Low-Grade Systemic Inflammation and the Response to Exercise Training in Patients With Advanced COPD*

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**Study objective:** Low-grade systemic inflammation may cause a chronic catabolic state that may affect trainability in patients with COPD as has been seen previously in healthy elderly. Therefore, the aim of the present study was to study the relationship between baseline circulating levels of inflammatory markers and the response to exercise training in clinically stable patients with COPD.

**Design:** An open prospective intervention study.

**Setting:** Tertiary care setting, University Hospital Gasthuisberg, Leuven, Belgium.

**Patients:** Seventy-eight clinically stable outpatients with COPD.

**Intervention:** A 12-week outpatient exercise-training program consisting of strengthening and endurance types of exercises.

**Measurements and results:** Circulating levels of inflammatory markers were assessed at baseline. Moreover, lung function, quadriceps force (QF), peak and functional exercise capacity, and health-related quality of life were determined at baseline and after the intervention. Sixty-five of the 78 consecutive outpatients completed the study protocol. QF, peak and functional exercise capacity and health-related quality of life improved significantly compared to baseline. The absolute changes in health-related quality of life showed weak relationships with baseline circulating levels of interleukin-8 (CXCL8) in the whole group \( n = 65; r = -0.26; p = 0.04 \). In addition, soluble tumor necrosis factor receptor p55 was strongly and positively related to the absolute changes in QF in the female patients only \( n = 18; r = 0.81; p = 0.0001 \), while CXCL8 was inversely related to the absolute change in the total score of the Chronic Respiratory Disease Questionnaire \( r = -0.65; p = 0.004 \).

**Conclusion:** Baseline markers of low-grade systemic inflammation did not clearly explain the variances in absolute changes in QF, the distance walked in 6 min, peak external load, or health-related quality of life following a 12-week exercise-training program. Hence, they seem not very constructive in the characterization of patients with advanced COPD who do or do not respond to exercise training.

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**Key words:** COPD; exercise training; gender differences; interleukin-8; physiotherapy; skeletal muscle strength; soluble tumor necrosis factor receptor; systemic inflammation; tumor necrosis factor-α

**Abbreviations:** CRP = C-reactive protein; CRDQ = Chronic Respiratory Disease Questionnaire; CXCL8 = interleukin-8; IQR = interquartile range; Nm = newton-meters; QF = quadriceps force; 6MWD = 6-min walking distance; sTNFR = soluble tumor necrosis factor receptor; TNF = tumor necrosis factor

Exercise training is the cornerstone of comprehensive rehabilitation programs in patients with COPD.1 Although specific exercise modalities can be applied to reverse muscle dysfunction, exercise intolerance, and reduced health-related quality of life,2–4 there is a substantial heterogeneity in the response to exercise training among patients with clinically stable COPD.5

To date, it remains unclear whether and to what extent systemic inflammation affects the response to exercise training. Of particular interest is how specific inflammatory markers are related to the response to exercise training. Our study investigated the relationship between baseline circulating levels of inflammatory markers and the response to exercise training, which included measures of skeletal muscle strength, pulmonary function, and health-related quality of life, in patients with stable COPD.

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extent markers of low-grade systemic inflammation may affect trainability in clinically stable patients with advanced COPD. Nonetheless, it can be hypothesized that the presence of a chronic catabolic state may limit the effects of ergogenic interventions. For example, patients with COPD who failed to gain weight during a refeeding program were shown to have high levels of soluble tumor necrosis factor receptor (sTNFR)-p55, which has been suggested as a substitute marker of tumor necrosis factor (TNF)-α. In addition, baseline circulating levels of sTNFR-p55 were inversely related to lower extremity muscle strength following a 12-week resistance training program and tended to be inversely related to the absolute increase in muscle strength in 90-year-old nursing home residents. Actually, increased systemic inflammation may even reduce the expression of insulin-like growth factor-I, which normally stimulates myofiber anabolic processes.

