Effects of Yogic Intervention as an Adjunct to Conventional Pharmacotherapy in Patients with COPD: A Randomized Controlled Study

Suresh Kumar Thokchom¹, Kavita Gulati*, Arunabha Ray², Bala Krishnan Menon² and Raj Kumar²

¹Department of Pharmacology, Vallabhbhai Patel Chest Institute, University of Delhi, India
²Department of Pulmonary Medicine, Vallabhbhai Patel Chest Institute, University of Delhi, India
³Hamdard Institute of Medical Sciences and Research, Hamdard University, New Delhi, India

*Corresponding Author: Kavita Gulati, Department of Pharmacology, Vallabhbhai Patel Chest Institute, University of Delhi, India.

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Abstract

Yoga is a traditional therapy, originated in ancient India, with health benefits that are being acknowledged globally. Yoga is shown to be beneficial in chronic inflammatory disorders; therefore the study was conducted to evaluate the effects of yogic intervention as an adjunct therapy on selective and novel marker of COPD viz. club cell secretory protein-16 (CC16), multidimensional scoring system - BODE index and oxidative stress. COPD patients were recruited as per inclusion/exclusion criteria and allocated randomly to either Group I (n = 20, age = 60.65 ± 1.84 years), who were administered conventional pharmacotherapy (inhaled corticosteroid with long acting β-agonist) for COPD or Group II (n = 21, age = 57.80 ± 2.68 years), given adjunct yogic intervention with conventional pharmacotherapy. The BODE index (body mass index, obstruction, dyspnea, exercise), marker of inflammation (CC16) and oxidative stress (SOD, 8-isoprostane) were evaluated in both the groups at 0 and 12 weeks of treatment and compared. The results showed a significant improvement in BODE index (by 25% in Group I, 70% in Group II), marker of inflammation (by 42.68% in Group I, 93.74% in Group II) and markers of oxidative stress (SOD: by 14.5% in Group I, 43.07% in Group II; 8-isoprostane: by 11% in Group I, 24% in Group II) after 12 weeks of treatments vs. baseline; however, the degree of improvement was markedly more in Group II as compare to Group I. Taken together, it can be suggested that, introducing yoga as adjunct therapy in COPD can enhance the efficacy of conventional pharmacotherapy.

Keywords: Biomarker; BODE Index; COPD; Dyspnea; Yogic Intervention

Introduction

Chronic obstructive pulmonary disease (COPD) is among the leading causes of morbidity and mortality throughout the world. According to global burden of disease study, COPD is presently the 4th leading cause of mortality worldwide [1] and further, it is predicted to become the 3rd leading cause of mortality by 2020. Globally, many people experience complications of this illness and die early [2]. COPD symbolizes an important global challenge that is a preventable and treatable disease.

The severity of COPD is strongly correlated with the irritation or inflammation in the bronchioles and is characterized by the presence of persistent airflow limitation due to obstruction which is not fully reversible [3]. Club or formerly clara cell secretory protein 16 (CC16) is a member of secretoglobulin family and is indicated as a novel and emerging biomarker of inflammation. CC16 is shown to have anti-
inflammatory and anti-toxicant properties against environmental exposure such as smoking [4-6]. It is mainly secreted by non-ciliated bronchiolar club cells in the distal airways and can be measured in systemic circulation. Several lines of evidence indicate that CC16 protects against obstructive lung diseases by maintaining homeostasis of the airway epithelium and its deficiency is strongly associated with COPD [7-9]. Further, in various clinical studies, severity and prevalence of COPD have been associated with chronically decreased number of clara cells in airways [10-14]. In addition, the four factors viz. body mass index, obstruction, dyspnea, and exercise (BODE index), constitute a multidimensional scoring system and capacity index to assess long-term outcomes of the disease in patients with COPD. BODE index can be used to determine the severity of COPD and is also correlated with other probable causative factors of the disease such as oxidative stress and inflammatory cytokines [15,16]. BODE index is considered to be a better predictor than FEV₁ (forced expiratory volume in 1 sec) alone for defining future progression of COPD [17].

