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# Effects of Metformin Alone versus in Combination with Other Oral Anti-Diabetic Drugs on the Immuno-Inflammatory Status in Chronic Obstructive Pulmonary Disease Patients with Type Two Diabetes in Suez Canal University Hospitals, A Comparative Descriptive Cross-sectional Study

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## ABSTRACT

**Background:** Chronic obstructive pulmonary disease (COPD) is a progressive inflammatory condition frequently complicated by type 2 diabetes mellitus (T2DM). Metformin, the first-line therapy for T2DM, possesses anti-inflammatory and antioxidant properties that may modulate systemic inflammation in COPD. However, the impact of metformin alone or combined with other oral antidiabetic drugs (OADs) on immuno-inflammatory markers in COPD patients remains underexplored.

**Objective:** To evaluate the effects of metformin, alone or in combination with other OADs, on clinical, biochemical, and inflammatory parameters in controlled COPD patients with coexisting T2DM.

**Methods:** This comparative descriptive cross-sectional study was conducted on 200 participants (40 per group) at Suez Canal University Hospital. Group A included COPD patients without T2DM; Group B, COPD + T2DM on metformin alone; Group C, COPD + T2DM on metformin plus other OADs; Group D, T2DM on metformin alone; Group E, T2DM on metformin plus other OADs. Clinical assessment included Modified Medical Research Council (mMRC) Dyspnea Scale, pulmonary artery pressure (PAP), and duration of disease. Laboratory evaluation comprised fasting blood glucose, serum insulin, total leukocyte count, neutrophil and lymphocyte counts, and serum interleukin-1β (IL-1β).

**Results:** No significant differences were found among COPD groups in age, gender distribution, residency, duration of COPD, mMRC grades, PAP, fasting glucose, insulin, or complete blood count parameters ($p>0.05$). IL-1β levels were significantly higher in COPD without T2DM ($10.2 \pm 2.1$ ng/mL) compared to all other groups ($p<0.001$), with no significant difference between metformin-alone and metformin-combination groups. Both metformin regimens were associated with lower IL-1β compared to COPD without diabetes.

**Conclusion:** Metformin, whether alone or combined with other OADs, is associated with reduced systemic inflammation—as indicated by lower IL-1β levels—in COPD patients with T2DM. These findings support the potential anti-inflammatory benefits of metformin in this population, although further longitudinal studies are warranted to confirm these effects and assess clinical outcomes.

**Keywords:** Type 2 Diabetes Mellitus, Metformin Therapy, Inflammatory Parameters, COPD Patients.

## INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a leading global health problem, affecting over 380 million people worldwide and ranking among the top causes of morbidity and mortality [(1)].

It is characterized by persistent, progressive airflow limitation and an exaggerated inflammatory response to noxious particles and gases [(2)].

Beyond its respiratory manifestations, COPD is now recognized as a systemic inflammatory condition affecting multiple organs [(3)].

Comorbidities substantially influence COPD prognosis and healthcare costs, with type 2 diabetes mellitus (T2DM) being one of the most prevalent [(4)]. Shared risk factors—including chronic inflammation, oxidative stress, aging, and corticosteroid exposure—contribute to this association [(5)].

T2DM affects more than 500 million adults globally and its prevalence continues to rise despite therapeutic advances [(6)]. In patients with both COPD and T2DM, dysregulated cytokine production—particularly increased interleukin-1β (IL-1β), IL-6, and tumor necrosis factor-α (TNF-α)—may exacerbate systemic inflammation and tissue damage [(7)].

Interestingly, some evidence suggests T2DM may confer a short-term survival advantage in COPD exacerbations, possibly due to the modifying effects of antidiabetic therapies [(8)]. Metformin, the first-line drug for T2DM, not only improves glycemic control but also exhibits anti-inflammatory and antioxidant effects that may benefit respiratory health. Experimental studies have shown metformin reduces airway glucose flux and bacterial growth in hyperglycemia, while clinical observations suggest improved respiratory function and symptom control in COPD–T2DM patients on metformin [(9)].