Previously, no physiologic variables have been related to changes in health-related quality of life following exercise training in patients with COPD. Nonetheless, changes in health-related quality of life may also be related to baseline low-grade systemic inflammation. In fact, health-related quality of life has been related to the frequency of acute exacerbations of COPD, which are known to induce transient increases in systemic inflammation. An open prospective intervention study was therefore designed to determine the relationships among the baseline circulating levels of TNF-α, sTNFR-p55, sTNFR-p75, and interleukin-8 (CXCL8), and the absolute changes in skeletal muscle force, exercise capacity, and health-related quality of life in patients with COPD. A priori, it was hypothesized that the patients with the highest circulating levels of inflammatory markers would have the worst response to exercise training.

**METHODS AND MATERIALS**

**Patients**

Seventy-eight consecutive patients with COPD who attended the respiratory outpatient clinic between May 2002 and October 2003 with complaints of dyspnea and poor exercise performance volunteered to participate (Table 1). Patients had no cardiovascular, renal, or neurologic disorders, and did not experience an acute COPD exacerbation in the 3-month period before baseline testing. The Medical Ethical Board of the University Hospitals Leuven approved this open prospective intervention study. All patients gave oral and written informed consent. The present patients did not participate in previous studies.

**Blood Analyses**

At baseline, venous blood was drawn from subjects in the supine position between 8:30 AM and 9:00 AM before functional baseline circulating levels of TNF-α, sTNFR-p55, sTNFR-p75, and CXCL8, were measured during a refeeding program and tended to be inversely related to lower extremity muscle strength following a 12-week resistance training program. As described previously, baseline circulating levels of TNF-α, sTNFR-p55, sTNFR-p75, and interleukin-8 (CXCL8), and the absolute changes in skeletal muscle force, exercise capacity, and health-related quality of life in patients with COPD. A priori, it was hypothesized that the patients with the highest circulating levels of inflammatory markers would have the worst response to exercise training. Clinical Investigations

**Functional Measurements**

Pulmonary function, quadriceps force (QF), peak exercise capacity, and the distance walked in 6 min were assessed before and after completing a 12-week exercise program. FEV₁ and FVC were measured according to the European Respiratory Society guidelines for pulmonary function testing. In addition, the diffusing capacity of the lung for carbon monoxide was measured by the single-breath method (6200; SensorMedics; Bihoven, the Netherlands). The results were expressed as a percentage of the predicted normal values of Quanjer and colleagues. Isometric QF was evaluated with the subject in the sitting position at 60° of knee flexion and 90° of hip flexion (Cybex Norm; Enraf-Nonius; Delft, the Netherlands). The test was performed at least three times, and the best of two reproducible test results was used for analysis. Values were related to the reference values of Deetman and colleagues. Peak exercise capacity was assessed by a maximal incremental cycle exercise test. After a 2-min resting period and 3 min of unloaded cycling, patients started at 20 W and cycled until symptom limitation at an incremental workload of + 10 W/min. Oxygen uptake (Vmax 29C; Viasys Media NV; Edegem, Belgium), heart rate (Mac VS/ST; Marquette Electronics Inc; Milwaukee, WI), and transcutaneous oxygen saturation (model 3900; Datex-Ohmeda; Hoevelaken, the Netherlands) were measured during the test. At the end of the test, symptom Borg scores for dyspnea and fatigue were obtained from all participants. The peak external work rate and peak oxygen uptake were normalized for height, age, and gender.

The 6-min walking distance (6MWD) was assessed in a 53-m-long course during a 6-min period. Patients did not participate in previous studies.12,13