Oxidative stress plays a major role in the pathogenesis of COPD and is characterized by increased generation of free radicals and reactive oxygen species in the lungs, causing extracellular matrix damage with chronic airway inflammation [18-20]. Systemic oxidative stress has been shown to affect the repair mechanism of respiratory muscles and the immune modulation process in COPD [20,21]. Superoxide dismutase (SOD) is one of the enzymes that can scavenge superoxide radicals by catalyzing superoxide anion to H₂O₂ and oxygen [22]. It is assumed that the imbalance between the pro-oxidant and antioxidant factors may result in oxidative burden which helps in progression of the disease [23]. However, there is paucity of defined mechanisms which explain the etiology of COPD.

Current medical treatment for COPD mainly depends on inhaled bronchodilators (β2-agonists), inhaled long-acting muscarinic receptor antagonists, oral phosphodiesterase-4 inhibitors and corticosteroids [3]. Such pharmacotherapy has certain limitations as they only partly minimize the symptoms with minimal modification of the disease course of COPD. They are also associated with undesirable adverse effects and drug insensitivity/refractoriness which further complicates COPD management [2]. Several studies have been conducted to explore new potential drugs such as monoclonal antibodies against interleukins-8 (IL-8) etc. for COPD, but no conclusive results have been achieved to date [24-26]. Therefore, finding an alternative approach or adjunct that can complement the conventional pharmacotherapy is an important goal for the better management of COPD.

Yoga is a practical traditional therapy, originated in ancient India, with health benefits that are being acknowledged globally. It consists of wide range of practices which help in developing a state of mental and physical well-being by uniting mind, body and spirit [27]. The primary components of yoga consist of i) physical postures (asanas) which help in developing strength and flexibility; ii) breathing techniques (pranayama) which enhance respiratory functions; iii) deep breathing maneuvers which help in releasing anxiety and iv) meditation which helps in supporting emotion and regulating the stress [28,29]. Our recent studies have shown the beneficial effects of adjunct yogic intervention on pulmonary functions and quality of life in patients with bronchial asthma and COPD [30,31]. However, Papp., et al. [32] showed limited efficacy of hatha yoga in improving the lung function parameters, pulmonary muscle strength and quality of life in patients with obstructive pulmonary disease. Thus, the studies to assess the efficacy of yogic intervention on obstructive lung disease are limited and the results are equivocal.

**Purpose of the Study**

The purpose of this study was to evaluate the effects of adjunct therapy with yoga on pulmonary functions and markers of inflammation in patients with COPD.

**Materials and Methods**

**Ethical considerations**

The study was registered under Clinical Trials Registry of India at [http://ctri.nic.in](http://ctri.nic.in) and the number allocated was CTRI/2018/03/012731. The protocol was approved by the Institutional Ethics Committee of the Vallabhbhai Patel Chest Institute, University of Delhi.
procedures in the study were performed according to the guidelines of ICH-GCP (International Conference on Harmonization - Good Clinical Practice). A written information sheet about the study details was provided to all the participants and written informed consent was obtained before the commencement of the trial.

**Study design and patient recruitment**

It was a randomized, controlled, prospective and non-blinded clinical study conducted on the patients with COPD. The present collaborative study was conducted at Pulmonary Medicine Unit, Viswanathan Chest Hospital jointly with Clinical Pharmacology Unit, Department of Pharmacology, V.P. Chest Institute, University of Delhi. Patients were diagnosed with COPD on the basis of clinical history, symptoms and pulmonary functions test (PFT) by the pulmonologist as per the guidelines of Global Initiative for Chronic Obstructive Lung Disease (GOLD I-II) [3]. Forty one patients with COPD were recruited from the outpatient department as per predefined inclusion and exclusion criteria, between April 2018 and March 2019. Patients were informed about the aims and methods of the study, expected duration of their participation, the benefits that are expected from the research and potential risks associated with the study, following which written informed consent was taken. Study participants were also assured about the maintenance of confidentiality of records, provisions for treatment and free will to leave the study at any time without giving any reason whatsoever.

