Catabolic/Anabolic Balance and Muscle Wasting in Patients With COPD*

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**Background:** The mechanisms leading to muscle wasting in patients with COPD are still uncertain. This study was undertaken to evaluate the relationships among circulating levels of catabolic factors (*ie*, interleukin [IL]-6 and cortisol), anabolic factors (*ie*, bioavailable testosterone [Tbio], dehydroepiandrosterone sulfate [DHEAS], and insulin-like growth factor [IGF]-I), and mid-thigh muscle cross-sectional area (MTCSA) in patients with COPD.

**Methods:** Serum levels of the above factors were measured in 45 men with COPD (mean [± SEM] FEV1, 43 ± 3% predicted; mean age, 67 ± 1 years) and 16 sedentary healthy men of similar age. MTCSA was quantified using CT scanning. Patients with COPD were subdivided into two groups according to the MTCSA (< 70 or ≥ 70 cm²).

**Results:** There was a greater prevalence of hypogonadism (*ie*, Tbio, < 2 nmol/L) in patients with COPD compared to control subjects (22% vs 0%, respectively). Patients with an MTCSA of < 70 cm² had significantly reduced levels of DHEAS compared to those in healthy subjects (p < 0.01). IL-6 levels were significantly higher in both subgroups of COPD patients compared to those in control subjects (p < 0.005). The cortisol/DHEAS, IL-6/DHEAS, IL-6/Tbio, and IL-6/IGF-I ratios were significantly greater in COPD patients with an MTCSA of < 70 cm² compared to those in control subjects (p < 0.05). The cortisol/DHEAS and IL-6/DHEAS ratios were also significantly greater in COPD patients with an MTCSA of < 70 cm² than in COPD patients with an MTCSA of ≥ 70 cm² (p < 0.05). In a stepwise multiple regression analysis, the IL-6/DHEAS ratio explained 20% of the variance in MTCSA (p < 0.005).

**Conclusion:** Catabolic/anabolic disturbances were found in COPD patients leading to a shift toward catabolism and possibly to the development of peripheral muscle wasting.

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**Key words:** atrophy; COPD; cytokines; insulin-like growth factor-I; muscle; testosterone; wasting

**Abbreviations:** BMI = body mass index; DHEA = dehydroepiandrosterone; DHEAS = dehydroepiandrosterone sulfate; IGF = insulin-like growth factor; IL = interleukin; LH = luteinizing hormone; MTCSA = mid-thigh muscle cross-sectional area; Tbio = bioavailable testosterone; TNF = tumor necrosis factor; TNF-R = tumor necrosis factor receptor

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It is now recognized that peripheral muscle dysfunction adversely affects clinical outcomes in COPD. Concomitantly with muscle structural changes, there is a loss of peripheral muscle mass in patients with this disease, often despite having a normal body mass index (BMI). Peripheral muscle wasting in COPD patients is associated with muscle weakness, decreased exercise capacity, impaired quality of life, and more importantly, decreased survival. Although a gain in peripheral muscle mass can be obtained with exercise training or anabolic drug supplementation, the magnitude of the improvement remains modest. A major issue is that no clear mechanistic explanations have been proposed to explain how muscle wasting takes place in COPD patients.

Chronic diseases lead to hormonal dysfunction and increased levels of circulatory proinflammatory...
cytokines, leading to a shift toward catabolism and eventually to the significant loss of muscle tissue. Proinflammatory cytokines such as tumor necrosis factor (TNF) and interleukin (IL)-6 can induce muscle wasting in animals, and there are also data to support their roles in human cachexia. Elevated blood levels of various proinflammatory cytokines have been reported in patients with several chronic diseases that are associated with wasting, including COPD, chronic heart failure, and cystic fibrosis. Low levels of anabolic steroids and growth factors also can contribute to the wasting process in patients with chronic diseases. Low levels of testosterone and insulin-like growth factor (IGF)-I already have been reported in COPD patients, but how this relates to muscle wasting has not been evaluated. Alterations in adrenal hormone metabolism also have been proposed to contribute to the wasting process in patients with chronic heart failure. Reduced levels of dehydroepiandrosterone (DHEA), an adrenal steroid, and a high cortisol/DHEA ratio are thought to create an imbalance between protein synthesis and degradation favoring catabolism over anabolism in patients with this disease. The potential role of the adrenal hormones in wasting associated with COPD has not been investigated.

