Open Access

Original Article

Doi. 10.65433/mjms.v4i2.241

# Effect of Metformin on Acute Exacerbations of Chronic Obstructive Pulmonary Disease

**Romale Nazir[1], Javaria Aslam[2], Sami Ahmad,[3] Mazhar Faiz Alam[4], Saleha Zafar,[5] Sehrish Nazir[6]**

*[1,2]Department of General Medicine, Bahawal Victoria Hospital, Quaid e Azam Medical College, Bahawalpur, Pakistan*

*[3,4]Department of Pulmonology, Bahawal Victoria Hospital, Quaid e Azam Medical College, Bahawalpur, Pakistan*

*[5]Associate Professor of Pathology QAMC Bahawalpur*

***Author`s Contribution***

*[1,2,5]Substantial contributions to the conception or design of the work; or the acquisition, interpretation of data for the work, [3,4]Drafting the work or revising it critically for important intellectual content, [4,6]Final approval of the version to be published,*

*Conflict of interest: None*

*Funding source: None*

*Article received: 28-03-26*

*Article accepted: 07-06-26*

*Correspondence*

*Javaria Aslam*

*javaslam50@gmail.com*

A B S T R A C T

Background: Chronic Obstructive Pulmonary Disease (COPD) is a progressive illness characterized by considerable mortality and morbidity. Metformin may help with COPD in more ways than just lowering blood sugar levels. It might additionally possess anti-inflammatory properties.

Objective: To evaluate the effect of metformin on acute exacerbations, pulmonary function, and quality of life in non-diabetic COPD patients.

Methodology: In this single-center, pragmatic randomized controlled trial, 152 non-diabetic COPD patients were randomly assigned either metformin (500 mg twice daily) or conventional treatment for a duration of 6 months. The primary outcome was how often acute exacerbations were experienced. Secondary outcomes encompassed change in pulmonary function tests, functional status through COPD Assessment Test (CAT), the BODE Index, and HbA1c levels.

Results: Total 144 patients completed randomization process among both groups. After 6 months, pulmonary functions, FEV1(52.6±10.2 Vs. 46.4±11.8, p<.001), FVC (72.1±8.1 Vs. 66.6±11.6, P<.001), and FEV1/FVC (72.6 ± 8.3 Vs. 69.1±9.1, p=.01) were significantly improved in the metformin group compared with the control group. There was no statistically significant difference in the frequency of acute exacerbations (3.19±2.7 Vs. 3.5±3.1, p=0.55), CAT score (15.8 ±10.6 Vs. 15.5±9.2, p=.86), mMRC (1.46±1.2 Vs. 1.4±1.1, p=.94) or BODE Index (3.1±2.5 Vs. 3.06±2.5, p=.47) across the groups. The metformin group had a more significant decrease in HbA1c (5.38 ± 0.27% vs 5.83 ± 0.58%; p<0.001).

Conclusion: Metformin significantly improved pulmonary function but failed to decrease exacerbation frequency or improving quality of life in non-diabetic COPD patients. Its key advantage is still controlling blood sugar levels.

Keywords: COPD, Metformin, Acute Exacerbations, Pulmonary Function

## Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a major global contributor to morbidity and mortality, currently identified as the third highest cause of death globally.[1] It has been characterized by a gradual, irreversible reduction in airflow and persistent inflammation, typically caused by prolonged exposure to cigarette smoke or other harmful particles. [2,3] Acute exacerbations of COPD (AECOPD) considerably deteriorate patient outcomes, elevate healthcare burden, and constitute the principal factors contributing to hospital admissions and economic burdens in COPD management.[4,5]

Standard pharmacological therapy, such as bronchodilators, inhaled corticosteroids, and combination regimens, alleviate symptoms and decrease exacerbation frequency; however, they fail to target the fundamental inflammatory or declining mechanisms integral to COPD disease process.[6,7] Research indicates that oxidative stress, persistent inflammation, and expedited pulmonary ageing are critical factors in disease advancement and acute deterioration.[8,9] Consequently, there exists growing interest in treatments that can target these processes and perhaps alter the progression of COPD.

Metformin is a first-line oral medication for Type 2 Diabetes Mellitus (T2DM) that is commonly used because it works well, is safe, and is cheap [10] In addition to its antihyperglycemic activity, metformin has antioxidant and anti-inflammatory effects, mainly by activating AMP-activated protein kinase (AMPK) and blocking pro-inflammatory signaling pathways.[11] Observational studies suggest that metformin may lower the likelihood of exacerbations and enhance outcomes in individuals with COPD and diabetes.[12] Nonetheless, evidence from randomized controlled studies in non-diabetic groups is still scarce and equivocal.