A total of 53 COPD patients (as per GOLD I-II) were enrolled as per inclusion and exclusion criteria. They were randomized into two groups (Group I, n = 27 and Group II, n = 26) using a computer generated table adapted from [http://www.randomizer.org](http://www.randomizer.org) [33]. Group I was given conventional pharmacotherapy (inhaled corticosteroid with long acting β-agonist). Group II was administered conventional treatment (inhaled corticosteroid with long acting β-agonist) along with yogic intervention for 50 minutes, under the supervision of well qualified and experienced yoga teacher (Table 2). Those patients who practiced yoga for at least five times in a week were considered for the study and analysis was done from the data collected from these patients. The appropriate control conditions of Relaxation, Meditation (point 6 and 7 in table 2) and Medical intervention were maintained. On the other hand, Group I patients were advised to take only the conventional pharmacotherapy of COPD that were prescribed to them by the pulmonologist and instructed for timely follow-ups (after 1, 2 and 3 months). During emergency situations such as acute exacerbations of chronic bronchitis, shortness of breath, chest tightness and worsening of cough, levosalbutamol was recommended in both the groups as rescue medication for the emergency management of COPD. There were 12 dropouts (7 from Group I and 5 from Group II) and a total of 41 patients attended the scheduled follow-up visit and completed all the study assessments. These details are shown in the CONSORT flow diagram (Figure 1). The clinical and demographic characteristics of enrolled COPD patients are shown in table 1.

![Table 1: Clinical and demographic characteristics of enrolled COPD patients of Group I and Group II.](image)

Group I (conventional pharmacotherapy); Group II (yoga + conventional pharmacotherapy); M/F: Male/Female; SaO₂: Percentage Arterial Oxygen Saturation; GOLD: Global Initiative for Obstructive Lung Disease.

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Inclusion criteria: 1) Patients between the ages of 40 to 65 years of any gender; 2) patients with clinically diagnosed COPD (GOLD I-II); 3) patients who were willing to participate independently and voluntarily in the study with the submission of written informed consent; 4) ambulatory and cooperative patients.

Exclusion criteria: 1) Patients who had airway infections during the last one month period or developed within one month of enrollment; 2) patients who suffered from any kind of illnesses other than COPD like liver, renal, rheumatic heart failure, diabetes mellitus and central nervous system disorders; 3) pregnant/lactating women; 4) history of hypersensitivity to any of the conventional drugs for COPD treatment.

The baseline physiological parameters such as pulse rate (PR), respiratory rate (RR), blood pressure (BP), percentage arterial oxygen saturation (SaO₂), body weight and other parameters, viz. pulmonary inflammatory marker (CC16), oxidative stress markers (SOD, 8-isoprostane), and BODE index, were recorded on the first day of the visit and after 12 weeks of respective treatments in patients of both the groups.

The yogic intervention program

The yoga training program was specially designed for COPD patients in consultation with yoga experts. After taking the baseline parameters, comprehensive yoga training was given daily for 50 minutes for 2 weeks in Group II patients and then instructed to follow the same on a regular basis for 10 more weeks and maintain a diary to monitor the compliance to yogic intervention. The list of the daily schedule of therapeutic yogic intervention assigned to Group II is shown in table 2. The therapeutic yogic approach used in the study consisted of physical practices, pranayama (breathing techniques), meditation and shavasan (relaxation techniques). The physical practice consisted of preliminary breathing exercise and loosening exercise followed by asanas. It included loosening exercises (yogic sukshmavyama for 10 cm).
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minutes) with simple neck, hand, shoulder and other body movements to loosen the joints followed by breathing exercises (4 minutes) which were rhythmic, comfortable and focused on specific body parts. It was then followed by different yoga exercises (asanas for 15 minutes) performed with smooth, comfortable bending movements and slow breathing in various physical positions (standing, sitting, prone and supine positions). After that, patients practiced three types of special breathing techniques (pranayama for 7 minutes) with comfortable, slow and deep breathing. The practices ended with the subject maintaining the final posture with body and mind completely relaxed (yoga niddra and meditation for 11 minutes).