Given these observations, it is important to clarify whether metformin alone or combined with other oral antidiabetic agents can modulate systemic inflammation and improve clinical outcomes in patients with COPD and T2DM.

So, this study aimed to evaluate the impact of type 2 diabetes mellitus and metformin therapy, either alone



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or in combination with other oral antidiabetic agents, on clinical characteristics, biochemical parameters, and inflammatory markers in patients with chronic obstructive pulmonary disease, type 2 diabetes mellitus, or both.

Specifically, to compare demographic factors, disease duration, fasting blood glucose, fasting serum insulin, white blood cell counts, neutrophil and lymphocyte levels, serum interleukin-1β, dyspnea scores, and pulmonary artery pressure among defined patient groups.

## PATIENTS AND METHOD

A comparative descriptive cross-sectional study was conducted from November 2022 to June 2023 at the Chest and Internal Medicine outpatient clinics, Suez Canal University Hospital, Ismailia, Egypt.

**Study population:**

The study included adult patients (≥40 years) with stable chronic obstructive pulmonary disease (COPD) and/or type 2 diabetes mellitus (T2DM). COPD diagnosis followed the GOLD criteria and patients were on regular treatment for at least one year with no acute exacerbation in the previous month. T2DM patients had been on metformin alone or in combination with other oral antidiabetic drugs for ≥6 months.

**Inclusion criteria:**

- Adults (≥40 years) with stable COPD and/or T2DM.
- COPD patients: GOLD Grade 1–3, no exacerbation in the last month.
- T2DM patients: on metformin alone or combined with other oral antidiabetics for ≥6 months.

**Exclusion criteria**:

- Insulin therapy.
- Acute COPD exacerbation in the last month.
- Concomitant inflammatory, infectious, or systemic diseases (e.g., hypertension, liver, renal, autoimmune, or malignant disorders).

**Sampling method and size:**

Non-probability convenience sampling was used. Based on the prevalence of T2DM among COPD patients (12.7%) and a 5% margin of error, the minimum required sample size was 34 per group. To account for dropouts, 40 patients per group were enrolled, totaling 200 participants.

**Study groups:**

- **Group A:** COPD patients on conventional long-acting bronchodilators.
- **Group B:** COPD + T2DM on metformin only.
- **Group C:** COPD + T2DM on metformin plus other oral antidiabetic agents.
- **Group D:** T2DM on metformin only.
- **Group E:** T2DM on metformin plus other oral antidiabetic agents.

**Data collection and measurements:**

1. **Demographic and clinical data:** Age, sex, residency, disease duration, medical history, and medications.
2. **Laboratory tests:**
   - Hemoglobin, total white blood cells (WBCs), neutrophils, lymphocytes.
   - Fasting blood glucose (FBG) and fasting serum insulin (ELISA).
   - Serum interleukin-1β (IL-1β), IL-6, and tumor necrosis factor-α (TNF-α) (high-sensitivity ELISA).
3. **Cardiopulmonary assessment:**
   - Pulmonary artery pressure (PAP) and left ventricular ejection fraction (LVEF) by echocardiography.
   - Pulmonary function tests (FVC, $FEV_1$, $FEV_1$/FVC) post-bronchodilator using spirometry.
   - GOLD classification for airflow limitation.
4. **Dyspnea severity:** Modified Medical Research Council (mMRC) Dyspnea Scale (grades 0–4).

**Ethical considerations:**

**The study was approved by the Faculty of Medicine, Suez Canal University Ethics Committee. Written informed consent was obtained from all participants. Data confidentiality was maintained, and all participants received appropriate medical care throughout the study. The study adhered to the Helsinki Declaration throughout its execution.**

***Statistical analysis***

Data were analyzed using SPSS version 26. Normality was assessed using the Kolmogorov-Smirnov test. Quantitative variables were presented as mean ± SD and compared using ANOVA or Kruskal–Wallis tests as appropriate. Qualitative variables were presented as frequencies (%) and compared using Chi-square or Fisher's exact tests. A p-value $<0.05$ was considered statistically significant.

