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Carnitine Deficiency in Chronic Obstructive Pulmonary Disease Patients

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Abstract

Chronic Obstructive Pulmonary Disease (COPD) is increasingly recognized as a systemic disease characterized by progressive airflow limitation as well as respiratory and peripheral muscle weakness. Deficiency in the levels of carnitine "an essential nutrient for optimal muscle function" has been associated with peripheral and respiratory muscle weakness in other diseases, but has not yet been examined in COPD patients. The aim of this study was to investigate whether plasma acyl carnitine fractions were reduced in patients with COPD, and examine if the deficiency correlated with COPD severity.

Patients and methods: A prospective case control study to compare acyl carnitine levels and other parameters in 81 COPD patients treated at the Pulmonology Department, King Fahad Specialist Hospital Dammam, with 48 age and sex matched healthy controls. All subjects participating in the study underwent a complete physical examination and detailed pulmonary function tests (PFTs). Blood samples were taken for acyl carnitine profiles as well as a panel of other tests including albumin, total protein, Iron, CRP and pre-albumin. Acyl carnitine profile was determined using LC-MS/MS analysis.

Results: COPD patients had significantly lower total carnitine levels compared to controls (43.9±6.5 and 22.7±11.9 respectively). Furthermore there was a significantly greater reduction in carnitine levels in patients with very severe COPD compared to patients with mild COPD.

Conclusion: Our study demonstrated a significant deficiency in carnitine levels in COPD patients, and the degree of deficiency correlated with the severity of COPD.

Keywords: COPD; Carnitine; Muscle Weakness

Introduction

Chronic obstructive pulmonary disease (COPD) is currently recognized as a systemic disease with pulmonary and extra-pulmonary manifestations. The pulmonary component is characterized by airflow limitation which is usually progressive and not fully reversible. The systemic manifestations are characterized by structural and metabolic alterations that include skeletal muscle dysfunction [1] and weakness. Respiratory muscle weakness has also been demonstrated in COPD patients [2,3] and has been shown to be associated with significant exercise limitation [4] and dyspnea [5]. Thus respiratory muscle weakness is considered an additional factor that adds to the increased morbidity and poor physical health of COPD patients [2]. Several factors are thought to contribute to the observed muscle weakness in COPD patients, such as hypoxia, hypercapnia, inflammation, deconditioning, steroid induced myopathy, and under nutrition [6,7]. Improvement in muscle power was found to have a positive impact on the overall status of COPD patients [8].

L-carnitine is an essential metabolite necessary for fatty acid metabolism and energy production in cardiac and skeletal muscle [9]. Carnitine is found in virtually all cells of higher animals and is synthesized almost exclusively in the liver [10]. Two essential amino acids: lysine and methionine serve as primary substrates for its biosynthesis [9]. Carnitine is derived from both dietary sources and endogenous biosynthesis [11] in the liver, however the majority of carnitine stores are of exogenous origin, mainly from meat and dairy products [11]. Carnitine plays an important role for optimal mitochondrial fatty acid oxidation [12] and muscle function. Skeletal muscles constitute the main reservoir of carnitine in the body and have a carnitine concentration at least 200 times higher than blood plasma [13]. Carnitine binds to activated acyl Coenzyme A to form acyl carnitine and free Co-A. Through this reaction, carnitine facilitates the transfer of activated fatty acids across the mitochondrial membrane for beta oxidation and protects against acyl-CoA accumulation, which may be deleterious to cellular function [14]. Carnitine can form different short, medium and long chain fatty acyl carnitines with several medium and long-chain endogenous or exogenous fatty acids. Impaired carnitine plasma levels have been recorded in different diseases including; DM [13,15,16], chronic kidney disease [17], liver [18,19] disease and end stage cancer patients [20], however, there are NO studies that evaluated plasma acyl carnitine levels in COPD patients. Only a recent study demonstrating a correlation between inspiratory muscle weakness and deficiency of carnitine in diabetic patients [8]. Given that carnitine deficiency is associated with inspiratory muscle weakness, and that respiratory and peripheral muscle weakness are important components of COPD, we hypothesized that carnitine deficiency might contribute to the muscle weakness characteristic of this disease. The aim of this study was to investigate whether plasma acyl carnitine fractions were reduced in patients with COPD, and examine if the deficiency correlated with COPD severity.

