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Supplementation with Qter® and Creatine improves functional performance in COPD patients on long term oxygen therapy

Fernando De Benedetto[a], Roberta Pastorelli[b], Manuela Ferrario[c], Francesca de Blasio[d,*], Stefano Marinari[a], Laura Brunelli[b], Emiel F.M. Wouters[e], Francesca Polverino[f], Bartolome R. Celli[g], on behalf of Interdisciplinary Association for Research in Lung Disease (AIMAR) Study Group[1]

[a] Department of Pneumology, SS Annunziata Hospital, Chieti, Italy
[b] Department of Environmental Health Science, IRCCS-Istituto di Ricerche Farmacologiche Mario Negri, Milano, Italy
[c] Department of Electronics, Information, and Bioengineering (DEIB), Politecnico di Milano, Milan, Italy
[d] Department of Medical Sciences, University of Turin, Italy
[e] Department of Respiratory Medicine, Maastricht University Medical Center, Maastricht, Netherlands
[f] University of Arizona, Tucson, AZ, United States
[g] Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, United States

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ABSTRACT

Background: Skeletal muscle dysfunction and poor functional capacity are important extra-pulmonary manifestations of chronic obstructive pulmonary disease (COPD), especially in COPD patients on long-term O_2 therapy (LTOT). Beside the role of pulmonary rehabilitation, the effect of nutritional interventions is still controversial, and there are knowledge gaps on the effective role of nutraceutical supplementation on hard endpoints. The aim of this study was to investigate the effects of nutritional supplementation with Coenzyme Q10 (QTer®) – a powerful antioxidant with the potential to reduce oxidative stress and improve mitochondrial function – and Creatine on functional, nutritional, and metabolomic profile in COPD patients on long-term O_2 therapy.

Methods: One-hundred and eight patients with COPD from 9 Italian hospitals were enrolled in this double-blinded randomized placebo-controlled clinical study. At baseline and after 2 months of therapy, the patients underwent spirometry, 6-minute walk test (6MWT), bioelectrical impedance analysis, and activities of daily living questionnaire (ADL). Also, dyspnea scores and BODE index were calculated. At both time points, plasma concentration of CoQ10 and metabolomic profiling were measured.

Findings: Ninety patients, who randomly received supplementation with QTer® and Creatine or placebo, completed the study. Compared with placebo, supplemented patients showed improvements in 6MWT (51 ± 69 versus 15 ± 91 m, $p < 0.05$), body cell mass and phase angle, sodium/potassium ratio, dyspnea indices and ADL score. The CoQ10 plasma concentration increased in the supplementation group whereas it did not change in the placebo group. The metabolomics profile also differed between groups. Adverse events were similar in both groups.

Interpretation: These results show that in patients with COPD, dietary supplementation with CoQ10 and Creatine improves functional performance, body composition and perception of dyspnea. A systemic increase in some anti-inflammatory metabolites supports a pathobiological mechanism as a reason for these benefits. Further trials should help clarifying the role of QTer® and Creatine supplementation in patients with COPD.

1. Introduction

Chronic obstructive pulmonary disease (COPD), an important cause of morbidity and mortality worldwide [1], is frequently associated with nutritional abnormalities and skeletal muscle dysfunction that contribute to exercise intolerance and poor health status [2]. The

* Corresponding author.
E-mail address: francesca.deblasio@unito.it (F. de Blasio).
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prevalence of malnutrition and micronutrient abnormalities [3] in COPD varies between 10 and 60% [4–10], being highest in patients with advanced COPD and/or chronic respiratory failure on long-term oxygen therapy (LTOT) [11]. Several mechanisms link malnutrition and COPD. Among these, systemic inflammation [12] seems to play a role in protein turnover [13,14] while the presence of hypoxemia in patients with COPD may increase the generation of inflammatory molecules [15] and worsen skeletal muscle dysfunction by reducing peripheral O_2 use [16]. Indeed, muscle biopsies from COPD patients have shown reduced mitochondrial density, lower oxidative enzyme activity and increased mitochondrial reactive oxygen species [17–19], with a shift in the proportion of muscle fiber type I to those of type II [20]. As a consequence, a lower content of high energetic phosphates has been documented in skeletal and respiratory muscles of these patients compared to healthy individuals [21,22]. Attempts have been made to reverse this state in malnourished COPD patients, using different anabolic medications [23–25] and hormones [26]. Although hormonal supplementation has led to increases in weight and muscle mass [10], there has been little if any improvement in functional capacity or health status [27]. The effect of nutritional supplementation is also controversial, although recent evidence provides evidence for some effect on malnourished patients [28].

Coenzyme Q10 (CoQ10) is a fat-soluble compound present in the mitochondria of cells. It is a member of the electron transport chain that participates in cellular respiration, helping generate energy in the form of adenosine three phosphate (ATP). Due to its limited solubility in water, CoQ10 has poor bioavailability and chemical instability [29]. One multicomposite variant of CoQ10 is the Qter®, which is more soluble in water, while retaining its antioxidant capacity [30]. Creatine is an organic acid that occurs naturally in vertebrates. It facilitates the recycling of ATP by recycling adenosine diphosphate (ADP) to ATP via donation of phosphate groups. Supplementation with QTer®, and Creatine has the potential to reduce oxidative stress and improve mitochondrial function [31], by improving protein turnover and mitochondrial energy production in patients with chronic heart failure [30]. Recently, a pilot randomized study of QTer® and Creatine supplementation in COPD showed that, compared with controls, COPD patients taking supplementation had beneficial effects on lean body mass and exercise tolerance [32].