The objective of this study is to assess the impact of metformin on the incidence of acute exacerbations, pulmonary function, and quality of life in non-diabetic individuals with COPD. We postulate that metformin, by its multifaceted properties, may decrease frequency of exacerbations and enhance clinical outcomes in these individuals.

## Methodology

The study design was a pragmatic, prospective two-arm, randomized controlled trial comparing metformin group (investigation group) with a control group of standard care, conducted at the Department of Medicine, Bahawal Victoria Hospital, Bahawalpur, from March 2023 to February 2024. The study was approved by the Ethical Review Committee vide no. ERC/268-31/QMC.

A total of 152 patients were randomized into two groups: 75 patients were allocated to the metformin group and 77 to the control group. All randomized patients were followed up at 3 months and again at 6 months. At the 6-month follow-up, 72 patients in the metformin group and 72 patients in the control group completed the study. Thus, 3 patients from the metformin group and 5 patients from the control group did not complete the 6-month follow-up.

Participants fulfilling the inclusion criteria were eligible for the study: informed consent, as documented by signature; minimum age 35 years and confirmed COPD (GOLD grades 2–4, according to GOLD guidelines), a smoking history of at least 10 pack-years, and a post-bronchodilator forced expiratory volume in one second (FEV1/FVC) ratio of less than 0.7. All the patients should be non-diabetic with HbA1c below 5.7%. Exclusion criteria were mental or physical disability, severe uncontrolled comorbidities, pregnancy or lactation, BMI <18.5 kg/m², known diabetes with HbA1c >6.4% and other long-term lung disorders. Any adverse events occurring during the outpatient visit, such as, gastrointestinal symptoms, lactic acidosis, increased respiratory symptoms, or cardiac events, were recorded and reported to the Ethical committee.

A total of 144 participants were randomly assigned to standard COPD care (control group) or metformin plus standard COPD care (study group) in 1:1 ratio. All individuals with confirmed COPD and referral to the chest department of Bahawal Victoria Hospital, were invited consecutively to participate in the study. All patients got the best possible care for their COPD according to GOLD recommendations.

At the beginning, three months later, and six months later, participants were tested for:

Acute exacerbations in term of worsening of symptoms requiring additional treatment or hospitalization, (2) Pulmonary function tests (FEV1, FVC, FEV1/FVC) through spirometry, (3) BODE Index (includes BMI, FEV1, distance walked in 6 minutes and modified medical research council dyspnea scale), (4) mMRC (Modified medical research council dyspnea scale) ranging from Grade 0 (breathleass with strenuous exercise, Grade 1, dyspneic when hurrying , Grade 2, stops to breathe on level ground, Grade 3, stops for breath after walking 100 meters, to Grade 4, too breathless to leave home. (5) HbA1c and (6) COPD Assessment Test (CAT) score, calculated through the CAT website.

The severity of CPOD will be assessed according to GOLD criteria given in Table 1.

Table 1. GOLD Classification of COPD

| GOLD Stage | Severity | FEV1 (% predicted, post-bronchodilator) |
|---|---|---|
| GOLD 1 | Mild | FEV1 ≥ 80% |
| GOLD 2 | Moderate | 50% ≤ FEV1 < 80% |
| GOLD 3 | Severe | 30% ≤ FEV1 < 50% |
| GOLD 4 | Very severe | FEV1 < 30% |

Primary outcome: No of acute exacerbations during the follow up period in term of requirement of additional treatments or hospital admissions for worsening dyspnea.

Secondary outcomes: Secondary outcomes were any change in FEV1/FVC, CAT score and BODE index to assess the disease progression among COPD patients. Any change in HbA1C was also noted as secondary outcome.

Table 2. BODE Index.

| | Points on BODE Index | | | |
|---|---|---|---|---|
| Variables | 0 | 1 | 2 | 3 |
| FEV1(% of predicted) | ≥65 | 50-64 | 36-49 | <35 |
| Distance walked in 6 min(m) | ≥350 | 250-349 | 150-249 | ≤149 |
| mMRC | 0-1 | 2 | 3 | 4 |
| BMI kg/m$^2$ | >21 | ≤21 | | |

Statistical Analysis: Data were analyzed using IBM SPSS version 26.0. Categorical variables were summarized as frequencies and percentages; continuous variables as mean ± SD. Group comparisons were made using independent t-tests or chi-square tests as appropriate. P<0.05 was considered statistically significant.