Patients and Methods

The study was approved by King Fahad Specialist Hospital Ethics and Research committee. The study was designed as a prospective single center case control study to compare acyl carnitine levels and

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other parameters in COPD patients and matched controls. All patients and control subjects gave their written informed consent before participating in the study. The study included 2 groups: 81 COPD patients aged (Mean ±SD) 61.1 ± 5.8 years seen at the Pulmonology Department of King Fahad Specialist Hospital Dammam, and 48 age and sex matched control subjects with no pulmonary disease. All subjects included in the study were on an unrestricted diet and none of them was vegetarian or taking medications that could affect carnitine status (e.g. carnitine supplements or TPN). All female patients were postmenopausal. All subjects participating in the study were evaluated with a complete history (including detailed caloric intake, cigarette smoking and the total cumulative doses of medications), physical examination, chest x- ray, and pulmonary function tests (PFT). Criteria for defining COPD patients were according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) Guidelines 2009 Update [21]; as a combination of clinical features such as dyspnea, chronic cough or sputum production, presence of risk factors and confirmation by obstructive spirometry demonstrating an FEV1/FVC ratio (forced expiratory volume in 1 second/functional vital capacity) of less than 70% post bronchodilator. The severity of the patients COPD was categorized according to spirometric criteria into mild (FEV1 ≥ 80% of predicted), moderate (FEV1 ≥ 50% to < 80%), severe (FEV1 ≥ 30% to < 50%) and very severe (FEV1 < 30%) [21].

Exclusion criteria included DM, other concomitant chronic hepatic or renal diseases, malignancy, and acute infections.

The following investigations were carried out for all subjects participating in the study: Pulmonary function tests performed according to a standard protocol described by the American Thoracic Society/European Respiratory Society [22] using Vmax29 Sensor Medics (VIASYS).

Venous blood samples were extracted from each subject after an overnight fast of 12 hours. Serum samples were analyzed for fasting serum glucose, urea, creatinine, albumin, total protein, sodium, potassium, chloride, alkaline phosphatase, liver enzymes (ALT, AST), calcium, phosphorous, magnesium, Iron, and pre-albumin. These parameters were measured using Siemens Diagnostics (Marburg GmbH, Germany) (RxL Dimension Clinical Chemistry analyzer). Acylcarnitines were analyzed as butyl esters using Applied Biosystems, API 2000 ESI triple-quadrupole mass spectrometer, combined with an Agilent autosampler for sample introduction [23]. In brief, 10µL plasma were used and extracted in methanol containing deuterated internal standards (Cambridge isotopes laboratories, Cat. no: NSK-B). After 20 min incubation the supernatant was dried under nitrogen at 40°C. Derivatization was carried out at 65°C for 15 min with an addition of 100µL 3mol/L butanolic HCl (Regis Technologies Cat. No: 201007). The resulting mixtures were dried again under nitrogen at 40°C and re-dissolved in 100µL mobile phase (acetonitrile: water 80:20). With the help of the autosampler 10µL of sample aliquots was injected into the mass spectrometer.

Statistical analysis

Comparison among the groups was conducted using the student t-Test test for normally distributed variables. The nonparametric Mann-Whitney U test was used for variables with a non-Gaussian distribution. Normally distributed variables were expressed as mean ± SD, while variables with non-Gaussian distribution were expressed as median, range, and 25 to 75 percentiles. For correlation studies, the Pearson correlation test was used. A P value of <0.05 was considered statistically significant. The commercial statistical software package used was SPSS 11.0 (SPSS Inc., Chicago, IL, USA).

Results

Pulmonary function data are summarized in (Table 1). 81 COPD patients included in the study patients were classified by spirometry criteria into mild (12 patients), moderate (39 patients), severe (18 patients) and very severe (12 patients) airflow obstruction according to the Gold COPD guidelines [21]. None of the controls subjects had a positive smoking history, while out of 81 COPD patients 44 subjects were current smokers at the time of the study (24.6 ± 11.2 pack years, 28 subjects had a past history of smoking(15.3 ± 6.9 pack years) and 9 subjects were non-smokers. The mean Fev1 in the COPD group was 52.9% predicted reflecting the distribution of patients across all 4 categories of severity with the majority of patients being in the moderate severity group. None of the control subjects showed any