At the molecular level, the maintenance of muscle mass is dependent on several intricate and redundant regulating pathways, and it is unlikely that disturbances in one single component of this complex system explain entirely the wasting process. In this regard, the interaction between catabolic and anabolic factors is interesting to consider. For instance, a low anabolic hormone level may synergize the catabolic effects of proinflammatory cytokines. Conversely, high anabolic hormone level may protect against the potentially negative impact of proinflammatory cytokines on muscle mass as exemplified in highly trained athletes in whom bursts of proinflammatory cytokines after a high-intensity activity do not lead to muscle wasting. Thus, investigating the balance between anabolic and catabolic factors may be more informative than individual anabolic and catabolic factors that are studied in an isolated fashion.

We have recently confirmed the important harmful prognostic implication of a reduced muscle mass on survival in patients with COPD. This was particularly true in patients with an FEV1 < 50% of predicted in whom a mid-thigh muscle cross-sectional area (MTCSA) of < 70 cm² was associated with a fourfold increase in mortality rate. The present study concerns a subset of these patients in whom blood was available to evaluate the relationships between blood levels of catabolic factors (ie, IL-6, TNF, and cortisol) and anabolic factors (ie, bioavailable testosterone [Tbio], DHEA sulfate [DHEAS], and IGF-I), and peripheral muscle wasting. The ratio between cortisol and DHEAS was taken as an index of adrenal steroid metabolism, while the ratios of IL-6 and the anabolic factors were used as markers of the catabolic/anabolic balance in these subjects.

Materials and Methods

Subjects

The study population consisted of 45 men with COPD who were in stable condition, who had participated in our previous study evaluating the impact of low muscle mass on survival in COPD, and in whom blood was available for the quantification of anabolic and catabolic factors. The diagnosis of COPD was based on smoking history and on pulmonary function test results showing irreversible airflow limitation. Patients with any active inflammatory diseases as well as any other chronic diseases, such as chronic heart failure or diabetes, were excluded from the study. No patients were receiving long-term oxygen therapy, and none had been exposed to systemic corticosteroids in the 6-month period preceding this study. Sixteen sedentary, healthy men who were ex-smokers and were of similar ages were recruited by means of a newspaper advertisement, and served as control subjects for biochemical markers. These subjects were free of any medication, and none reported a significant drinking history. They were evaluated by a physician who was involved in the present study to confirm their healthy status. The institutional ethics committee approved the research protocol, and written consent was obtained in each case.

Protocol

Anthropometric Measurements and Pulmonary Function Tests: After height and weight were measured, standard pulmonary function tests, including those for spirometry, lung volumes, and diffusion capacity, were performed, and the results were compared to normal values reported in the studies of Knudson et al and Goldman and Becklake, respectively. For control subjects, only spirometry values were obtained.

CT Scan of the Thigh: In order to evaluate MTCSA, a CT scan of the right thigh halfway between the pubic symphysis and the inferior condyle of the femur was performed, as previously described. Blood Sampling and Analysis: After a resting period of 30 min, antecubital venous blood was sampled between 8:00 AM and 9:00 AM in overnight fasted subjects. Blood was centrifuged for 15 min, put into aliquots, and stored at −80°C until further analysis. Commercial immunoassays were used to measure the serum levels of luteinizing hormone (LH) [Assym; Abbot Laboratories; Abbot Park, IL] and cortisol (Elecsys 1010; Roche Diagnostics; Basel, Switzerland), while serum levels of Tbio and DHEAS were determined using a commercial radioimmunoassay (Coat-A-Count Testosterone and Coat-A-Count DHEA-SO₄, respectively; Diagnostic Products Corporation; Los Angeles, CA). Tbio dosage was preceded by an ammonium sulfate precipitation
of sex hormone-binding globulin-bound testosterone, as previously described. The intraassay and interassay coefficients of variation were as follows: LH, 6.6% and 6.4%, respectively; cortisol, 3.2% and 5.6%, respectively; Tbio, 7.4% and 15.5%, respectively; and DHEAS, 5.3% and 6.3%, respectively. Blood serum levels of IL-6, TNF, TNF receptor (TNF-R) 55, TNF-R75, and IGF-I were determined using commercial enzyme-linked immunosorbent assay kits (R&D Systems; Minneapolis, MN) with limits of detection at 0.094 pg/mL, 0.12 pg/mL, 3.0 pg/mL, 1.0 pg/mL, and 0.026 ng/mL, respectively.