## Results

Among the 144 participants, 90% were male, mean age was 53.3 ± 8.2 years, and 66.7% resided in rural areas. Baseline demographic and clinical characteristics were comparable between groups (Table 3).

Pulmonary Functions and clinical parameters are compared among both groups after 3 months of randomization (Table 4).

After six months of randomization, participants who used the metformin were more likely to have better pulmonary function (higher FEV1, FVC, and FEV1/FVC) and improved glycemic control (lower HbA1c). However, there were no significant differences in the frequency of acute exacerbations, CAT score, or BODE Index between the groups Table 5.

| Table 3. Baseline Demographic and Clinical Characteristics Between the Groups. | | | |
|---|---|---|---|
| Characteristics | Metformin (n=72) | Control (n=72) | p-value |
| Male, n (%) | 64 (88.9%) | 66 (91.7%) | 0.39 |
| Female, n (%) | 8 (11.1%) | 6 (8.3%) | |
| Mean Age ±SD | 52.9±7.1 | 53.7±9.2 | .56 |
| Rural residence, n (%) | 48 (66.7%) | 48 (66.7%) | 0.57 |
| Smoking years (mean ± SD) | 22.49 ± 7.00 | 23.96 ± 7.97 | 0.24 |
| BMI (kg/m², mean ± SD) | 25.95 ± 3.17 | 26.20 ± 4.43 | 0.69 |
| HbA1c (% mean ± SD) | 5.43 ± 0.19 | 5.42 ± 0.20 | 0.63 |
| Comorbidities: | | | 0.12 |
| - CVA | 0 (0%) | 3 (4.2%) | |
| - Hypertension | 13 (18.1%) | 3 (4.2%) | |
| - None | 59(81.9%) | 66 (91.6%) | |
| FEV1 (% of predicted) Mean ±SD | 50.6±9.9 | 47.2±11.2 | .05 |
| FVC (% of predicted) (Mean ±SD) | 72.7±8.3 | 69.1±11.7 | .03 |
| FEV1/FVC (Mean ±SD) | 69.2±8.1 | 67.9±8.3 | .34 |
| No. of exacerbations in previous 3 months (Mean ±SD) | 4±2.9 | 3.3±2.8 | .12 |
| CAT Score (Mean ±SD) | 16.8±10.7 | 16.25±9.4 | .73 |
| 6 Minute Walk Distance (Mean ±SD) | 331.5±108.1 | 345.9±123.1 | .45 |
| mMRC Dysponea Scale (Mean ±SD) | 1.5±1.1 | 1.2±1.1 | .08 |
| BODE Index (Mean ±SD) | 3.19±2.4 | 2.85±2.4 | .39 |

No cases of lactic acidosis occurred. Gastrointestinal symptoms were managed by switching to extended-release metformin.

| Table 4. Pulmonary Function and Clinical Parameters 3 months Post-randomization | | | |
|---|---|---|---|
| Parameter | Metformin (n=72) | Control (n=72) | p-value |
| HbA1C | 5.4±0.18 | 5.5±.35 | 0.001 |
| FEV1 (% predicted, mean ± SD) | 50.8±11.5 | 46.9±11.4 | 0.04 |
| FVC (% predicted, mean ± SD) | 72.3±7.8 | 68.1±11.7 | 0.012 |
| FEV1/FVC (mean ± SD) | 69.9±11.7 | 68.4±8.8 | 0.378 |
| CAT Score (mean ± SD) | 16.1±10.7 | 15.6±9.4 | 0.73 |
| 6-minute walk distance (mean ± SD, meters) | 337.8±110.5 | 342.7±130.2 | 0.81 |
| Number of exacerbations in last 3 months | 3.3±2.4 | 3.1±3.1 | 0.70 |
| mMRC Dyspnea Scale (mean ± SD) | 1.5±1.2 | 1.2±1.02 | 0.271 |
| BODE Index (mean ± SD) | 3.1±2.5 | 3.06±2.5 | 0.844 |

