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# The Effect of Therapeutic Exercises Model on Oxidative Stress and Gait Speed in Chronic Obstructive Pulmonary Disease

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## ABSTRACT

Background: Chronic obstructive pulmonary disease (COPD) has a high mortality and morbidity worldwide. Oxidative stress and inflammation are potentially important mechanisms in the pathogenesis of COPD where there is an imbalance between oxidants (free radicals) and antioxidants. High-intensity therapeutic exercise might reduce the plasma oxidative stress level while increasing exercise capacity and lowering lactic acid levels in moderate-to-severe COPD patients. This study aimed to obtain an effective therapeutic exercise model in the levels of oxidative stress and walking speed with an appropriate prescription for stable COPD patients. Methods: This study was a randomized clinical trial. The subjects were those aged over 50-85 years old. A total of 43 subjects were analyzed. The subjects underwent several tests (six-minute walk test, 4-meter gait speed, quadriceps muscle strength, and laboratory test), while given pulmonary rehabilitation and measured for the MDA and GSH levels. Statistical analysis was done by univariate analysis, Paired T-test and Friedmann test. Results The study result showed an insignificant increase of GSH values in the type II training group ($p=0.688$) and a reduction in the type III group ($p=0.56$). Our study also found a significant difference in gait speed between the three exercise groups ($p<0.001$). Conclusion: Type II training is the most effective regimen in reducing the MDA plasma levels and increasing plasma GSH levels. The changes in blood MDA and GSH levels would be more noticeable if additional samples and extended training periods were applied in lung rehabilitation programs.

**Keywords:** COPD, Therapeutics Exercise, Oxidative Stress, Gait Speed

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## INTRODUCTION

Chronic obstructive pulmonary disease (COPD) has a high mortality and morbidity worldwide.[1] It is a lung disease characterized by persistent airflow limitation.[2] COPD causes disabilities and progressive ailment that reduces physical activities, functional abilities, and quality of life.[2] Improving the quality and duration of life of COPD patients is a distinct challenge. Pulmonary rehabilitation has been confirmed to be effective in improving the activities of daily living.[3] Although the benefits of physical exercise on pulmonary function in patients with COPD are limited, physical training is the most important component of the pulmonary rehabilitation program. Both endurance and resistance muscular training improves muscle function and exercises tolerance in COPD. [4] Oxidative stress and inflammation are potentially important mechanisms in the pathogenesis of COPD where there is an imbalance between oxidants (free radicals) and antioxidants.[5] Exercise increases the antioxidant capacity of the body, but vigorous exercise or acute weight training has the opposite effect and increases oxidative stress. [6,7] Therapeutic exercise can reduce oxidative stress levels in moderate to severe COPD as well as to increase exercise capacity and decrease lactic acid levels. Providing appropriate therapeutic exercise by combining aerobic and strengthening exercise is essential to build an efficient exercise condition to increase the antioxidant capacity without increasing oxidative stress.[8] Walking speed has been reported as a problematic activity in the daily lives of COPD patients.[9] Gait deficit is an intrinsic risk factor for fall risk in COPD, indicating the clinical value of gait assessment in COPD.[10] Exercise training has a beneficial effect on gait characteristics in older adults, including increased walking speed, cadence, stride length, and shorter stride times.[11] Effective exercise interventions have been shown to improve lower leg muscle function and exercise capacity in patients with COPD, thus having a beneficial effect on gait characteristics in COPD patients.[12] This study was conducted to obtain an effective therapeutic exercise model in terms of the level of oxidative stress and walking speed with an appropriate prescription for stable COPD patients.