Statistical Analysis

Blood samples and CT scans were analyzed without knowledge of the clinical status. All data are reported as the mean (SEM). In order to evaluate the relationship between catabolic and anabolic factors, and peripheral muscle mass, patients with COPD were subdivided according to their MTCSA, using a cut point of 70 cm², according to Marquis et al. In that study, an MTCSA of <70 cm² was strongly associated with mortality in COPD patients. Analysis of variance and post hoc Tukey comparison tests were used to compare COPD subgroups and control subjects. Simple linear regressions were performed in order to evaluate the possible relationships between catabolic and anabolic factors, and peripheral muscle mass. In COPD, a stepwise multiple regression analysis was performed with MTCSA as the dependent variable and age, FEV₁ % predicted, Tbio, DHEAS, IGF-I, cortisol, IL-6, cortisol/DHEAS ratio, IL-6/ Tbio ratio, IL-6/DHEAS ratio, and IL-6/IGF-I ratio as the independent variables. A p value of <0.05 was considered to be statistically significant.

RESULTS

The anthropometric characteristics of both subgroups of patients and control subjects are shown in Table 1. Twenty-seven patients with COPD had an MTCSA of ≥70 cm² (56 ± 2 cm²), while the remaining 18 patients had an MTCSA of <70 cm² (58 ± 2 cm²). For comparison, the mean MTCSA in the 16 healthy individuals was 96 ± 4 cm². Patients with an MTCSA of <70 cm² had a significantly lower BMI compared to patients with an MTCSA of ≥70 cm² and subjects in the control group. The impairment in pulmonary function, PaO₂ and PaCO₂ was similar in both groups of COPD patients.

The blood levels of catabolic and anabolic factors in control subjects and patients with COPD expressed in absolute and relative values are provided in Table 2 and Figure 1, top, A, respectively. Tbio levels were similar between groups (p > 0.05) and were within the normal range for men of the sixth decade (mean level, 3.3 nmol/L; SEM, 1.3 nmol/L). However, 6 of 27 patients (22%) with an MTCSA of ≥70 cm² and 4 of 18 patients (22%) with an MTCSA of <70 cm² could be classified as hypogonadic, which was defined as a Tbio level of <2 nmol/L, while the levels of none of the control subjects were below this level. Of the 10 hypogonadic patients, 7 patients had low or normal levels of LH, suggesting an hypogonadotrophic hypogonadism, while the remaining 3 patients had appropriate elevations of LH, suggesting a testicular dysfunction. Patients with an MTCSA of <70 cm² had significantly reduced levels of DHEAS compared to control subjects (p < 0.01). The group mean values for LH, cortisol, IGF-1, TNF, TNF-R55, and TNF-R75 were not significantly different among the three groups. IL-6 levels were significantly higher in both subgroups of COPD patients compared to those in control subjects (p < 0.005), but the levels were not significantly different between the COPD subgroups. Among all subjects, IL-6 was negatively correlated with Tbio (r = −0.33; p = 0.01) and DHEAS (r = −0.38; p = 0.0035).