### Table 1—Baseline Characteristics*

<table>
<thead>
<tr>
<th>Variables</th>
<th>Completed Study</th>
<th>Dropped Out of Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, No.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>47</td>
<td>11</td>
</tr>
<tr>
<td>Female</td>
<td>18</td>
<td>2</td>
</tr>
<tr>
<td>Age, yr</td>
<td>65 (8)</td>
<td>65 (9)</td>
</tr>
<tr>
<td>Height, cm</td>
<td>167 (8)</td>
<td>169 (8)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>23.9 (5.1)</td>
<td>24.8 (4.7)</td>
</tr>
<tr>
<td>FEV₁, L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% predicted</td>
<td>1.21 (0.53)</td>
<td>1.12 (0.26)</td>
</tr>
<tr>
<td>FEV₁/FVC ratio, %</td>
<td>45 (18)</td>
<td>40 (11)</td>
</tr>
<tr>
<td>TL_co₂</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mmol/min/kPa</td>
<td>3.87 (1.64)</td>
<td>3.81 (1.25)</td>
</tr>
<tr>
<td>% predicted</td>
<td>47 (18)</td>
<td>45 (15)</td>
</tr>
<tr>
<td>PaO₂, mm Hg</td>
<td>67 (9)</td>
<td>64 (13)</td>
</tr>
<tr>
<td>PaCO₂, mm Hg</td>
<td>41 (5)</td>
<td>43 (8)</td>
</tr>
</tbody>
</table>

*Values are given as the mean (SD), unless otherwise indicated. TL_co₂ = transfer factor for carbon monoxide in the lungs.
hospital corridor. Encouragement was standardized, and the best of two test results was expressed as a percentage of the predicted value.

Health-related quality of life was measured with the disease-specific Chronic Respiratory Disease Questionnaire (CRDQ), which contains the following four domains: dyspnea (five questions); fatigue (four questions); mastery of the complaints (four questions); and emotional functioning (seven questions). Each question was rated on a 7-point scale (ie, 1 to 7 points). Consequently, scores can range from 20 (worst) to 140 (optimal).

Exercise-Training Program

Patients attended the outpatient clinic three times per week (90-min sessions) for 12 weeks to execute the exercise training. Briefly, the program consisted of high-intensity whole-body endurance or interval exercises (ie, ergometry cycling, treadmill walking, and arm cranking) and local dynamic strengthening exercises (ie, dynamic strengthening exercises of the quadriceps muscles, pectoral muscles, and triceps brachia muscles on a leg-press or an exercise machine [AT 1000B-Atech multigym; Fysiomed; Edegen, Belgium, respectively].

The initial intensity for cycling was set at 60% of the peak load for 10 min. Increases in workload were based on Borg symptom scores, trying to achieve a workload of 75% of the peak load for 25 min in week 12. The treadmill walking speed was set at 60% of the average speed obtained from the distance walked in 6 min for 10 min in the first week up to 25 min in week 12. Arm cranking started at 4 min, increasing to 9 min in week 12. Resistance training started at 70% of the initial one-repetition maximum in the first week (3 × 8 repetitions). Every week, the load was increased by 5% of the one-repetition maximum. The modified Borg symptom scale was used to determine training intensity during the exercise-training program. A Borg symptom score of 4 to 6 for dyspnea and/or fatigue was set as the target.

Table 2—Baseline Muscle Force, Exercise Capacity, and CRDQ Scores*

<table>
<thead>
<tr>
<th>Variables</th>
<th>Completed Study</th>
<th>Dropped Out of Study</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skeletal muscle force test, % predicted</td>
<td>76 (23)</td>
<td>63 (16)</td>
<td>0.07</td>
</tr>
<tr>
<td>Functional exercise test 6MWD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>m</td>
<td>419 (121)</td>
<td>387 (133)</td>
<td>0.39</td>
</tr>
<tr>
<td>% predicted</td>
<td>64 (17)</td>
<td>59 (19)</td>
<td>0.28</td>
</tr>
<tr>
<td>Dyspnea, points</td>
<td>6 (2)</td>
<td>5 (3)</td>
<td>0.34</td>
</tr>
<tr>
<td>Fatigue, points</td>
<td>5 (2)</td>
<td>4 (2)</td>
<td>0.52</td>
</tr>
<tr>
<td>Peak exercise test</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak load, % predicted</td>
<td>54 (22)</td>
<td>44 (19)</td>
<td>0.11</td>
</tr>
<tr>
<td>Peak VO$_2$, % predicted</td>
<td>55 (24)</td>
<td>49 (26)</td>
<td>0.45</td>
</tr>
<tr>
<td>Peak HR, % HRmax calculated</td>
<td>85 (11)</td>
<td>83 (15)</td>
<td>0.52</td>
</tr>
<tr>
<td>Peak VE, % MVV</td>
<td>95 (19)</td>
<td>96 (17)</td>
<td>0.75</td>
</tr>
<tr>
<td>Dyspnea cycle, points</td>
<td>7 (2)</td>
<td>5 (2)</td>
<td>0.001</td>
</tr>
<tr>
<td>Fatigue cycle, points</td>
<td>6 (3)</td>
<td>4 (2)</td>
<td>0.03</td>
</tr>
<tr>
<td>CRDQ</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea, points</td>
<td>16 (5)</td>
<td>14 (5)</td>
<td>0.25</td>
</tr>
<tr>
<td>Fatigue, points</td>
<td>15 (5)</td>
<td>13 (5)</td>
<td>0.21</td>
</tr>
<tr>
<td>Emotional functioning, points</td>
<td>29 (8)</td>
<td>26 (9)</td>
<td>0.29</td>
</tr>
<tr>
<td>Mastery, points</td>
<td>18 (6)</td>
<td>15 (6)</td>
<td>0.18</td>
</tr>
<tr>
<td>Total, points</td>
<td>78 (19)</td>
<td>69 (15)</td>
<td>0.17</td>
</tr>
</tbody>
</table>