## MATERIAL AND METHODS

This study included 43 patients with COPD referred for a Pulmonary Rehabilitation (PR) program in the Persahabatan specialized rehabilitation center in Jakarta, Indonesia. COPD was diagnosed based on the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines. Patients with COPD were eligible if they were between 50-85 years of age and clinically stable, as evaluated by a physician. Patients were excluded when they presented with any cognitive impairment, neuromuscular or musculoskeletal ailments affecting their

gait, and or if they used supplemental oxygen and/or walking aids. The study was approved by the local ethics committee. All patients gave written informed consent before participating in this study. This study was a randomized clinical trial. All participants were separated into three groups: low-intensity exercise with strengthening exercises 50% from 1 RM (n=15), moderate-intensity exercise with strengthening exercises 75% from 1 RM (n=14), and control group (n=14). Patients underwent a six-minute walk test, 4-meter gait speed, quadriceps muscle strength tests, and laboratory tests before and after the training program. Aerobics was performed using a treadmill (Cardioline). The Borg scale, respiratory rate, heart rate, blood pressure, and oxygen saturation were monitored at the beginning and the end of exercise. Aerobic exercises will be considered safe if patients did not present with any clinical adverse event during or after exercise. PR consisted of 24 sessions (3 times/ week for 8 weeks). Physical exercise training was the core of the PR program, comprising exercises to strengthen muscle groups in the lower extremities and treadmill walking. After 24 sessions, an outcome assessment was conducted to evaluate the effects of the therapeutic exercise for each patient. The oxidative stress level was assessed by MDA and GSH. Functional mobility was assessed by 4-meter gait speed. Quadriceps muscle function was evaluated by a sandbag. The MDA levels were measured using the HPLC fluorescence immunodiagnostic method using the MDA reagent (immunodiagnostic) and Zorbax Eclipse XDB-C18 using the HPLC Malondialdehyde kit. EDTA venous blood plasm was used as the material fluorescence detector that will record the chromatogram.
The GSH levels were measured using spectrophotometry by counting the thionine functional group's formation using the BIOXYTECHÒ GSH-420 kit, Oxis. The sample works' absorbency result was read at 420 nm wavelengths, directly proportional to the GSH concentration. EDTA venous blood plasm were used as samples.
Data analysis was performed by SPSS version 20. Univariate analysis was used to show frequency distribution by descriptive statistic form and mean comparative test based on the sex of each variable. Bivariate analysis Paired T-test and Friedmann test were used to find the correlation between dependent and independent variables to determine whether or not the correlation was statistically significant.

## RESULTS

Table 1. Research Subjects' Characteristics

| Variable | Groups | | | p |
|---|---|---|---|---|
| | Type I (n=15) | Type II (n=14) | Type III (n=14) | |
| Gender | | | | |
| - Male | 10 (66.7) | 9 (64.3) | 10 (71.4) | 0.718[b] |
| - Female | 5 (33.3 %) | 5 (35.7 %) | 4 (28.6 %) | |
| Patient age | 65.2 (±7.82) | 67.9 (±8.16) | 70.57 (±7.93) | 0.937[a] |
| COPD Grade | | | | |
| Grade A | 0 (0.0 %) | 1 (7.1 %) | 0 (0.0 %) | 0.957[b] |
| Grade B | 10 (66.7 %) | 8 (57.1 %) | 5 (35.7 %) | |
| Grade C | 2 (13.3%) | 3 (21.4%) | 5 (35.7%) | |
| Grade D | 3 (20%) | 2 (14.3%) | 4 (28.6%) | |
| BMI | 19.79 (±4.40) | 21.26 (±4.38) | 19.59 (±4.66) | 0.823[a] |
| Spirometry classification | | | | |
| Mild-moderate | 12 (80.0 %) | 13 (92.9 %) | 7 (53.8 %) | <0.001[b] |
| Severe-very severe | 3 (20.0 %) | 1 (7.1 %) | 6 (46.2%) | |
| | | | | |

[a]Levene test
[b]Chi-Square/Fisher test

The characteristics for exercise group type I, type II, and type III were not significantly different. Therefore, it can be concluded that these three groups had the same characteristics. The subjects in this study were predominantly male, which accounted for 29 subjects (67%) and aged ≥60 years old, which accounted for 35 subjects (81%). In comparison, 14 women subjects were accounted for (33%), and 8 subjects aged <60 years old were accounted for (19%). In this study, the BMI was classified based on the BMI as per to the Asia Pacific Guideline. The BMI of most subjects, which accounted for 19 subjects (44%), were within normal range with a mean BMI of 20.21 kg/m$^2$.