<table>
<thead>
<tr>
<th>S.no.</th>
<th>Name of the practice</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Shat kriyas (Kapalabhati)</td>
<td>3 min</td>
</tr>
<tr>
<td>2.</td>
<td>Yogic sukshmayama Ucharana-sthala and vishuddha-chakra-suddhi, Buddhi and srishtishaktivikasaka Gardan (Neck) Griva-shakti-vikasakriya - 4 Bhuja-valli-shaktivikasakakriya, Shoulders chalankriyas, Vakshasthalashaktivikasaka 1 and 2, Kati shaktivikasak 2 and 5, Knees chalankriya</td>
<td>10 min</td>
</tr>
<tr>
<td>3.</td>
<td>Breathing maneuvers (Chest breathing, Full yogic deep breathing)</td>
<td>4 min</td>
</tr>
<tr>
<td>5.</td>
<td>Pranayama (Nadishodhana - 20 rounds, Bhramari- 10 times, Suryabhedan - 20 times)</td>
<td>7 min</td>
</tr>
<tr>
<td>6.</td>
<td>Yoga-niddra</td>
<td>4 min</td>
</tr>
<tr>
<td>7.</td>
<td>Meditation</td>
<td>7 min</td>
</tr>
</tbody>
</table>

Table 2: List of practices during yogic intervention.

Follow-up schedule

Physical examinations and other physiological parameters such as PR, RR, BP, SaO₂ and body weight were performed in both the groups (Group I and Group II) at baseline and after 12 weeks of therapy. Further, the four important variables of BODE index i.e. BMI (body mass index), FEV₁, mMRC (modified Medical Research Council dyspnea scale), 6MWD (six minute walking distance) and specific pulmonary inflammatory marker, clara cell protein 16 (CC16) and oxidative stress markers (SOD, 8-isoprostane) were also measured in both Group I and Group II at baseline and after 12 weeks of treatment. The CONSORT flow diagram (Figure 1) illustrates the entire design of this study. If the patients practiced yoga for at least 5 times in a week, they were considered compliant to the study and data arising from them was used for the analysis.

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Sample collection
For the study, blood (5 ml) was drawn from antecubital vein of patients of both groups at baseline i.e. day 0 and after 12 weeks of treatment. The blood was allowed to clot by leaving it undisturbed at room temperature for 1 hour and then serum was separated by centrifugation at 3000 rpm for 10 minutes, divided into aliquots and frozen at -80°C for subsequent biochemical analysis.

Estimation of serum CC16
The collected and stored serum samples were thawed and CC16 levels were measured in duplicate at a 25-fold dilution using a commercially available ELISA kit (BioVendor, Karasek, Czech Republic) as per the manufacturer’s protocol. Briefly, the test samples were added to the precoated microplate wells with a polyclonal anti-human club cell protein antibody and incubated for 60 minutes followed by washing. The biotin-labeled polyclonal anti-human club cell protein antibody was added and then incubated for another 60 minutes. It was followed by a second wash and then streptavidin-horseradish peroxidases (HRP) conjugate was added and incubated for another 60 minutes. After incubation of plate, a washing was given and then TMB (tetramethylbenzidine) substrate solution was added to react with the conjugate. The reaction was stopped by addition of an acidic solution and reading was taken by microplate reader (LLC SpectraMax 190, Molecular Devices, USA) at 450 nm and expressed as ng/ml (assay range 2 - 50 ng/ml).

