Does pulmonary rehabilitation decrease plasma myostatin levels in patients with COPD?

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TO THE EDITOR:

Myostatin, a member of the TGF-β superfamily, is a negative regulator of skeletal muscle development and growth. Muscle and circulating levels of myostatin are increased in patients with COPD. Myostatin seems to be a marker for impaired muscle regenerative capacity. Pulmonary rehabilitation (PR) is a well-established treatment that increases muscle strength and exercise capacity, thus reducing the impact of COPD. Therefore, we hypothesized that myostatin levels would decrease after PR in patients with COPD. In clinical practice, it is easier to assess plasma myostatin than muscle myostatin because the latter requires a muscle biopsy. However, the effect of PR on plasma myostatin levels is unknown. The mechanisms of muscle depletion and muscle changes after PR would be better understood with more knowledge of the effect that PR has on plasma myostatin levels. Therefore, we aimed to investigate the effects of PR on plasma myostatin levels in patients with COPD.

The study included patients with spirometry-confirmed COPD (Global Initiative for Chronic Obstructive Lung Disease stages II to IV) who were clinically stable for at least four weeks prior to the protocol. The additional criteria were being a nonsmoker for ≥ 6 months, having a smoking history ≥ 20 pack-years, and being ≥ 40 years of age. Patients who were using oral corticosteroids were excluded, as were those who had participated in any exercise program in the last year, those who had a lung disease other than COPD, and those with any musculoskeletal or neurological disorder that could compromise their ability to perform any of the PR exercises or study assessments. In a sample of patients without cachexia, Vogiatzis et al. reported a reduction in mRNA expression of myostatin in muscle after endurance training (effect size: 1.28, two-tailed α: 0.05). Therefore, 8 patients would be required in order to achieve a power of 80%. Anticipating patient dropouts and greater variability in plasma myostatin levels, we tripled the sample size (N = 24). The sample size was calculated by using the free statistical software program G*Power, version 3.1.9.2.

Plasma myostatin levels, exercise capacity—as quantified by the six-minute walk test (6MWT) and six-minute walk distance (6MWD)—and the impact of PR on COPD—as determined with the COPD Assessment Test (CAT)—were assessed at baseline, after 24 sessions of PR, and after 48 sessions of PR. Each PR session included aerobic training, lower limb strength training, upper limb resistance training, education, and nutritional orientation. Aerobic training was performed on a treadmill for 30 min (initially at 60% of the average 6MWT speed). The workload was increased progressively in accordance with the patient-reported level of dyspnea (Borg CR10 scale score: 4-6). Lower limb training involved the quadriceps and triceps surae muscles with free weights or using an extension machine (two sets of 10-15 repetitions). Upper limb training was performed in diagonal axes with free weights or elastic bands. Each diagonal was performed in two sets of 2 min each. The first 24 sessions occurred three times a week, the last 24 occurring twice a week.

Data are reported as means ± standard deviations. Correlations were analyzed using Spearman’s test. Generalized estimating equation, considering the Gamma model, and Bonferroni post hoc test were used in order to compare the three time points (at baseline, after 24 PR sessions, and after 48 PR sessions) in terms of plasma myostatin levels, 6MWD, and CAT scores. Statistical significance was set at p < 0.05. Data were analyzed using the IBM SPSS Statistics software package, version 20.0 (IBM Corporation, Armonk, NY, USA).

At baseline, plasma myostatin levels showed no correlation with age (r = −0.294; p = 0.184), body mass index (r = 0.272; p = 0.221), FEV1 (r = −0.037; p = 0.869), CAT score (r = 0.207; p = 0.367), or 6MWD (r = −0.059; p = 0.793). Of the 24 patients included in the study, 22 (13 males) completed 24 PR sessions. Among those 22 patients, the mean age was 64.8 ± 7.9 years, the mean FEV1/FVC ratio was 0.48 ± 0.1, the mean FEV1 was 34.4 ± 13.8% of the predicted value, and the mean body mass index was 27.2 ± 5.1 kg/m². Only 16 of the 24 patients completed all 48 PR sessions. Although exercise capacity and the impact of COPD improved after the first 24 PR sessions, there was no additional improvement after completion of all 48 PR sessions (Figures 1A and 1B). In addition, no significant
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changes in plasma myostatin levels were found after 24 or 48 PR sessions (Figure 1C).