The pattern of adrenal steroid metabolism and the

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<tr>
<th>Table 1—Subject Characteristics*</th>
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<td>Variables</td>
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<td>Age, yr</td>
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<td>BMI</td>
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<td>TLC, % predicted</td>
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<td>DLCO, % predicted</td>
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<td>Pco₂, mm Hg</td>
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<td>MTCSA, cm²</td>
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* | TLC = total lung capacity; DLCO = diffusing capacity of the lung for carbon monoxide. Values are mean (SEM).
† | p < 0.05 vs control subjects and COPD patients with MTCSA ≥ 70 cm².
‡ | p < 0.01 vs control subjects.
§ | p < 0.05 vs the two other groups.
values for catabolic/anabolic ratios expressed as percentages of the control values are shown in Figure 1, bottom, B. In general, the magnitude of these ratios increased with the level of muscle atrophy. The adrenal steroid metabolism was altered in COPD patients with an MTCSA of < 70 cm², as indicated by a greater cortisol/DHEAS ratio compared to control subjects and COPD patients with an MTCSA of ≥ 70 cm² (p < 0.01). The IL-6/Tbio ratio, IL-6/DHEAS ratio, and IL-6/IGF-1 ratio were significantly greater in COPD patients with an MTCSA of < 70 cm² compared to control subjects (p < 0.05). The IL-6/DHEAS ratio was also significantly greater in COPD patients with an MTCSA of < 70 cm² than in COPD patients with an MTCSA of ≥ 70 cm² (p < 0.05). The IL-6/Tbio ratio and IL-6/IGF-1 ratio were significantly greater in COPD patients with an MTCSA of ≥ 70 cm² than in control subjects (p < 0.05). None of the ratios involving TNF, TNF-R55, and TNF-R75 were significantly different among the three groups.

Univariate analysis indicated that only the IL-6/DHEAS ratio (r = -0.40; p < 0.01) was significantly correlated with MTCSA. There was no correlation between any of the catabolic and anabolic factors taken individually and MTCSA. No significant correlation was found between BMI and any catabolic and anabolic factors taken individually or any of the catabolic/anabolic factor ratios. In a stepwise multiple regression analysis, the IL-6/DHEAS ratio explained 20% of the variance in MTCSA (p < 0.005). The addition of any other variable in the analysis did not significantly improve the ability of this model to predict MTCSA.

**Discussion**

In this study, peripheral muscle atrophy was associated with disturbances in catabolism and anabolism and not with the level of impairment in lung function. Marked elevations of catabolic/anabolic factor ratios (ie, cortisol/DHEAS, IL-6/Tbio, IL-6/DHEAS, and IL-6/IGF-1), particularly in patients with COPD and low MTCSAs, indicate that there was a shift toward catabolism in COPD patients. Although none of the catabolic or anabolic factors were related to MTCSA, IL-6/DHEAS ratio, which is a marker of the catabolic/anabolic balance, was found to be a significant correlate of MTCSA.

**Catabolic Factors**

Consistent with the results of previous studies, IL-6 blood levels were significantly elevated in patients with COPD compared to those in healthy subjects. IL-6 is a proinflammatory cytokine that is involved in the induction of the acute inflammatory response and the induction of B-lymphocyte proliferation and differentiation. At the muscle level, IL-6 is able to initiate catabolism by activating proteolysis through the ubiquitin proteasome pathway. Interestingly, there appears to be a regulating loop between proinflammatory cytokines and anabolic steroids. Increased levels of proinflammatory cytokines reduce testosterone secretion by interfering with Leydig cell function. Furthermore, anabolic hormone deficiency contributes to elevated IL-6 levels since the expression of this cytokine is down-regulated by testosterone and DHEAS. The interactions between cytokines and anabolic steroids in our patients were supported by the negative correlation between IL-6, on the one hand, and Tbio and DHEAS, on the other hand.

**Anabolic Factors**

The prevalence of hypogonadism in COPD patients in the present study was lower than that previously reported. This can be explained by the

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**Table 2**—Serum Levels of Anabolic and Catabolic Factors