BODE index
The four important parameters of BODE index viz. body mass index (B), airflow obstruction (O), dyspnea (D) and exercise capacity (E) were done to assess the COPD patients of both the groups at baseline and 12 weeks of treatment using the following tools:

- Body mass index (B): BMI was calculated according to the formula: BMI (B) = weight (kg)/height (m)² [34].
- Airflow obstruction (O): PFT was performed with spirometer (NDD easy one PC Ultrasonic Spirometer; NDD Medical Technologies Inc, USA). The best reading of FEV₁, FVC, FEV₁/FVC from three consecutive tests was considered according to ATS (American Thoracic Society) criteria and used for BODE scoring [35].
- Dyspnea (D): The modified Medical Research Council (mMRC) scale was used to determine the severity of dyspnea based on a questionnaire to the patient [36,37].
- Exercise capacity (E): 6MWD was performed in a corridor (40 meters) within hospital premises. Patients were directed to walk as fast as possible they could. Parameters such as PaO₂, PR, BP were measured before and after the procedure and the distance walked in 6 minutes was recorded [38].

The scores for airflow obstruction, dyspnea and exercise capacity range from 0 (lowest value) to 3 (highest value) whereas for BMI, the value ranges from 0 (lowest value) to 1 (highest value) as shown in table 3. The overall BODE index was calculated for each patient of both the groups by adding the score of each of these four variables. The overall final score of BODE index ranges from 0 to 10 points; higher the score greater the severity of the disease and risk of death.

Estimation of serum superoxide dismutase (SOD) and 8-isoprostane
SOD is a major superoxide-scavenging enzyme that scavenges superoxide radicals in the lung and catalyzes the dismutation (or partitioning) of the superoxide (O₂⁻) radical into either ordinary molecular oxygen (O₂) or hydrogen peroxide (H₂O₂). It is a systemic marker of oxidative stress and their levels were estimated in serum sample of patients by using commercially available enzyme linked immunosorbent assay (ELISA) kits from Qayee-Biotechnology Co. Ltd Shanghai, China. The assay (range 6.25 - 400 ng/ml) procedure was followed according to the manufacturer’s instructions. Briefly, test samples and HRP-labeled superoxide dismutase antibodies were added to precoated wells followed by incubation for 60 minutes at 37°C. Then, the plate was washed to remove the unbound enzyme followed by addition of chromogen solution A and B provided in the kit. Upon addition of stop solution, the reaction was terminated and color changed.
to yellow. The concentration of SOD was positively correlated with the optical density that was measured using microplate reader (LLC SpectraMax 190, Molecular Devices, USA) at 450 nm and expressed as ng/ml.

The serum levels of 8-isoprostane (assay range 1.25 nmol/ml-80 μmol/ml) was measured in blood samples of both the groups using commercially available ELISA kits (Qayee-Biotechnology Co. Ltd Shanghai, China) at 0 day and after 12 weeks of treatment and compared. Briefly, enzyme wells pre-coated with 8-isoprostane antibodies was used and standards, test samples and HRP-labeled 8-isoprostane antibodies were added to the respective wells. The plate was incubated for 60 minutes followed by washing to remove the unbound enzyme. Colored complex was developed upon addition of chromogen solution A and B and the reaction was stopped by addition of acidic solution and absorbance was read by ELISA microplate reader (LLC SpectraMax 190, Molecular device, USA) at 450 nm and expressed as nmol/ml.

**Statistical analysis**

All data were expressed as mean ± SEM (standard error mean). The data of CC16, SOD, 8-isoprostane and BODE index were analyzed by paired t-test using the Graph Pad Prism 5 software. A \( p \) value of < 0.05 was considered as a level of significance in all statistical tests. The results were compared by paired t-test (within group pre-post analysis). The between group analysis did not show any significant difference, therefore % improvements in various parameters by 2 treatment regimens were compared.