Parameter	Controls (n: 48)	Patients (n: 81)	P value
Carbon Monoxide Diffusing Capacity% of Predicted	86.88 ± 3.6	83.44 ± 6.8	0.02
Total Lung Capacity% of predicted	86.7 ± 3.6	86.88 ± 5.1	0.8
FEV1/FVC% of predicted	81.2 ± 5.3	56.0 ± 6.6	0.013
FEV1% of predicted	85.4 ± 3.7	52.9 ±15.4	0.001
FVC% of predicted	85.4 ± 3.7	86.6 ± 3.9	0.016

Data are presented as Mean ±SD
FEV1: Forced Expiratory Volume (1st second)
FVC: Forced Vital Capacity
*P value < 0.05 significant different between controls and patients groups
**P value< 0.01 highly significant

Table 1: Respiratory function tests for COPD patients and controls.

Parameter	Controls (n: 48)	Patients (n:81)	P Value
Age (years)	58.1 ± 4.7	61.1 ± 5.8	0.9
Males/females	31/17	47/34	0.1
BMI (Kg/m2)	24.1 ± 2.7	23.3 ± 3.2	0.02
Smoking History (%)	0	Smokers: 44 (54.3%) Ex-Smokers: 28 (34.5%) Non-smokers: 9 (11.1%)	NA
Albumin (g/L)	39.1 ± 3.2	32.9 ± 5.6*	0.03
Corrected calcium (mmol/L)	2.2 ± 0.09	2.19 ± 0.12	0.1
Sodium(mmol/L)	139.6 ± 3.3	135.7 ± 11.1	0.73
Potassium(mmol/L)	4.1 ± 0.32	4.4±0.47	0.1
Cholesterol (mmol/L)	4.55 ± 0.65	4.2 ± 0.67	0.8
TG (mmol/L)	0.82 ± 0.29	1.35 ± 0.62	0.001
BUN (mmol/L)	5.1 ± 1.17	5.2 ± 1.08	0.8
Creatinine (µmol/L)	77.3 ± 12.4	80.8 ± 12.1	0.7
Iron(µmol/L)	20.7 ± 4.3	8.1 ± 3.6	0.001
Hb (g/dl)	14.7 ± 1.2	13.3 ± 2.4*	0.021
Leucocytic /cmm^3	5.6 ± 1.2	7.2 ± 2.5	0.002
phosphorous(mmol/L)	1.31 ± 0.21	.94 ± 0.270	0.01
ALP (U/L)	84.82 ± 22.15	118.90 ± 40.8**	0.009
25 OH Vitamin D (ng/ml))	11.8 ± 3.7	10.0 ± 4.5	0.575
CRP (mg/L)	3.2 ± 1.4	3.8 ± 1.9	0.001
Random glucose (mmol/L)	5.0 ± 0.5	5.6 ± 1.2	0.02
Prealbumin (mg/L)	260.2 ± 59.9	199.9 ± 52.9	0.018

Data are presented as Mean ±SD for normally distributed variables
BMI : Body mass index
Hb: Hemoglobin BUN: Blood urea nitrogen ALP: Alkaline phosphatase, NA: not available
* = Significant difference versus the control group (P<0.05)
** = Significant difference versus the control group (P<0.05)

Table 2: Clinical and Biochemical parameters of the studied groups.

degree of airflow obstruction, and as expected there were significant differences in the patients and controls groups with regards to FEV1/FVC ratio and FEV1 predicted values reflecting the presence and severity of airway obstruction in COPD patients as opposed to normal values in control subjects. There was no significant difference in the TLC in both groups, excluding any co-existing restrictive lung disease in the COPD patients. In COPD patients FEV1 correlated positively with plasma total carnitine (r: 0.77& P=000)

Clinical and biochemical data of the studied groups are illustrated in Table 2. There was no significant difference regarding age or blood pressure in the two groups. Similarly, there was no difference between the patient and control group regarding the serum level of corrected calcium, sodium, potassium, chloride, urea, creatinine. COPD patients iron level was significantly lower than controls (P<0.001). COPD patients had significantly lower hemoglobin levels (P<0.01). Similarly COPD patients had lower BMI, plasma phosphate and albumin levels than controls and a significantly higher alkaline phosphatase (P<0.01). Conversely there were significantly increased levels of leucocyte count and CRP (P<0.01) in COPD patients. Serum prealbumin level was significantly lower in COPD patients compared to controls (P=0.01). Pre-albumin serum level correlated positively with free carnitine and total carnitine level with a P value<0.001 (r: 0.51 & 0.54 respectively). Similarly serum albumin level positively correlated with total and free carnitine levels (r: 0.524 & 0.473 respectively, P<0.001).