<table>
<thead>
<tr>
<th>Factors</th>
<th>Control Subjects (n = 16)</th>
<th>COPD Patients MTCSA ≥ 70 cm² (n = 27)</th>
<th>COPD Patients MTCSA &lt; 70 cm² (n = 18)</th>
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<tbody>
<tr>
<td>Tbio, nmol/L</td>
<td>3.3 (0.3)</td>
<td>3.0 (0.2)</td>
<td>3.3 (0.4)</td>
</tr>
<tr>
<td>LH, U/L</td>
<td>5.4 (0.6)</td>
<td>5.8 (0.5)</td>
<td>6.0 (0.8)</td>
</tr>
<tr>
<td>DHEAS, μmol/L</td>
<td>3.0 (0.3)</td>
<td>2.5 (0.3)</td>
<td>1.6 (0.3)†</td>
</tr>
<tr>
<td>Cortisol, nmol/L</td>
<td>340 (18)</td>
<td>363 (22)</td>
<td>332 (29)</td>
</tr>
<tr>
<td>IGF-1, ng/mL</td>
<td>81 (6)</td>
<td>74 (5)</td>
<td>72 (9)</td>
</tr>
<tr>
<td>IL-6, pg/mL</td>
<td>2.1 (0.3)</td>
<td>4.6 (0.6)†</td>
<td>5.4 (0.8)†</td>
</tr>
<tr>
<td>TNF, pg/mL</td>
<td>3.45 (0.23)</td>
<td>3.03 (0.13)</td>
<td>3.53 (0.41)</td>
</tr>
<tr>
<td>TNF-R55, pg/mL</td>
<td>1611 (93)</td>
<td>1719 (95)</td>
<td>1873 (334)</td>
</tr>
<tr>
<td>TNF-R75, pg/mL</td>
<td>3047 (117)</td>
<td>3222 (131)</td>
<td>3211 (230)</td>
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*Values given as the mean (SEM).
†p < 0.01 vs control subjects and COPD patients with MTCSA ≥ 70 cm².
‡p < 0.005 vs control subjects.
absence of chronic hypoxemia or the lack of use of systemic steroids in our patients, two factors interfering with proper gonadal function. A marked reduction in DHEAS also was found in patients with an MTCSA of < 70 cm² compared to control subjects, while IL-6 serum levels were significantly increased in both patient subgroups. The adrenal steroid metabolism was altered in COPD patients with an MTCSA of < 70 cm², as indicated by a greater cortisol/DHEAS ratio compared to control subjects and COPD with an MTCSA of ≥ 70 cm². The IL-6/DHEAS, IL-6/Tbio, and IL-6/IGF-1 ratios were significantly greater in COPD patients with an MTCSA of < 70 cm² compared to control subjects. The cortisol/DHEAS and IL-6/DHEAS ratios were also significantly greater in COPD patients with an MTCSA of < 70 cm² than in COPD patients with an MTCSA of ≥ 70 cm². Values are given as the mean ± SEM. * = p < 0.01; † = p < 0.005; ‡ = p < 0.05.

Figure 1. Group mean values of serum levels of individual anabolic and catabolic factors (top, A) and catabolic/anabolic ratios (bottom, B) expressed as a percentage of control values. The serum DHEAS level was significantly reduced in COPD patients with an MTCSA of < 70 cm² compared to control subjects, while IL-6 serum levels were significantly increased in both patient subgroups. The adrenal steroid metabolism was altered in COPD patients with an MTCSA of < 70 cm², as indicated by a greater cortisol/DHEAS ratio compared to control subjects and COPD with an MTCSA of ≥ 70 cm². The IL-6/DHEAS, IL-6/Tbio, and IL-6/IGF-1 ratios were significantly greater in COPD patients with an MTCSA of < 70 cm² compared to control subjects. The cortisol/DHEAS and IL-6/DHEAS ratios were also significantly greater in COPD patients with an MTCSA of < 70 cm² than in COPD patients with an MTCSA of ≥ 70 cm². Values are given as the mean ± SEM. * = p < 0.01; † = p < 0.005; ‡ = p < 0.05.

metabolite of DHEA, which is produced by the adrenal glands and is the most abundant steroid present in the blood. DHEAS may act directly at the tissue level or after conversion to androstenedione or androstenediol, and finally to testosterone. Testos-
terone and DHEAS exert their anabolic actions on skeletal muscle through several mechanisms. Testosterone increases net protein synthesis within the muscle using the intracellular amino acid pool. In aging men and women, DHEAS may contribute to anabolism indirectly by increasing serum IGF-I levels, although the discovery of specific binding sites for DHEAS on skeletal muscle cells supports a direct action of DHEAS on these cells.