Table 2. The Correlation of Type I, II, and III Training towards MDA Levels

| Intervention | Base MDA (mg/L) | MDA 24 (mg/L) | p-value | 95% CI |
|---|---|---|---|---|
| Type I | 3.61 (±0.43) | 3.60 (±0.48) | 0.943 | 0.007 (-0.208-0.223) |
| Type II | 3.88 (±0.30) | 3.72 (±0.19) | 0.081 | 0.158 (-0.022-0.339) |
| Type III | 2.92 (±0.35) | 3.09 (±0.25) | 0.05 | -0.168 (-0.337-0.0001) |

Paired-T test

We found no significant difference between the three exercise types for the effect of therapeutic exercise on plasma MDA level before and after exercise. We also found an insignificant reduction of plasma MDA level on the type

I and type II exercise group and an insignificant increase on the type III exercise group.

Table 3. The Effect of Exercise Model Type I, Type II, and Type III on the GSH level.

| Intervention | GSH Base (mg/dL) | GSH 24 (mg/dL) | p-value | 95% CI |
|---|---|---|---|---|
| Type I | 717.33 (±94.91) | 711.66 (±124.14) | 0.892 | 5.667 (-82.064-93.398) |
| Type II | 724.71 (±99.42) | 742.57 (±104.70) | 0.688 | -17.875(-111.795-76.080) |
| Type III | 750.21 (±119.94) | 728.28 (±84.23) | 0.56 | 21.928 (-57.344-101.201) |

Paired-T test

Our study result showed an insignificant plasma GSH level increase on the type II exercise group and an insignificant of GSH level reduction on the type I and type III exercise group.

Table 4. The Effect of Exercise Model Type I, Type II, and Type III on Gait Speed.

| Intervention | 4 meter Base walk test (m/s) | 4 meter 3 walk test (m/s) | 4 meter 24 walk test (m/s) | p-value |
|---|---|---|---|---|
| Type I | 1,02(0,50-1,60) | 1,03(0,80-1,73) | 1,33 (1,09-2,35) | <0,001* |
| Type II | 0,84(0,69-1,96) | 1,12(0,80-2,23) | 1,41 (0,8-2,54) | <0,001* |
| Type III | 0,80(0,48-1,62) | 0,93(0,50-1,93) | 1 (0,68-2,34) | <0,001* |

Friedman Test

Our study found a significant difference in gait speed between the three exercise groups, with gait speed ranging from 0.2m/s – 0.57m/s. The most change occurred in the type II exercise group while the least was in the type III exercise group.

## DISCUSSION

We found no significant difference between the three exercise groups on the effect of therapeutic exercise on the plasma MDA level before and after exercise. We found an insignificant plasma MDA level reduction on the type I and type II exercise group. We also found an insignificant increase in plasma MDA level on the type III exercise group. The study by Mercken *et al.* on COPD patients found no significant difference between plasma MDA levels before and after exercise in both submaximal and maximal intensity. The study also found that healthy people and COPD patients respond well to exercise, indicated by decreased plasma MDA levels. However, the exercise's response, as seen in the reduction of MDA levels in the healthy subjects, was more effective than those in COPD subjects. [4] Yessica *et al.* stated that plasma MDA levels were increased in patients with any degree of COPD compared to healthy subjects.[13] The most prominent risk factor in increasing lipid peroxidation were cigarette smoke or other pollutants, which were free radicals that could increase plasma MDA levels. Nielsen *et al.* found that people exposed to daily cigarette smoke have a higher plasma MDA concentration than those who are not exposed. [14] This statement was also supported by the study by Coullard *et al.* and Koechilin *et al.* that showed an increase of plasma MDA level after strengthening exercises with weight on COPD patients. Low-moderate intensity exercises could increase myocellular antioxidant capacity, which helps reduce the SOR level. If these exercises were carried out continuously, they could repair present oxidative damages. [10,15] Other than correct and appropriate pulmonary rehabilitation, the underlying mechanism of reducing oxidative stress on COPD patients might also be affected by a balanced nutritional adjustment and specific pharmacology.[4] Exercise response that reduces oxidative stress can be attained after regular exercising for at least 2-3 months. Such response could be achieved by several mechanisms, including the increase of proteasome's activity, DNA repair enzyme's activity, enzymatic antioxidant's activity in the liver cells such as superoxide dismutase and glutathione peroxide resulting in decreased oxidative stress and DNA binding with redox sensitive factors.[16] We found an increase of plasma MDA level in the type III exercise group (which is the control group) due to such a high number of subjects with a severe-very severe spirometry classification compared to the other two groups. [17] In this study, a reduction of plasma MDA levels in COPD patients was seen in the type I exercise group, although the decrease was not as substantial as the type II exercise group.