**RESULTS**

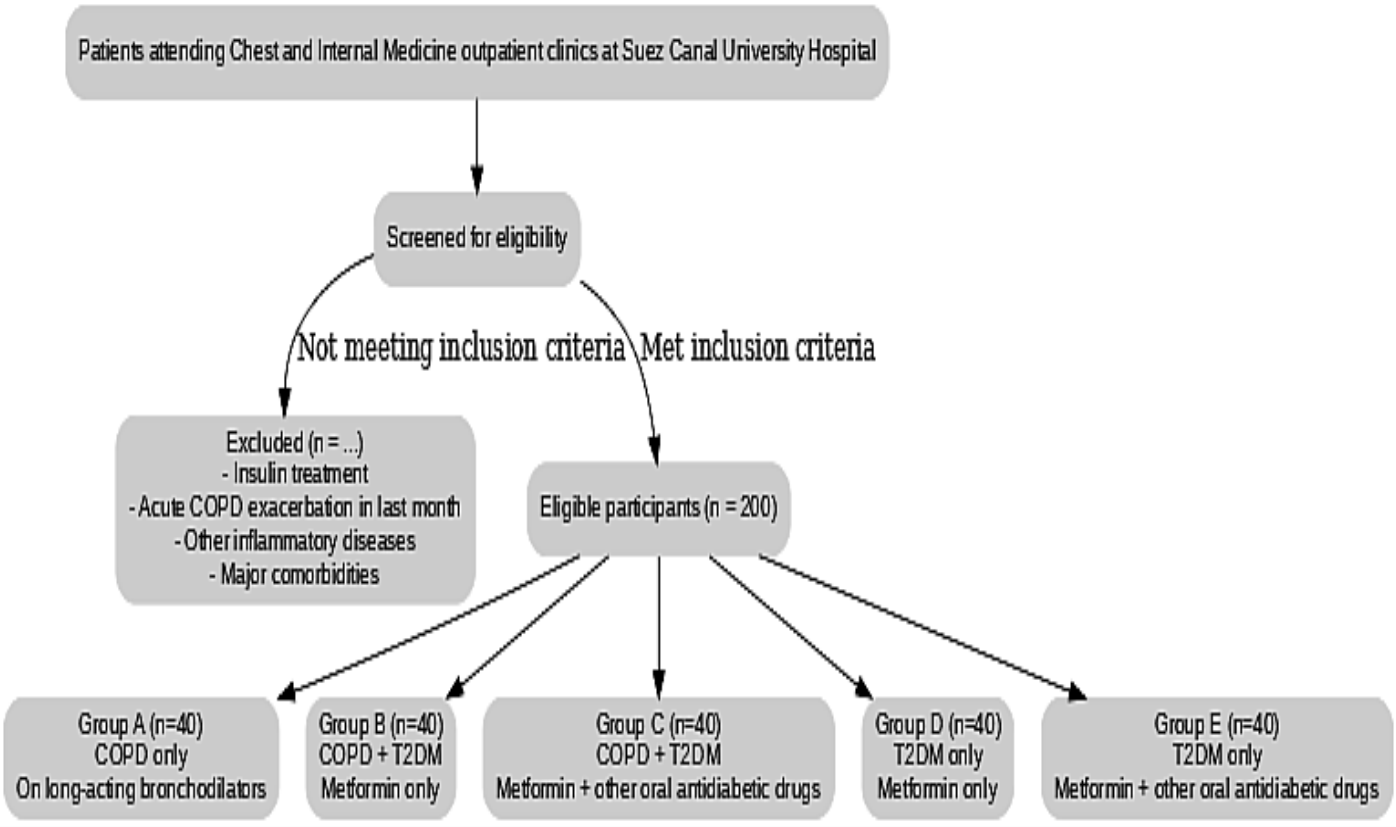


**Figure (1): Consort flowchart.**

The mean age was comparable across all study groups, with no statistically significant difference observed (p = 0.767). Group A had a mean age of 63.9 ± 8.3 years, Group B 64.4 ± 7.9 years, Group C 63.4 ± 7.5 years, Group D 63.4 ± 7.6 years, and Group E 61.9 ± 9.1 years. Regarding residency, urban dwellers were predominant in all groups, ranging from 65% to 82.5%, with no statistically significant variation among groups **(Figure 2)**.