Hereby, we tested the hypothesis that supplementation of QTer® and Creatine in COPD patients with chronic respiratory failure on LTOT would improve functional capacity and dyspnea, as well as body composition and metabolomics profile.

2. Methods

2.1. Participants

One-hundred and eight patients from 9 Italian hospitals were screened for this study between May 2014 and June 2015. A consort table is shown in supplemental Figure S1. Patients of both genders between 60 and 85 year-old, with a modified Medical Research Council (mMRC) score > 2, a forced expiratory volume in 1 s (FEV_1)/forced vital capacity < 0,7, FEV_1 < 70% predicted, and receiving supplemental LTOT were included. The patients were clinically stable, without exacerbations of COPD or hospitalizations in the 4 weeks prior to enrollment. All the patients were receiving pharmacological therapy consisting in the administration of bronchodilators in the different combinations (LABA, LAMA, LABA + LAMA, LABA + ICS, LABA + ICS + LAMA). The therapy was optimized in order to achieve an optimal control of the symptoms. The therapeutic scheme was not changed for the entire duration of the study in any of the study subjects. Patients were excluded if they were on mechanical ventilation, had uncontrolled diabetes mellitus, severe heart, renal, or hepatic failure and current or pre-existing malignant disease within the 3 years. Other exclusion criteria were: persistent infections, chronic oral steroid and/or immunosuppressive therapy, inability to complete the tests included, and use of statins or amino acid supplements.

Table 1
Main clinical variables collected during the study at the baseline.[a]

	Active N = 45	Placebo N = 45
Age (years)	73 ± 7	73 ± 7
Gender (M/F)	34/11	34/11
BMI (Kg/m^2)	32.1 ± 10.2	29.6 ± 8.4
FEV_1 (% pred)	55 ± 21	57 ± 19
FVC (% pred)	68 ± 20	67 ± 22
Fat-free mass (%)	68 ± 15	69 ± 11
Fat mass (%)	32 ± 15	31 ± 11
BCM (%)	24 ± 7	24 ± 8
Na/K	1.32 ± 0.39	1.30 ± 0.36
PhA (degrees)	4.56 ± 1.05	4.55 ± 1.26
6MWD (m)	214 ± 143	213 ± 134
SpO_2-pre test (%)	92 ± 3	92 ± 3
SpO_2-post test (%)	87 ± 5	85 ± 4
mMRC	2.07 ± 0.78	2.20 ± 0.63
BDI1	1.98 ± 0.85	1.82 ± 0.94
BDI2	1.91 ± 0.73	1.84 ± 0.60
BDI3	1.84 ± 0.67	1.98 ± 0.66
Borg scale	3.78 ± 1.76	3.36 ± 1.67
BODE index	4 (3; 6)	5 (3; 6)
ADL	5.36 ± 1.13	5.44 ± 1.16
CoQ10 (ng/mL)	413 ± 188	484 ± 333

Note: Data are presented as mean ± SD, except for BODE, presented as median (25°,75°).
AbbreviationsBMI = body mass index; FEV1 = forced expiratory volume in 1 s; FVC = forced vital capacity; BCM = body cell mass; PhA = phase angle; 6MWD = 6-minute walk test; SpO2 = arterial oxygen saturation; mMRC = modified Medical Research Council; BDI = Baseline Dyspnea Index; ADL = activities of daily living; CoQ10 = Coenzyme Q10.
[a] No significant difference between Active group and Placebo group at the baseline was observed in any of the variables.

2.2. Study design

In this multicenter double-blinded placebo-controlled study (EUFSC-13-001), one-hundred and six patients were randomized to 160 mg Coenzyme QTer® + 170 mg Creatine, or placebo twice daily for 2 months (8 weeks, Table 1 in the supplemental section). No additional nutritional supplementation was prescribed. Randomization schedule was generated using PROC PLAN statistical analysis software. The protocol was approved by the ethical committee of each hospital, and written informed consent was obtained from all patients. The protocol was notified to the Italian Ministry of Health according to guidelines on studies of food supplements [33].

Clinical evaluation and plasma samples were obtained at baseline (V1) and after two months of treatment (V2). At 6 and 12 months, patients were contacted via telephone and information about exacerbations, defined as a rapid change in clinical symptoms of such intensity to require the use of antibiotics and/or systemic steroids [34], or hospitalizations due to due to exacerbation of COPD, during the past year was obtained (shown in supplemental Material).

2.3. Primary endpoint and lung function

A 6-minute walk test (6MWT) with measurement of blood oxygen saturation (SpO2) was performed according to American Thoracic Society (ATS) standards [35]. Predicted values of the 6MWT were calculated using a reference equation [36] and the difference between predicted and measured values were recorded. Post-bronchodilator spirometry was performed following international guidelines [37].