*Values are given as the mean (SD), unless otherwise indicated. QF = quadriceps force; 6MWD = distance walked in 6 min; VO$_2$ = oxygen uptake; HR = heart rate; % HRmax = percentage of calculated maximal heart rate (220 - age); VE = ventilation; MVV = maximum voluntary ventilation.

Statistical Analysis

The results at baseline and following the exercise training are presented as the mean ± SD or the median (interquartile range [IQR]). A two-tailed paired t test or a Wilcoxon test was used to compare the baseline results for the patients who dropped out and for those who completed the protocol. In addition, a two-tailed paired t test was used to determine the changes following the exercise-training program. The level of significance was set equal to 0.05. Relationships between baseline systemic inflammation and functional outcomes were studied using the Spearman correlations coefficient. The present study has a great number of correlations. The authors, therefore, chose to set the level of significance at 0.01.

RESULTS

Baseline

Table 1 shows the baseline characteristics of the patients who completed the exercise-training program (n = 65) and of those who did not complete it (eg, no 12-week assessment). Patients who dropped out due to various reasons (Fig 1 of the online data supplement) had similar baseline characteristics as those who completed the protocol.

Patients who completed the program generally had moderate-to-severe airway obstruction, normal body mass index, and a moderately reduced arterial oxygen tension (Table 1). Moreover, reduced skeletal muscle force, poor health-related quality of life, and decreased functional and peak exercise capacity were present at baseline (Table 2). The latter was
Correlations With Training Load

The change over time in training load for the quadriceps-strengthening exercise was weakly related to the absolute change in QF ($r = 0.26$; $p = 0.058$); the change over time in treadmill walking speed was related to the absolute change in walked distance in 6 min ($r = 0.40$; $p = 0.003$); and the change over time in cycle ergometer load was related to the absolute change in peak external cycle load ($r = 0.49$; $p = 0.0006$). The absolute change in total CRDQ score was related to change over time in cycle ergometer load ($r = 0.37$; $p = 0.012$) and treadmill walking speed ($r = 0.36$; $p = 0.008$). The number of hospitalizations during the exercise-training program were related to the absolute changes in QF ($r = -0.28$; $p = 0.025$), the distance walked in 6 min ($r = -0.26$; $p = 0.037$), the peak external cycle load ($r = -0.41$; $p = 0.0006$), and the total CRDQ score ($r = -0.30$; $p = 0.019$).

Exercise Training

Patients participated in a mean of 29 ± 6 exercise sessions. On average, training intensity for quadriceps-strengthening exercise, treadmill walking, and ergometer cycling could be increased over time (Fig 2, 3, and 4 of the online data supplement). Fifteen of 65 patients who completed the exercise-training program were hospitalized because of an acute exacerbation during the 12-week exercise-training program (median, 1 exacerbation; IQR, 1 to 3 exacerbations).