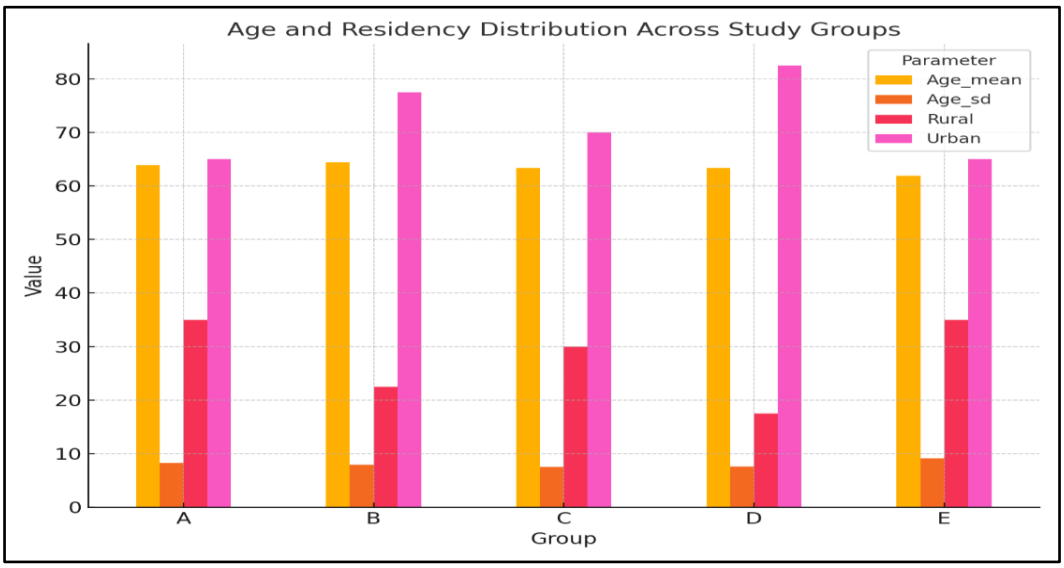


**Figure (2): Age and Residency Distribution of the Studied Groups**

Group A: COPD patients on conventional therapeutic regimens of long-acting bronchodilators. Group B: COPD patients on conventional therapeutic regimens of long-acting bronchodilators with T2DM on metformin only. Group C: COPD patients on conventional therapeutic regimens of long-acting bronchodilators with T2DM on metformin in combination with other anti-diabetic drugs. Group D: T2DM patients on metformin only for at least 6 months. Group E: T2DM patients on metformin and other anti-diabetic for at least 6 months.

Gender distribution did not differ significantly between the groups (p = 0.791). Males represented approximately half of the participants in most groups, with percentages ranging from 45% in Group E to 60% in Group D, while females accounted for the remaining participants **(Figure 3)**.