In our patients, low blood testosterone levels could be explained by a disturbance in the hypothalamic-pituitary axis (i.e., low or normal LH values) or at the gonadal level (i.e., high LH values), although the exact nature of these disturbances remains to be elucidated. Low PaO₂ and systemic use of corticosteroids can alter the function of the hypothalamic-pituitary axis, but these factors did not seem to play a role in our patients. As mentioned above, the direct effects of proinflammatory cytokines on the testis may lead to decreased testosterone production. Leydig cell atrophy has been reported in COPD patients and also may contribute to low testosterone production.

IGF-I has been implicated in several important functions such as cell differentiation, growth, and maintenance of skeletal muscle. Despite the fact that similar serum levels of IGF-I were observed in control subjects and both subgroups of patients, a possible role for this system in COPD-associated muscle atrophy cannot be excluded. For instance, the availability and biological effects of IGF-I may be modulated by IGF-binding proteins, and it is conceivable that alterations in the circulating levels of these binding proteins may have decreased the bioavailability of IGF-I in COPD patients. Interestingly, an increased level of IL-6 can exert a suppressive action on IGF-I by up-regulating the expression of IGF binding protein-1. Alternatively, abnormal interactions with the cell surface receptor may hamper the proper action of IGF-I on muscle.

**Interactions Between Catabolic and Anabolic Factors and Muscle Wasting**

The absence of correlation between any catabolic or anabolic factor and MTCSA may seem to deny their potential role in muscle wasting in COPD patients. However, this finding is not unexpected, considering that muscle homeostasis is extremely complex and may be influenced by several factors other than the hormonal milieu such as age, level of physical activity, and the nutritional status. Despite this, the progressive rise in catabolic/anabolic ratios with worsening of muscle atrophy (Fig 1, bottom, B) is quite striking and supports the idea that wasting is a cumulative effect of a long-term exposure to an abnormal hormonal milieu. The stepwise regression analysis showing that the IL-6/DHEAS ratio was the only significant correlate of MTCSA also illustrates that evaluating the balance between catabolism and anabolism may be more relevant to muscle wasting than looking at individual changes in any catabolic/anabolic factor. Interestingly, a disruption in the normal balance between catabolism and anabolism also has been associated with the occurrence of cachexia in patients with chronic heart failure. Taken together, the available information suggests that the evaluation of the catabolic/anabolic balance and the interaction between catabolic and anabolic factors should be considered when evaluating muscle atrophy in chronic diseases. Another important finding of the present study is that muscle wasting in COPD patients cannot be predicted by the level of impairment in lung function. Rather, patients with an MTCSA of < 70 cm² can be differentiated from those with an MTCSA of ≥ 70 cm² on the basis of greater disturbances in the hormonal determinants of catabolism and anabolism. Conceivably, the catabolic/anabolic imbalance may influence the clinical picture and perhaps the survival of patients with COPD, offering a valid target for future therapeutic interventions.

**Limitations of the Study**

Although a biological link between catabolic/anabolic disturbances and muscle wasting is plausible, the correlation between the serum level IL-6/DHEAS ratio and MTCSA does not necessarily imply a causal relationship. In this regard, longitudinal studies evaluating long-term changes in the anabolic/catabolic balance and muscle mass will be useful. The activities of the different catabolic and anabolic factors also should be evaluated at the muscle level. In this study, serum levels of catabolic and anabolic factors were evaluated on only one occasion, and, to avoid any bias, this was done at the same time in the morning. Although speculative, daily fluctuations in the blood levels of these factors may occur such that serial sampling could have provided a better overview of the cytokine and hormonal abnormalities in COPD patients than could a single evaluation.

In summary, several abnormalities in catabolic and anabolic mediators resulting in a shift toward catabolism were found in patients with COPD showing peripheral muscle atrophy. Although this catabolic/anabolic imbalance is a likely contributor to the wasting process in COPD patients, further work is necessary to evaluate the action of catabolic and anabolic factors at the muscle level.
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