Changes After Exercise Training

In contrast to the peak oxygen uptake (2 ± 27% of the initial value; $p = 0.66$), significant improvements were found in QF (10 ± 25 Newton-meters [Nm]; 16 ± 38% of the initial value; $p = 0.002$), 6MWD (48 ± 74 m; 14 ± 25% of the initial value; $p = 0.0001$), peak external workload (8 ± 16 W; 12 ± 28% of the initial value; $p = 0.0001$), and CRDQ total score (14 ± 14 points; $p = 0.0001$) following the 12-week combined program of aerobic and strengthening exercises. Similar changes were found after stratification for gender (Table 1 of the online data supplement).

Correlations With Baseline Circulating Levels

The relationships between baseline circulating levels of inflammatory markers with the absolute changes in skeletal muscle force, exercise capacity, and health-related quality of life are summarized in Table 4. In brief, a weak but nonsignificant inverse relationship was found between baseline circulating levels of CXCL8 and the absolute change in total CRDQ score ($r = -0.26$; $p = 0.04$).

Correlations After Stratification by Gender

In the male patients with COPD ($n = 47$), none of the baseline circulating levels of inflammatory markers were significantly related to the absolute changes in QF, exercise capacity, or health-related quality of life. On the contrary, in the female patients ($n = 18$) baseline circulating levels of CXCL8 and of sTNFR-p75 were inversely related to the absolute change in total CRDQ score (CXCL8: $r = -0.65$; $p = 0.004$; sTNFR-p75: $r = -0.60$; $p = 0.01$). Moreover, a strong relationship was found between the baseline circulating levels of sTNFR-p55 and the absolute change in QF in the female patients ($r = 0.81$; $p = 0.0001$) [Fig 1].

**Discussion**

Previously, studies have shown that the response to exercise training in patients with COPD was clearly limited by the ventilatory system in combination with high Borg symptom scores for fatigue and/or dyspnea. The patients who dropped out during the exercise-training program had the lowest baseline skeletal muscle force (Table 2). No significant differences were found between the baseline circulating levels of inflammatory markers of the patients who dropped out and those who completed the exercise-training program (Table 3). Nonetheless, the female patients who completed the protocol had significantly lower median baseline circulating levels of TNF-α, sTNFR-p55, and sTNFR-p75 than the male patients who completed the protocol (Table 3).

**Table 3—Baseline Circulating Levels of Inflammatory Markers in Patients With COPD**

<table>
<thead>
<tr>
<th>Variables</th>
<th>All Patients (n = 78)</th>
<th>Patients Who Dropped Out of Study (n = 13)</th>
<th>Patients Who Completed Study (n = 65)</th>
<th>Male Patients (n = 47)</th>
<th>Female Patients (n = 18)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP, mg/mL</td>
<td>5.2 (3.0–11.8)</td>
<td>6.0 (3.0–41.1)</td>
<td>5.2 (0.0–9.9)</td>
<td>5.4 (3.0–9.6)</td>
<td>4.7 (3.0–11.9)</td>
<td>0.98</td>
</tr>
<tr>
<td>CXCL8, pg/mL</td>
<td>3.3 (2.4–4.1)</td>
<td>3.3 (2.5–3.7)</td>
<td>3.3 (2.4–4.1)</td>
<td>3.3 (2.4–4.2)</td>
<td>3.1 (2.7–4.0)</td>
<td>0.95</td>
</tr>
<tr>
<td>TNF-α, pg/mL</td>
<td>19.8 (13.5–29.1)</td>
<td>20.8 (12.8–25.0)</td>
<td>19.3 (13.6–29.5)</td>
<td>20.6 (15.4–31.9)</td>
<td>15.9 (11.2–19.9)</td>
<td>0.015</td>
</tr>
<tr>
<td>sTNFR-p55, ng/mL</td>
<td>1.58(1.46–2.53)</td>
<td>1.83(1.46–2.62)</td>
<td>1.93(1.46–2.50)</td>
<td>2.07(1.54–2.76)</td>
<td>1.64(1.24–1.77)</td>
<td>0.014</td>
</tr>
<tr>
<td>sTNFR-p75, ng/mL</td>
<td>3.55(3.06–4.78)</td>
<td>3.70(3.03–4.96)</td>
<td>3.86(3.10–4.76)</td>
<td>4.06(3.28–4.89)</td>
<td>3.38(2.52–4.05)</td>
<td>0.029</td>
</tr>
</tbody>
</table>