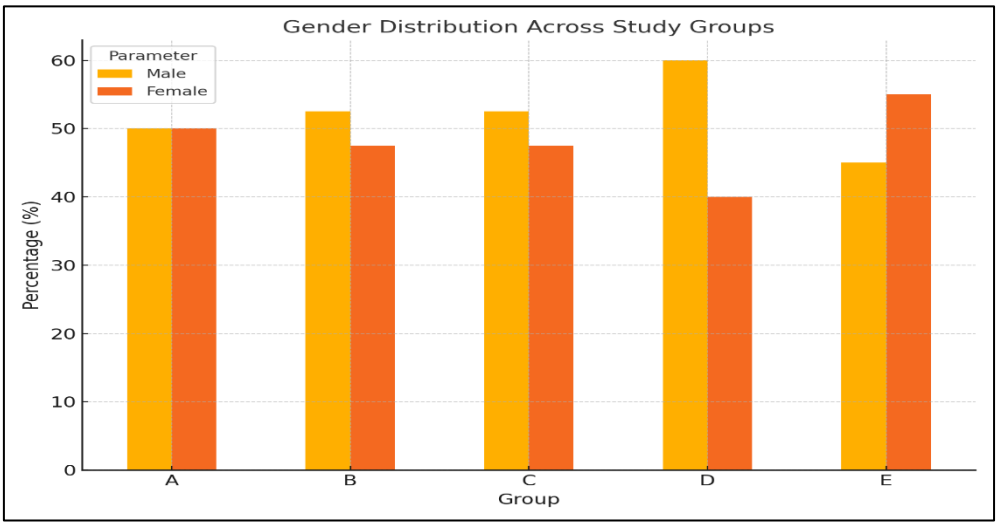


**Figure (3): Gender Distribution among Study Groups**

The mean duration of COPD ranged from 7.6 ± 2.6 years in Group B to 8.6 ± 2.3 years in Group A, with no statistically significant difference (p = 0.146). Similarly, the duration of T2DM varied from 15.1 ± 5.8 months in Group E to 17.7 ± 5.4 months in Group B, without a significant intergroup difference (p = 0.189) **(Figure 4)**.

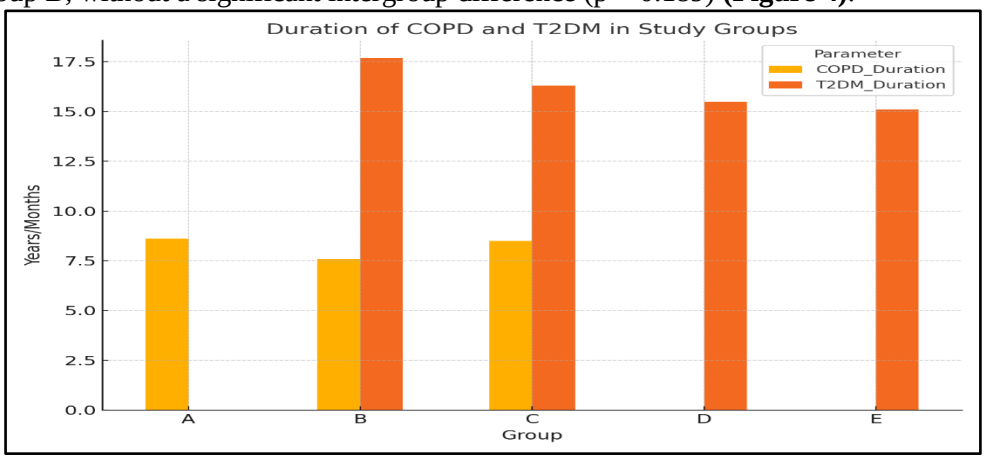


**Figure (4): Duration of COPD and T2DM among Study Groups**

No statistically significant differences were found in fasting blood glucose (FBG) levels across groups (p = 0.291), with means ranging from 127.4 ± 4.8 mg/dL in Group B to 133.3 ± 3.7 mg/dL in Group A. Serum insulin levels were also comparable among groups (p = 0.732), with means ranging from 6.1 ± 2.9 µIU/mL in Group C to 7.3 ± 2.3 µIU/mL in Group A **(Figure 5)**.