**Results**

**Effects of yogic intervention on the levels of serum CC16**

The analysis of results showed that CC16 levels were significantly different before and after 12 weeks of their respective treatment in both the groups (I = conventional pharmacotherapy, II = yoga + conventional pharmacotherapy). However, the level of CC16 was remarkably higher in Group II (yoga + conventional pharmacotherapy) than in Group I (conventional pharmacotherapy) as compared to their corresponding baseline values. In Group I, the level of CC16 at baseline (day 0) was 4.71 ± 0.56 ng/ml which was increased to 6.72 ± 0.57 ng/ml \((p < 0.01)\) after 12 weeks of conventional treatment. On the other hand, in Group II, its level at baseline was 4.79 ± 0.60 ng/ml which was increased to 9.28 ± 0.92 ng/ml after 12 weeks of conventional treatment along with yogic intervention. The increase in serum level of CC16 after the treatment in Group I was 42.68% and in Group II it was 93.74% as compared to the respective baseline value. The results are summarized in figure 2.
**Effect of yoga on BODE index**

Individual components of BODE index (BMI, FEV$_1$, mMRC dyspnea scale, 6MWD) were also compared at baseline (0 day) and after 12 weeks of treatment in both Group I and II. There was no significant difference in BMI before the treatment and after 12 weeks of treatment in either group. However, a significant difference was found in the remaining three components i.e. FEV$_1$, mMRC, dyspnea scale, 6MWD when compared to their corresponding baselines scores. The findings in each individual components of BODE for patients participating in this study are summarized in table 4.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Groups</th>
<th>Baseline</th>
<th>After 12 weeks</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m$^2$)</td>
<td>Group I</td>
<td>22.67 ± 0.63</td>
<td>22.83 ± 0.66</td>
<td>0.71%</td>
</tr>
<tr>
<td></td>
<td>Group II</td>
<td>23.52 ± 1.10</td>
<td>24.10 ± 1.04</td>
<td>2.47%</td>
</tr>
<tr>
<td>FEV$_1$ (%)</td>
<td>Group I</td>
<td>59.05 ± 1.50</td>
<td>66.60 ± 2.18*</td>
<td>12.78%</td>
</tr>
<tr>
<td></td>
<td>Group II</td>
<td>61.10 ± 1.69</td>
<td>75.40 ± 3.56*</td>
<td>23.40%</td>
</tr>
<tr>
<td>mMRC dyspnea</td>
<td>Group I</td>
<td>1.60 ± 0.11</td>
<td>1.25 ± 0.16*</td>
<td>20.00%</td>
</tr>
<tr>
<td>scale</td>
<td>Group II</td>
<td>1.65 ± 0.11</td>
<td>0.70 ± 0.15**</td>
<td>57.58%</td>
</tr>
<tr>
<td>6MWD (meters)</td>
<td>Group I</td>
<td>369.90 ± 15.98</td>
<td>416.38 ± 17.80*</td>
<td>12.57%</td>
</tr>
<tr>
<td></td>
<td>Group II</td>
<td>382.72 ± 13.32</td>
<td>457.06 ± 11.52*</td>
<td>19.43%</td>
</tr>
</tbody>
</table>

**Table 4:** Comparison of variables of BODE index between COPD patients of Group I and II.

All data are expressed as mean ± SEM; (Group I: conventional pharmacotherapy, n = 20; Group II: yoga + conventional pharmacotherapy, n = 21); *p < 0.05, **p < 0.01 vs. baseline using paired t-test (BMI, FEV$_1$, mMRC, 6MWD score at recruitment time = 0 day); BMI: Body Mass Index; FEV$_1$: Forced Expiratory Volume in 1 Second; mMRC: Modified Medical Research Council Dyspnea Scale; 6MWD: Six Minute Walking Distance.

**Figure 2:** Comparison of serum levels of Clara cell secretory protein 16 (CC16) between group I and group II after 12 weeks of treatment.