*Values are expressed as median (IQR), unless otherwise indicated.
independent of baseline age, baseline FEV1, and baseline arterial blood gas levels. On the contrary, worse baseline physical fitness and muscle weakness, and somewhat worse ventilatory reserve could partially explain the relative response to a 12-week exercise-training program. This, however, appears to be common sense.

This is the first clinical study to investigate whether and to what extent the initial levels of systemic inflammation may affect trainability in patients with clinically stable COPD. On average, baseline circulating levels of CXCL8, TNF-α, and sTNFRs do not explain much or even anything about the variances in absolute changes in QF, 6MWD, peak external load, and total CRDQ score following a 12-week exercise-training program. Therefore, they do not seem to be very constructive in the characterization of patients with COPD who do or do not respond to exercise training. Nonetheless, strong gender differences were present in the calculated correlations.

**Systemic Inflammation and Changes in Skeletal Muscle Force**

In the present study, QF improved significantly following a 12-week exercise-training program. This improvement showed only nonsignificant relationships with baseline circulating levels of inflammatory markers in the patients who completed the exercise-training program. Nevertheless, positive relationships were found between the change over time in training load of the various training exercises and the absolute changes in skeletal muscle force and exercise capacity following the exercise-training program. This is in line with the specificity principle of exercise training. This may indirectly suggest that the role of physical inactivity in the development of skeletal muscle weakness in patients with COPD is larger than the role of baseline low-grade systemic inflammation.

Previous studies, however, have suggested that the presence of high circulating levels of sTNFR-p55 may limit the effects of ergogenic interventions (ie, nutritional supplements or exercise training). For example, patients with COPD who failed to gain weight during a refeeding program were shown to have high levels of sTNFR-p55. Moreover, baseline circulating levels of sTNFR-p55 tended to be inversely related to the absolute increase in muscle strength following a 12-week resistance training in 90-year-old female nursing home residents (n = 9; r = −0.53; p = 0.10). In contrast, a strong positive relationship was found between baseline circulating levels of sTNFR-p55 and the absolute change in QF in the female COPD patients in the present study (Fig 1). At this moment, an explanation for this discrepancy is lacking. Circulating sTNFRs p55 and p75 represent a natural mechanism that protects against circulating TNF-α and are up-regulated in response to endotoxin. Hence, sTNFRs can probably be used as markers of TNF-α, but they do have an antiinflammatory function. Consequently, sTNFRs may have a marked protective effect against skeletal muscle breakdown by blocking TNF-α and may, therefore, improve the response to exercise training in patients with COPD. In fact, recombinant sTNFR-p55 was a 5-fold to 30-fold more potent inhibitor of recombinant human TNF-α than was recombinant sTNFR-p75. To date, new pharmacologic therapies for patients with rheumatoid arthritis include a sTNFR-p55 construct (lenercept) to target circulating levels of TNF-α. Such a drug may also be used in the future management of patients with COPD.
COPD. To study the safety and efficacy of such a drug may therefore be of clinical interest in patients with COPD.

Systemic Inflammation and Changes in Quality of Life

The total CRDQ score improved to be statistically significant and was inversely related to baseline circulating levels of CXCL8 and sTNFR-p75 in the female COPD patients. These findings suggest that low-grade systemic inflammation may affect the changes in health-related quality of life following exercise training and that they are somehow interrelated. This hypothesis is favored by the observation that circulating levels of CXCL8 are elevated during acute COPD exacerbations, which have been shown to reduce the health-related quality of life in these patients. On the other hand, the treatment of ankylosing spondylitis with etanercept (sTNFR-p75) improved the quality of life in these patients.