It is known that quadriceps myostatin mRNA expression is inversely correlated with quadriceps strength, 6MWD, physical activity, and quadriceps endurance. However, in the present study, plasma myostatin levels did not correlate with the 6MWD or the CAT score. Plasma myostatin correlates positively with muscle myostatin mRNA expression in healthy controls but not in patients with type 2 diabetes. Whether plasma myostatin reflects muscle myostatin mRNA expression in patients with COPD is yet to be known.

Previous studies have investigated the effect of exercise training on muscle myostatin in patients with COPD. Lewis et al. found no changes in myostatin mRNA muscle abundance after resistance training, testosterone administration, or a combination of both. Troosters et al. observed that, among patients hospitalized with COPD exacerbation, the levels of myostatin mRNA expression were lower in those who underwent quadriceps resistance training than in those who did not. Conversely, Vogiatzis et al. found that muscle myostatin was downregulated at the mRNA and protein levels after high-intensity cycling training, although only in patients without cachexia. The authors found that mean muscle fiber cross-sectional area increased in the patients with and without cachexia, although the increase was significantly smaller in the former. In addition, patients in both groups showed a decrease in the proportion of type IIB fibers and an increase in the capillary-to-fiber ratio, with no significant differences between the two groups.

Although there is no consensus regarding the effect that exercise training has on muscle myostatin, even less is known about its effect on plasma myostatin. One study reported that plasma myostatin levels decreased by approximately 20% after 10 weeks of high-intensity resistance training in healthy men. To our knowledge, this is the first study to investigate the effect of exercise training on circulating myostatin in patients with COPD. In contrast to previous studies, our study assessed the impact of PR that combines resistance and aerobic exercise.

A crucial caveat in quantifying myostatin is that the current methods fail to distinguish between its active and inactive forms. In fact, myostatin abundance might not necessarily reflect myostatin activity. Whether the proportional relationship between the two forms can change after exercise training remains to be determined. In addition, the abundance of endogenous inhibitors of myostatin or the degree to which they interact with myostatin might be affected by exercise training.

Our study has some limitations. First, because of the lack of a control group, we were unable to investigate the behavior of plasma myostatin in patients with COPD who did not undergo PR. Second, information regarding muscle mRNA expression, muscle strength, and muscle volume would enrich the interpretation of the data. However, information regarding plasma myostatin response to exercise is novel, whereas the determination of plasma myostatin is easier and less invasive than are muscle biopsies in clinical practice.

Figure 1. Pulmonary rehabilitation (PR) outcomes. In A, six-minute walk distance (6MWD) at baseline (392.0 ± 92.8 m), after 24 PR sessions (463 ± 82 m), and after 48 PR sessions (442 ± 111 m). In B, COPD Assessment Test (CAT) score at baseline (5.04 ± 1.80), after 24 PR sessions (3.78 ± 0.80), and after 48 PR sessions (3.93 ± 1.10). In C, plasma myostatin levels at baseline (3,346 ± 2,228 pg/mL), immediately before PR session 24 (2,997 ± 2,049 pg/mL), and immediately before PR session 48 (2,813 ± 1,580 pg/mL).
In summary, although PR improved functional capacity and reduced the impact of COPD in this sample of patients, plasma myostatin levels remained stable. There is a need for further studies investigating the relationship between muscle and plasma myostatin, as well as their interactions with their inhibitors.

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AUTHOR CONTRIBUTIONS

Araujo CLP—research conceptualization, methodology, formal analysis, investigation, resources, data curation, original draft writing, project administration, funding acquisition, and approval of final version. Silva IRV—research methodology, formal analysis, investigation, resources, original draft writing, and approval of final version. Dal Lago P—research conceptualization, methodology, data curation, investigation, resources, original draft writing, review, editing, supervision, project administration, funding acquisition, and approval of final version.