## Discussion

This randomized controlled trial explored the impact of metformin on acute exacerbations and clinical outcomes in non-diabetic individuals with COPD. Our results suggest that metformin significantly improved pulmonary function parameters, such as FEV1, FVC, and FEV1/FVC ratios. However, it did not significantly lower the number of acute exacerbations or improve quality of life, as measured by the CAT score or the BODE index, during the six-month follow-up period. The notable enhancement in spirometric values reported in the metformin group corresponds with studies indicating that metformin's anti-inflammatory and antioxidant properties may enhance lung structure and function.[13] Metformin promotes AMP-activated protein kinase (AMPK), which has been demonstrated to diminish airway inflammation, alleviate oxidative stress, and regulates cellular metabolism and autophagy, potentially decelerating the advancement of airway remodeling in COPD.[14,15] Animal studies have corroborated this by demonstrating less emphysematous alterations and a decelerated disease progression subsequent to metformin administration.[16]

Our findings contribute to the existing evidence by validating enhancements in lung function across a clinical cohort of non-diabetic COPD patients. Nonetheless, the absence of a substantial disparity in acute exacerbation frequency and clinical indices, including CAT and BODE scores, between the metformin and control groups aligns with other preceding clinical trials.[17,18] In a randomized controlled trial with non-diabetic COPD patients, Hitchings et al.[17] determined that metformin did not influence exacerbation rates or quality of life, despite minor enhancements in metabolic indicators. Likewise, a systematic review and meta-analysis conducted by Zhu et al.[18]determined that although metformin may provide safety and some advantages in pulmonary function, its impact on clinical outcomes in non-diabetic COPD patients is still restricted. These results indicate that although metformin may enhance specific physiological markers, its conversion into significant

therapeutic advantages for symptom burden or exacerbation risk remains ambiguous, particularly in non-diabetic people.

A major finding in our study is the notable decrease in HbA1c in the metformin group relative to controls. This confirms metformin's well-known ability to lower blood sugar levels[19] and shows that it is safe and has metabolic benefits even for people with chronic lung disease who don't have diabetes. The lack of severe side effects, such as lactic acidosis—a theoretical worry in individuals with chronic respiratory diseases—reinforces the growing evidence about the safety of metformin in the COPD population.[20,21] Some studies have indicated metformin's extensive preventive function, including decreased mortality and hospitalization rates in COPD patients with concurrent diabetes, potentially attributable to its anti-inflammatory and endothelial-protective properties.[12,22]

Our results must be understood within the framework of many restrictions. The study was executed at a single Centre, and the sample population was primarily male, which may restrict generalizability. The follow-up period was relatively brief (six months), potentially inadequate to assess long-term impact on exacerbation rates or disease progression. Additionally, the removal of patients with substantial comorbidities or severe disease may have resulted in a selection bias, favoring individuals with comparatively stable COPD.

Despite these constraints, this study provides significant evidence to the developing domain of COPD management. The findings corroborate recent studies suggesting that the advantages of metformin in non-diabetic COPD patients may primarily be limited to physiological enhancements in lung function, lacking a definitive decrease in acute exacerbation rates or significant advancements in patient-centered outcomes.[17,18,23] Subsequent multicenter investigations with bigger and more heterogeneous populations, extended follow-up periods, and the examination of metformin's impact on certain COPD phenotypes characterized by significant systemic inflammation or metabolic dysfunction, are essential.[24]

In conclusion, metformin enhanced pulmonary function in non-diabetic COPD patients; however, it did not markedly decrease exacerbation frequency or enhance clinical indicators of disease burden and quality of life. Its key advantage is still its ability to control blood sugar and its possible safety profile, not its ability to change the course of COPD in people who don't have diabetes.

## Conclusion

Metformin improved pulmonary function in non-diabetic COPD patients; however, it did not significantly decrease acute exacerbations or enhance clinical outcomes. Its role in COPD management seems restricted to its anti-hyperglycemic properties.

.