Table 3 summarizes the acyl carnitine level in controls and COPD patients. There was a significant reduction in free carnitine, acetyl carnitine, isovaleryl and hexanoyl carnitines (P<0.01) in COPD patients. Some of the medium chain and long chain acyl carnitine also showed significant reduction in COPD patients compared to controls (Octenoylcarnitine, Myristoleylcarnitine Hydroxymyristoylcarnitine and Palmitoylcarnitine (P≤0.01). Other acyl carnitines did not significantly differed between controls and COPD patients.

COPD patients had a significantly lower total carnitine (43.96.5 and 22.7±11.9 µmol/L respectively) and acetyl carnitine/Total carnitine (0.2±0.19 and 0.17±0.11 respectively) ratio than controls (figure 1a).

Free carnitine and acetyl carnitine were significantly higher in mild COPD than very severe COPD (P<0.01). Other acyl carnitines did not show significant difference with COPD disease severity (figure 1b).

Total carnitine showed a significant difference between the different stages of GOLD classification of COPD (P< 0.01). The mean ± SD of total carnitine in mild, moderate, severe and very severe COPD patients were as follows respectively: 35.9±6.9 & 27.8±7.7, 12.6±7.8 & 7.8±0.68 µmol/L. There was no significant difference between males and females regarding total carnitine level. Total and free carnitine levels correlated negatively with CRP. P<0.01 (r values -0.379& -0.376 respectively).

When total carnitine levels were evaluated in COPD patients according to their smoking history, there was no significant difference between the smokers, ex-smokers and non-smokers (P>0.05). Total carnitine levels in smokers, ex-smokers and non-smokers were as follows: 24.2±12.9, 20.4 ±11.3 and 22.1±10.6 µmol/L respectively.

