	47.44±17.38	7.14	0.000*
Myostatin (μg/ml)	31.76±9.58	48.63±21.12	6.21	0.000*
TWEAK (pg/ml)	447.49±84.36	583.45±241.42	4.36	0.000*
TNF-α (pg/ml)	6.39±4.76	13.78±2.73	11.58	0.000*
IL-1β (pg/ml)	5.57±0.30	6.31±1.45	1.67	0.067
IL-6 (pg/ml)	8.09±0.44	8.31±0.88	1.55	0.120
CRP (mg/L)	3.25±0.14	3.43±0.56	1.46	0.145
NF-κB (score)	1.21±0.74	1.44±0.65	1.87	0.060

Legend: *Comparison with the normal control group, p<0.01.

Table VII. Correlation between QMVC and the risk factors in COPD patients.

	Non-standardized coefficient	Standard error	ÐÐÐÐÐ ?????	*t*-value	*p*-value
Constant	7.743	2.505		2.4912	0.003
Sex	7.577	0.679	0.518	9.0744	0.000
FEV1% pred	0.113	0.034	0.245	3.6776	0.000
Myostatin	-0.06	0.036	-0.226	2.3344	0.005
TWEAK	-0.004	0.014	-0.187	2.4568	0.003
MNI	-0.267	0.077	-0.163	2.5616	0.002
SPD	-0.045	0.037	-0.144	1.716	0.036
FEV_1 pred	0.518	0.137	0.426	3.2584	0.000
TNF-α	-1.823	0.665	-0.284	2.2384	0.007

regression analysis indicated that the severity of the decline in functions of the quadriceps femoris and the degree of airflow obstruction in pulmonary function were significantly and positively correlated, suggesting that the decline in function of peripheral skeletal muscle in COPD patients is a major factor causing limitations of daily activities. In terms of contractility and endurance, the declines in QMVC and TwQmax were more significant than those of Tf; it showed that the extremity skeletal muscle function of patients with COPD was reduced, showing decreased contractility. The decline in contractility in COPD patients was more significant, which suggests that a decrease in quadriceps QMVC is a more important factor affecting the activity limitation of COPD patients. Given this result, we propose that COPD is not only a chronic local inflammatory disease characterized by airway limitation, but also a chronic disease involving multiple systems of the body. The decline in peripheral skeletal muscle functions is one of the significant systemic effects[23].

The regression analysis of quadriceps function in COPD patients showed a positive correlation between QMVC, lung function index and FEV_1%pred. Additionally, the endurance time (Tf) was significantly and positively correlated with FEV_1%pred. This suggested that the decline in functions of the quadriceps femoris in COPD patients was closely associated with the severity of airway limitation. The results of the MNI rating in this study indicated that the MNI score in COPD patients was significantly higher than that in the normal control group. The majority of patients suffered from malnutrition to different degrees. As one of the systemic effects of COPD, malnutrition can directly lead to decreased muscle volume, muscle wasting, and myasthenia. The regression analysis showed that the MNI scores of the COPD patients were significantly and negatively correlated with QMVC. The results further demonstrated that COPD is a multi-systemic disease, and malnutrition is one of the systemic effects[24]. Furthermore, this indicates that malnutrition is one of the factors directly or indirectly involved in the incidence of SMD. Malnutrition in COPD patients may be associated with the high degree of airflow obstruction and expression of multiple inflammatory factors. The possible mechanism of malnutrition in the occurrence of SMD is: 1. The overloaded work of respiratory muscles increases the mechanical work, catabolism, and energy expenditure. The long-term malnutrition of patients causes muscle wasting (SMW); 2. High catabolism closely associated with systemic inflammation leads to malnutrition and myasthenia (SMW); 3. Inappetence and decreased ingestion associated with dyspnea lead to malnutrition and SMD.

Based on the previous research[25] on the relationship between systemic inflammation and SMD in COPD patients in recent years, we screened eight cytokines that may participate in the occurrence of SMD. The results indicated that all cytokines were increased in the blood of COPD patients, although there were only significant differences in the levels of SPD, TWEAK, myostatin, and TNF-α. In addition, the stepwise regression analysis showed that SPD, TWEAK, and myostatin were significantly and negatively correlated with the QMVC testing results, while TNF-α and the endurance time were negatively correlated. The results further demonstrated that COPD is a chronic systemic inflammatory disease. Furthermore, the occurrence of SMD in the COPD patients was closely associated with systemic inflammation.

Conclusions

Based on a comprehensive analysis of these results, we suggest that decreased daily activity in COPD patients is not the direct cause of SMD, although it can indirectly induce the incidence of SMD. The dyspnea arising from declined pulmonary functions and limitations of daily activity interacts as both cause and effect, since they can induce the incidence of SMD or exacerbate the severity of SMD. The pathophysiological basis of this vicious circle is associated with changes in structure and biochemical function of skeletal muscle because of long-term disuse. Additionally, chronic systemic inflammation and the decrease in daily activities may interact as both cause and effect and participate in or promote the occurrence of SMD. The relationship between daily activities and the functions of the quadriceps femoris and its definitive mechanism require further investigation.

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Conflict of Interests

The Authors declare that they have no conflict of interests.

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