All data are expressed as mean ± SEM, (Group I: n = 20; Group II: n = 21); *p < 0.05 vs baseline data of respective group (values at day 0) using paired t-test; Group I (conventional pharmacotherapy); Group II (yoga + conventional pharmacotherapy); CC16: Clara Cell Secretory Protein 16.
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Figure 3 shows the overall score of BODE index comprising of all the four individual variables calculated as per table 3. Both Group I (conventional pharmacotherapy) and Group II (yoga + conventional pharmacotherapy) exhibited significant reductions in the BODE score as compared to their corresponding baseline value. In Group I, the baseline BODE index score was 3.10 ± 0.31 which was reduced to 2.30 ± 0.29 (p < 0.02) after 12 weeks of conventional treatment. In Group II, the score was reduced from its baseline value i.e. 3.00 ± 0.30 to 0.90 ± 0.26 (p < 0.01). Thus, the BODE scores in Group I and Group II were reduced by 26% and 70% respectively after 12 weeks of treatment.

Effects of yogic intervention on the serum levels of SOD and 8-isoprostone

The results showed that level of serum SOD was increased significantly (p < 0.02) in Group II after 12 weeks of adjunct yogic intervention compared to the baseline values. Although, the level of SOD was also increased from 84.24 ± 9.94 ng/ml (baseline) to 96.46 ± 9.59 ng/ml (after 12 weeks) in Group I, it was not statistically significant (p > 0.05). The serum levels of 8-isoprostone were reduced significantly in both the groups of patients by the respective treatments. In Group I, the level of 8-isoprostone was decreased from 2.23 ± 0.12 nmol/ml (baseline) to 2.00 ± 0.08 nmol/ml (after 12 weeks) i.e. by 11%. In Group II, the levels decreased from 2.16 ± 0.10 nmol/ml to 1.64 ± 0.10 nmol/ml (p < 0.01) i.e. by 24%. The results are shown in figure 4a and 4b.

Discussion

This is the first study providing the impact of yogic intervention on the specific markers of COPD viz. BODE index, CC16 protein and oxidative stress markers in patients with COPD. The BODE index has been developed as a new, combined, multidimensional, valid tool to predict more accurately the disease process as well as survival of COPD patients [17]. It comprises of body mass index, FEV₁ (% predicted, post bronchodilator value), the mMRC dyspnea scale and 6MWD. In this study, all four individual components of BODE index i.e. FEV₁, mMRC and 6MWD were found to be significantly improved by yogic intervention (50 minutes/day). In the present study, the increased
FEV$_1$ values provide evidence of significant improvement in lung function in both Group I and Group II patients with COPD; however, the percentage improvement was remarkably more in the yogic intervention group. These results are consistent with our earlier findings showing efficacy of yoga in improving pulmonary functions in patients of bronchial asthma [30]. The yogic intervention including breathing exercises may have led to improvement in the pulmonary functions partly by expanding alveoli and its membrane and improving blood circulation and supply of oxygen. Several other studies have also reported that adjuvant yogic therapy (slow and fast deep-breathing techniques) lead to strengthening of the pulmonary muscle and improved pulmonary functions in patients with chronic obstructive pulmonary disease [39,40]. The present results showed a negative correlation between yogic intervention and dyspnea, as measured by using mMRC. In both the groups (I and II), shortness of breath was improved after 12 weeks of treatment, however, the degree of improvement was markedly more in Group II as compared to Group I. Previous studies evaluating the effect of yoga on dyspnea in patients with COPD, also suggested a negative relationship between yogic deep breathing and dyspnea [41,42]. Tan, et al. recently reported similar findings in response to 20 minutes of mindful breathing that resulted in rapid reduction of dyspnea in patients with lung diseases [43].