Discussion

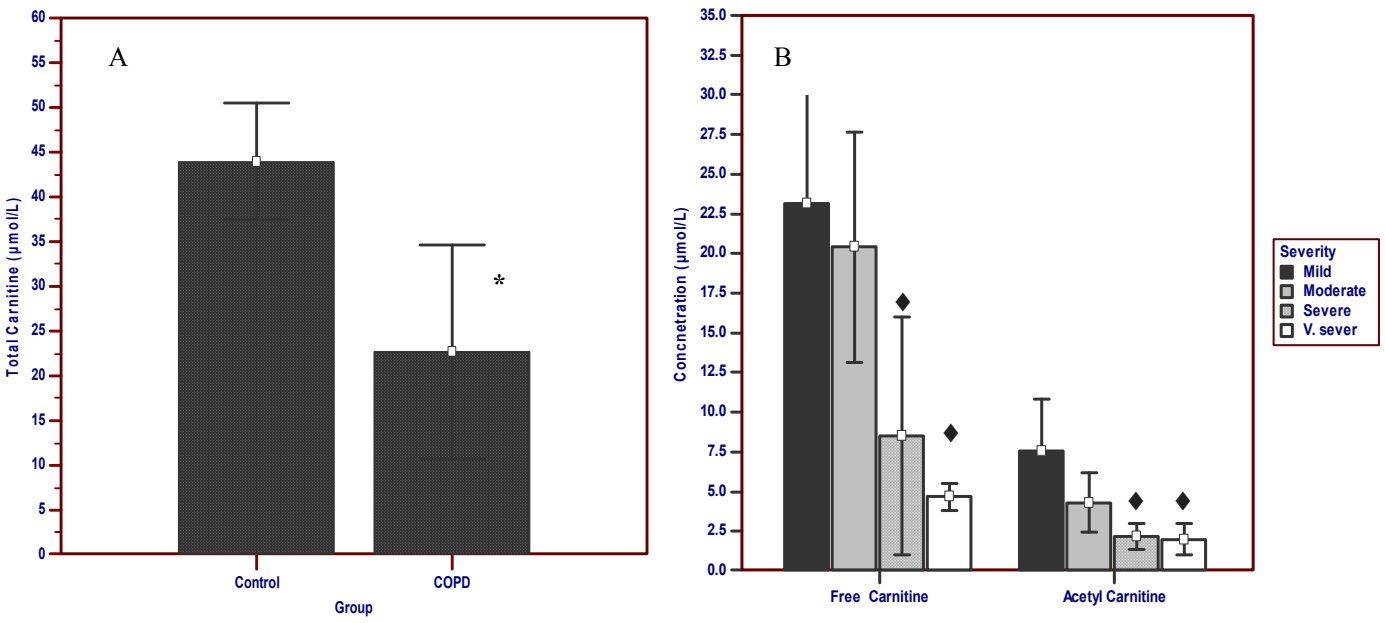
This study showed significantly reduced plasma total and free carnitine levels in COPD patients compared to age and sex matched controls. Individual acyl carnitines (acetyl carnitine, isovaleryl and hexanoyl carnitines as well as octenoylcarnitine, Cecenoylcarnitine, Myristoleylcarnitine, Hydroxymyristoylcarnitine, Palmitoylcarnitine and Stearoylcarnitine) showed significant reductions in COPD patients compared to healthy subjects. Furthermore, the reduction of free carnitine and acetyl carnitine was more pronounced in patients with increasing degrees of COPD severity. This significant reduction in carnitine levels in COPD patients may represent an additional factor that increases the respiratory and peripheral muscle weakness in COPD patients. In addition to other mechanisms, carnitine deficiency may affect the oxidative metabolism of fatty acids, leading to increased myopathy and muscle weakness. Carnitine deficiency is a feature of diabetes mellitus, and Kiliçli et al. [8] have demonstrated that there is a correlation with the degree of carnitine deficiency, and reduced inspiratory muscle strength in diabetic patients. As shown in Table 3, different fractions of acyl carnitines showed significant reduction in COPD patients compared with healthy control subjects. These fractions included not only free carnitine and short chain acyl carnitine (acetyl carnitine, isovaleryl) but also medium chains (hexanoyl, octenoylcarnitine, Cecenoylcarnitine), and long chain acyl carnitines (Myristoleylcarnitine, Hydroxymyristoylcarnitine, Palmitoylcarnitine and Stearoylcarnitine). Increased short, medium and long chain acyl carnitines have been described before in healthy subjects [24], especially during exercise. This reduction in the free carnitine level together with some short, medium and long chain acyl carnitines found in our patients points towards a state of generalized reduction in carnitine status in COPD patients. Short and mediun chain acyl carnitines may represent a more readily available source of energy to the muscles compared to long chain acyl carnitines as they can cross the mitochondrial membrane more easily than long chain acyl carnitines for sequential steps of B-oxidation [12].

COPD patients had a significantly higher serum CRP and blood leucocyte count than controls. This most probably indicates the underlying inflammatory process in COPD which manifests in elevated CRP levels that have also been documented by several other authors [25]. Moreover, CRP negatively correlated with both free and

Carnitine fraction (µmol/L)	Controls	Patients	P value
F ree carnitine (C0)	33.54±6.42	15.849.70*	<0.01
Acetylcarnitine (C2)	6.65 ± 4.4	3.97 2.59*	<0.01
Propionylcarnitine (C3)	0.487 ± 0.16	0.404 0.33	0.088=P
Butyrylcarnitine (C4)	0.295 ± 0.28	0.313 0.28	P= 0.352
Isovalerylcarnitine (C5)	0.133 ± 0.19	0.113 0.04*	<0.01
Hexanoylcarnitine (C6)	0.174 ± 0.02	0.140 0.03*	<0.01
Octanoylcarnitine (C8)	0.064 ± 0.03	0.0790 0.03	P= 0.68
Octenoylcarnitine (C8:1)	0.141 ± 0.07	0.0982 0.08*	P= 0.019
Decanoylcarnitine (C10)	0.095 ± 0.05	0.173 0.14	P=0.34
Cecenoylcarnitine (C10:1)	1.082 ± 0.75	0.856 0.22*	<0.01
Lauroylcarnitine (C12)	0.180 ± 0.25	0.058 ± 0.02	P= 0.94
Myristoylcarnitine (C14)	0.044 ± 0.02	0.0198 0.03	P= 0.17
Myristoleylcarnitine (C14:1)	0.043 ± 0.02	0.023 0.03*	P<0.01
Hydroxymyristoylcarnitine (C14OH)	0.047 ± 0.02	0.0318 0.01*	P<0.01
Palmitoylcarnitine (C16)	0.172 ± 0.03	0.111 0.03*	P<0.01
Palmitoleylcarnitine (C16:1)	0.015 ± 0.01	0.0227 0.01	P= 0.57
Hydroxypalmitoleylcarnitine (C161OH)	0.011 ± 0.01	0.013 0.013	P=0.56
Oleylcarnitine (C18:1)	0.097 ± 0.03	0.119 0.01	P=0.9
Stearoylcarnitine (C18)	0.148 ± 0.154	0.057 0.02 *	P<0.01
Hydroxyoleylcarnitine (C18 OH)	0.058 ± 0.0242	0.061 0.01656	<0.4