## References


1. Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380(9859):2095-128. doi:10.1016/S0140-6736(12)61728-0.
2. Mannino DM, Buist AS. Global burden of COPD: risk factors, prevalence, and future trends. Lancet. 2007;370(9589):765-73. doi:10.1016/S0140-6736(07)61380-4.
3. Lu HH, Zeng HH, Chen Y. Early chronic obstructive pulmonary disease: a new perspective. Chronic Dis Transl Med. 2021;7(2):79-87. doi:10.1016/j.cdtm.2021.02.003.
4. Press VG, Konetzka RT, White SR. Insights about the economic impact of chronic obstructive pulmonary disease readmissions post implementation of the hospital readmission reduction program. Curr Opin Pulm Med. 2018;24(2):138-46. doi:10.1097/MCP.0000000000000454.
5. Sorge R, DeBlieux P. Acute exacerbations of chronic obstructive pulmonary disease: a primer for emergency physicians. J Emerg Med. 2020;59(5):643-59. doi:10.1016/j.jemermed.2020.07.001.
6. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: 2023 report. Available from: GOLD 2023 Report. Accessed June 2024.
7. Tashkin DP, Strange C. Inhaled corticosteroids for chronic obstructive pulmonary disease: what is their role in therapy? Int J Chron Obstruct Pulmon Dis. 2018;13:2587-601. doi:10.2147/COPD.S172240.
8. Kukrety SP, Parekh JD, Bailey KL. Chronic obstructive pulmonary disease and the hallmarks of aging. Lung India. 2018;35(4):321-7. doi:10.4103/lungindia.lungindia_266_17.
9. Bezerra FS, Lanzetti M, Nesi RT, et al. Oxidative stress and inflammation in acute and chronic lung injuries. Antioxidants. 2023;12(3):548. doi:10.3390/antiox12030548.
10. Drzewoski J, Hanefeld M. The current and potential therapeutic use of metformin—the good old drug. Pharmaceuticals (Basel). 2021;14(2):122. doi:10.3390/ph14020122.

11. Rena G, Hardie DG, Pearson ER. The mechanisms of action of metformin. Diabetologia. 2017;60(9):1577-85. doi:10.1007/s00125-017-4342-z.
12. Bishwakarma R, Zhang W, Lin YL, Kuo YF, Cardenas VJ, Sharma G. Metformin use and health care utilization in patients with coexisting chronic obstructive pulmonary disease and diabetes mellitus. Int J Chron Obstruct Pulmon Dis. 2018;13:793-800. doi:10.2147/COPD.S150047.
13. Park CS, Bang BR, Kwon HS, et al. Metformin reduces airway inflammation and remodeling via activation of AMP-activated protein kinase. Biochem Pharmacol. 2012;84(12):1660-70. doi:10.1016/j.bcp.2012.09.025.
14. Rena G, Hardie DG, Pearson ER. The mechanisms of action of metformin. Diabetologia. 2017;60(9):1577-85. doi:10.1007/s00125-017-4342-z.
15. Bezerra FS, Lanzetti M, Nesi RT, et al. Oxidative stress and inflammation in acute and chronic lung injuries. Antioxidants.2023;12(3):548. doi:10.3390/antiox12030548.
16. Polverino F, Wu TD, Rojas-Quintero J, et al. Metformin: experimental and clinical evidence for a potential role in emphysema treatment. Am J Respir Crit Care Med. 2021;204(6):651-66. doi:10.1164/rccm.202012-4510OC.
17. Hitchings AW, Lai D, Jones PW, Baker EH. Metformin in severe exacerbations of chronic obstructive pulmonary disease: a randomised controlled trial. Thorax. 2016;71(7):587-93. doi:10.1136/thoraxjnl-2015-208035.
18. The article matching this topic is: Zhu A, Teng Y, Ge D, Zhang X, et al. Role of metformin in treatment of patients with chronic obstructive pulmonary disease: a systematic review. J Thorac Dis. 2019;11(10):4371-8. doi:10.21037/jtd.2019.09.84.
19. Drzewoski J, Hanefeld M. The current and potential therapeutic use of metformin—the good old drug. Pharmaceuticals (Basel). 2021;14(2):122. doi:10.3390/ph14020122.
20. Salpeter SR, Greyber E, Pasternak GA, Salpeter EE. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. Cochrane Database Syst Rev. 2010;(4):CD002967. doi:10.1002/14651858.CD002967.pub4.
21. Hitchings AW, Archer JR, Srivastava SA, Baker EH. Safety of metformin in patients with chronic obstructive pulmonary disease and type 2 diabetes mellitus. COPD. 2015;12(2):126-31. doi:10.3109/15412555.2015.898052.
22. Mendy A, Gaughan DM, Salo PM, et al. Reduced mortality from lower respiratory tract disease in adult diabetic patients treated with metformin.
23. Sexton P, Metcalf P, Kolbe J. Respiratory effects of insulin sensitisation with metformin: a prospective observational study. COPD. 2014;11(2):133-42. doi:10.3109/15412555.2013.808614.
24. Burke H, Wilkinson TMA. Unravelling the mechanisms driving multimorbidity in COPD to develop holistic approaches to patient-centred care. Eur Respir Rev. 2021;30(160):210041. doi:10.1183/16000617.0041-2021.