Another most common feature of patients with COPD is exercise intolerance and 6MWD helps to determine such functional incapability or functional changes [41]. In our current study, significant improvement in 6MWD was seen in both the groups (Group I and Group II) of COPD patients, but better functional performance in covering longer distance within 6 minutes was found in patients of Group II (yoga + conventional pharmacotherapy). Similar findings were also reported earlier supporting the valuable prognostic effect of yogic intervention on functional capabilities in patients with COPD [41]. Further, the percent improvement in levels of CC16 in Group II was greater as compared to that in Group I, indicating better control of the airway inflammation in patients who practiced yogic exercises regularly. This is the first study to report significant augmentation of CC16, a biomarker of protection against inflammation of airway epithelium in COPD.
by yogic intervention. The levels of circulatory CC16 were found to be inversely associated with BODE index score, as the Group II patients showed increase in the level of CC16 with decline in the BODE index score. These findings are in agreement with previous reports which demonstrated a negative correlation between CC16 and disease severity in patients with COPD [44,45].

Airway inflammation is usually associated with superoxide free radical generation, resulting in elevated oxidative stress and thereby further enhancing the process of inflammation [23]. Interestingly, the increase in CC16 after 12 weeks of yoga practice was accompanied with a significant increase in the antioxidant enzyme, SOD. It catalyzes the dismutation (or partitioning) of the superoxide (O$_2^-$) radical into either ordinary molecular oxygen (O$_2$) or hydrogen peroxide (H$_2$O$_2$) [22]. This increase in antioxidant enzyme in Group II may be due to the stimulatory effects of yogic exercises on the various redox signaling pathways thereby inducing the increased production of antioxidant enzymes [46]. Some of the recent studies have also reported such positive impact of yogic intervention on oxidative stress markers in different pathophysiological conditions [47-49]. Further, the level of 8-isoprostane, a chemically stable prostaglandin analog, formed in vivo by free radical-catalyzed peroxidation of arachidonic acid, was markedly reduced in Group II (yoga + conventional pharmacotherapy) as compared to Group I (conventional pharmacotherapy). This finding further emphasized the protective effect of yoga against oxidative stress by maintaining the homeostatic balance between the pro-oxidant and antioxidant factors. Thus, yoga may improve pulmonary functions (evidenced by improved BODE score) by reducing oxidative stress which is proposed as one of the leading causes of COPD. The results suggested that practice of yoga may be a useful adjunct to conventional treatment for the better management of COPD.

The current study, however, has certain limitations. A long term study involving yogic intervention in a large sample size could have stated the differences between the Group I (conventional pharmacotherapy) and Group II (yoga + conventional pharmacotherapy) more clearly. In addition, the small sample size in each group could have come in the way of drawing a clinical conclusion. Apart from quantifying only one antioxidant assay (SOD) in the present study, an addition of two more in vivo antioxidant assays such as glutathione, catalase etc., would have given better understanding of free radical scavenging capacity. Further, estimation of other important biochemical inflammatory markers (myeloperoxidase assay and migration of eosinophil, neutrophil, and mononuclear cells in blood sample) and quantification IL-4, IL-5 and IL-13 secreted from Th2 cells could have enhanced the output of the study. Further, impact of yogic intervention on social and emotional functions, which are relevant to COPD, was not assessed in this study, and could be the subject matter of future research.

**Conclusion**

Taken together, our results showed that yogic intervention had a positive influence on pulmonary functions and augmented CC16 protein, a biomarker for anti-inflammatory effects, in COPD patients. This was accompanied with reduced oxidative stress as evidenced by decreased 8-isoprostane (marker of lipid peroxidation) and increased SOD (a marker of antioxidant defense), suggesting that the effects of yoga may be mediated by maintaining a homeostatic balance between pro-oxidant and antioxidant factors. Thus, the present study provides evidence to support the hypothesis that yoga therapy may be included as an acceptable, potential and non-pharmacological adjunct to conventional pharmacotherapy for better management of COPD.

**Conflict of Interest**

The authors state that they have no financial interest or any conflict of interest in the study.

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