Results are expressed as Mean ± SD
*: Significant difference P<0.01

Table 3: Plasma Carnitine esters profile in COPD patients and healthy Controls.



♦: P value<0.05 significant difference versus mild COPD
*: P value {0.05 significant difference versus control group

Figure 1: Total, free and acetyl carnitine in COPD patients and healthy controls. Bars represent the mean values of different analytes in the studied groups.

total plasma carnitine levels. This inverse correlation may be related to the positive antioxidant and anti-inflammatory effects of carnitine. A recent study indicated that carnitine can improve cellular defense against chronic inflammation and oxidative stress, most likely by modulating the specific signal transduction cascade activated by an overproduction of proinflammatory cytokines and oxidative stress [26]. Thus the present state of carnitine deficiency may be a contributing factor for the underlying inflammation and subsequent oxidative stress in COPD patients.

In COPD patients, the observed carnitine deficiency may be secondary to poor nutritional intake. This hypothesis is supported by the finding of significantly lower iron, hemoglobinm, albumin and prealbumin levels in COPD patients compared to controls. Several authors suggested prealbumin as a biomarker for nutritional status and correlated its plasma level with nutritional deficiency [27-29]. L-Carnitine is widely distributed in foods from animal, but not plant sources, and is also synthesized by the liver and kidney. As there was no significant difference between COPD patients and the normal healthy controls regarding liver and renal function tests, the observed reduction in plasma carnitine levels is most likely secondary to poor nutritional intake of carnitine and/or its precursors. Alternatively, the observed deficiency in carnitine levels may be due to the state of iron deficiency observed in COPD patients. Trymethyllysine hydroxylase is the first enzyme in the biosynthetic pathway of L-carnitine [30]. It requires iron as a cofactor for optimal function. Thus iron deficiency per se may negatively affect endogenous carnitine synthesis and result in lower plasma carnitine.

In summary the current study showed a significant reduction in carnitine levels in COPD patients which is most likely mainly due to a nutritional deficiency of intake of L-Carnitine. The level of Carnitine deficiency has been shown to correlate with the degree of peripheral and respiratory muscle weakness, and the fact that carnitine levels in our study were inversely correlated with the degree of COPD severity lends weight to the contribution of the carnitine deficiency to respiratory muscle dysfunction. Several recent studies have focused on interventions to train and strengthen peripheral and respiratory muscle strength with programs of Pulmonary rehabilitation and inspiratory muscle strength [31,32] with overall positive impact on COPD patients. We propose that carnitine supplementation could be evaluated as an independent intervention to assess its effects on respiratory muscles and lung function in COPD patients.

Although knowledge is growing on the circulating carnitine ester profile features in various disease conditions, our study is unique as being the first to evaluate carnitine ester profiles in COPD patients. However an important shortcoming of our study is that we did not measure directly the strength of respiratory muscles in patients and controls, rather we focused on lung function as the clinically relevant entity in assessing the pulmonary status of COPD patients. Future studies of the carnitine profile in COPD patients could add indices of respiratory muscle strength as well as lung function before and after carnitine supplementation to further assess the importance of this essential metabolite in COPD patients.

Conflict of interests

The authors declare no conflict of interest.

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