Our study result showed an insignificant increase of plasma GSH level on the type II exercise group. At the same time, there was an insignificant decrease in plasma GSH level in the type I and type III exercise groups. The study by Oh-ishi *et al.* on COPD patients showed an increase of glutathione oxidase (GSSG) and decrease of glutathione (GSH) after ergocycle exercise with similar intensity as normal daily activities.[18] Finsterer J (2012), in a combination study of aerobic exercise with a 70% VO2max ergocycle and strength exercises using dumbbells, found that GSH plasma was decreased by 21% and GSSH levels increased by 25%.[19] Both these studies supported our result on the type I and type III exercise groups. Keep in mind that severe COPD patients were more prone to fatigue during daily physical activities.[20] Another factor that affects the decrease in plasma GSH levels in the body is the use of theophylline as a drug that relaxes the airway muscles, as this drug could reduce the activity of vitamin B6. Pyridoxin or vitamin B6 functions as an important buffer compound for cysteine synthesis to combine with glutamate and glycine to form GSH.[21] In this study, type II exercise had the most effect on decreasing plasma MDA levels and increasing plasma GSH levels. In this study, the increased antioxidant levels inside the body were indicated by the increase of plasma GSH levels, with the highest increase seen in the type II exercise group.

Changes in plasma MDA and GSH levels would be more noticeable if more samples were involved and in a longer period of pulmonary rehabilitation program.

Our study found a significant difference in gait speed between the three exercise groups, with gait speed ranging from 0.2m/s – 0.57m/s. The most change occurred in the type II exercise group, while the least change was from the type III exercise group. Ilgin *et al*. stated that a 6-min walk test (6MWT) is associated with the severity of COPD, quality of life (questionnaire), the severity of dyspnea, and lower limb weakness.[22] Liu *et al*. (2019) showed that 55% of participants experienced an increase of 30-meter distance traveled or more with the 6MWT after undergoing pulmonary rehabilitation. The duration of therapeutic exercises for each individual can increase the strength of the lower leg muscles. Therefore, increasing the gait speed of COPD patients. [23] DePew *et al*. found that the four-meter walk test's gait speed on COPD patients was strongly correlated with the 6MWT distance (r=0.7, p<0.01).[24] Kon *et al*. found a significant increase of four-meter walk test result in COPD patients after undergoing the exercise program. Therefore, the four-meter walk test has the potential to be a simple, functional test for COPD patients, especially for weaker individuals.[25] McClellan R. *et al*. (2014) suggested that gait speed is proportionally related with the height, lower limb muscle strength, VO2max, and inversely related with age, depressive symptoms, and poor physical health status. In his study, there was an increase in gait speed after being given a pulmonary rehabilitation program. Patients with higher forced expiratory volume ($FEV_{1}$) experienced a more substantial increase in gait speed after the rehabilitation program.[26] Kon *et al*. found a remarkable variability in gait speed at a specific pulmonary function level as measured by $FEV_1$ in COPD patients[25]. Each type of exercise model type I, type II, and type III in this study have the potential to increase gait speed. Therefore, the selection of an exercise model can be adjusted according to the severity of COPD patients. If the aim of the exercise is to only increase gait speed and improve functional capacity, then type I and type III should be the primary choice for severe COPD patients, albeit the increase of gait speed is not as high as the type II exercise model.

Type II exercise is the exercise regimen that is most effective at reducing plasma MDA levels and increasing plasma GSH levels and increasing gait speed. Changes in MDA levels and GSH levels in blood plasma would be more noticeable if more samples were involved and in a longer period of pulmonary rehabilitation program.

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