Gender Differences

The male and female patients had comparable changes following 12 weeks of high-intensity exercise training (Table 1 of the online data supplement). Nonetheless, an unexpectedly strong significant positive relationship was found between the baseline circulating levels of sTNFR-p55 and the change in QF only in the female patients. Although the number of female patients studied was relatively small (n = 18), the relationship does not appear to be based on chance (r = 0.81; p = 0.0001) [Fig 1].

The observed sex-specific differences in the aforementioned relationship may originate from a deficient sTNFR-p55/p75 production in response to increased circulating levels of TNF-α in male patients compared to those in the female patients. However, the ratio between circulating TNF-α and sTNFRs was not significantly different between male and female patients with COPD (Table 3 of the online data supplement).

It can be hypothesized that, besides physical inactivity, the origin of skeletal muscle weakness is gender-specific. For example, low circulating levels of testosterone may be more important in the development and/or maintenance of skeletal muscle weakness in male patients with COPD and, in turn, in the response to exercise training. In the female patients, the role of circulating levels of testosterone in the development of skeletal muscle force is most probably less obvious, while the role of systemic inflammation may have a greater influence. This may even result in a gender-specific approach of skeletal muscle weakness in COPD. This would be in line with the observation that gender differences in COPD care and outcomes exist.

Methodological Considerations

This study has clear limitations. A healthy control group was lacking. Therefore, the presence of low-grade systemic inflammation in the patients with COPD can be questioned in the present study. Nonetheless, a recent metaanalysis has shown that low-grade systemic inflammation is also present in patients with advanced but clinically stable COPD. Moreover, the present circulating levels of sTNFR-p55 and sTNFR-p75 were clearly higher than those reported previously in healthy adults and the healthy elderly. Therefore, the present authors think that it is reasonable to conclude that increased systemic inflammation was present in the current sample of patients with COPD.

At baseline, the circulating levels of inflammatory markers were measured on only one occasion. It may be argued that at least two baseline levels should be taken to obtain a stable baseline value. Nevertheless, all patients were clinically stable at baseline, and the circulating levels of inflammatory markers were equal to those obtained in a sample of clinically stable male patients with COPD in a previous unrelated study. In fact, to date transient changes in systemic inflammation have only been reported during acute exacerbations of COPD.

It is arguable whether the present relevant question has been answered. For example, the patients in the present study generally had a normal body mass index (Table 1), while COPD patients who were losing weight (body mass index, approximately 18 kg/m²) certainly had higher circulating levels of inflammatory markers. Consequently, the latter subgroup may respond poorly to exercise training. On the other hand, the absolute increase in muscle strength following a 12-week resistance training program in 90-year-old female nursing home residents appeared to be dependent on the circulating baseline levels of sTNFR-p55, which were clearly lower than those obtained in the present study. Therefore, the present authors had reasoned a priori that the low-grade systemic inflammation in clinically stable patients with advanced COPD may already be sufficient to predispose patients to be a low responder or nonresponder to the high-intensity exercise-training program.

Future Directions

The present results are hypothesis-generating rather than definitive. Future studies are warranted to corroborate the present findings and to explain why some of the relationships have only been found
in female patients with COPD. Moreover, the possible relationship between chronic low-grade systemic inflammation and health-related quality of life needs to be studied in longitudinal studies.

Although no relationship has been found between baseline circulating levels of TNF-α and the changes in QF, the present results (Fig 1) provide a first clinical indication that giving anti-TNF to female patients with COPD at the start of or perhaps even in combination with an exercise-training program may increase the magnitude of improvement in QF. Recently, the severity of quadriceps weakness in patients with COPD has been related to the deletion allele of the angiotensin-converting enzyme polymorphism. Moreover, substantial heterogeneity in the responsiveness to exercise training has been reported in healthy elderly individuals and has been related to genetic components. Although discrepant results have been reported, the polymorphisms of the gene encoding the angiotensin-converting enzyme may be involved in the response to exercise training in patients with COPD.

CONCLUSIONS

In the present study, baseline low-grade systemic inflammation did not explain many of the effects following a 12-week exercise-training program in patients with COPD, except for sTNFR-p55 in the female patients.

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