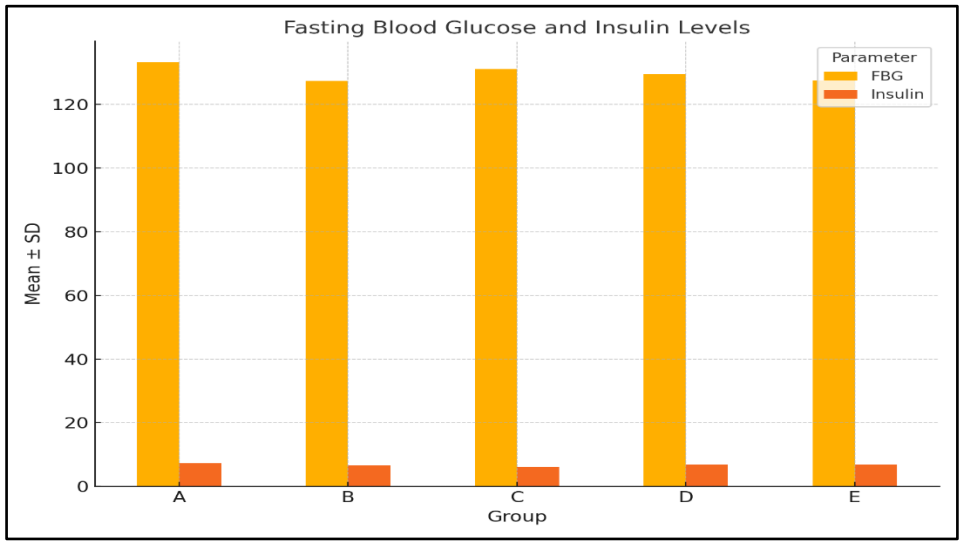


**Figure (5): Fasting Blood Glucose and Serum Insulin Levels among Study Groups.**

No significant differences were revealed in total WBC counts among the groups (p = 0.789), with means ranging from 13.9 ± 2.7 ×10⁹/L in Groups D and E to 14.5 ± 2.7 ×10⁹/L in Group B. Neutrophil counts showed a non-significant trend toward higher values in COPD groups, particularly Group B (6.98 ± 3.1 ×10⁹/L), compared to T2DM-only groups (p = 0.063). Lymphocyte counts were similar across all groups (p = 0.873) **(Figure 6)**.

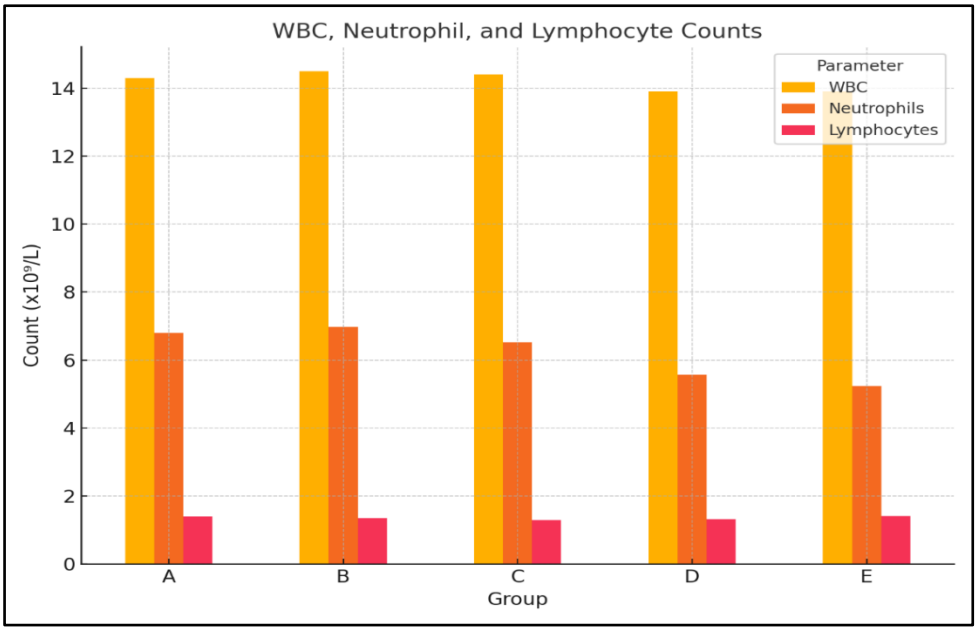


**Figure (6): Total White Blood Cells, Neutrophil, and Lymphocyte Counts among Study Groups.**

Serum IL-1β levels differed significantly between the study groups (p < 0.001). Group A (COPD only) exhibited the highest mean IL-1β concentration (10.2 ± 2.1 ng/mL), which was significantly higher than all other groups (p < 0.05). The lowest levels were observed in Group E (5.8 ± 2.7 ng/mL), followed closely by Groups C, D, and B **(Figure 7)**.

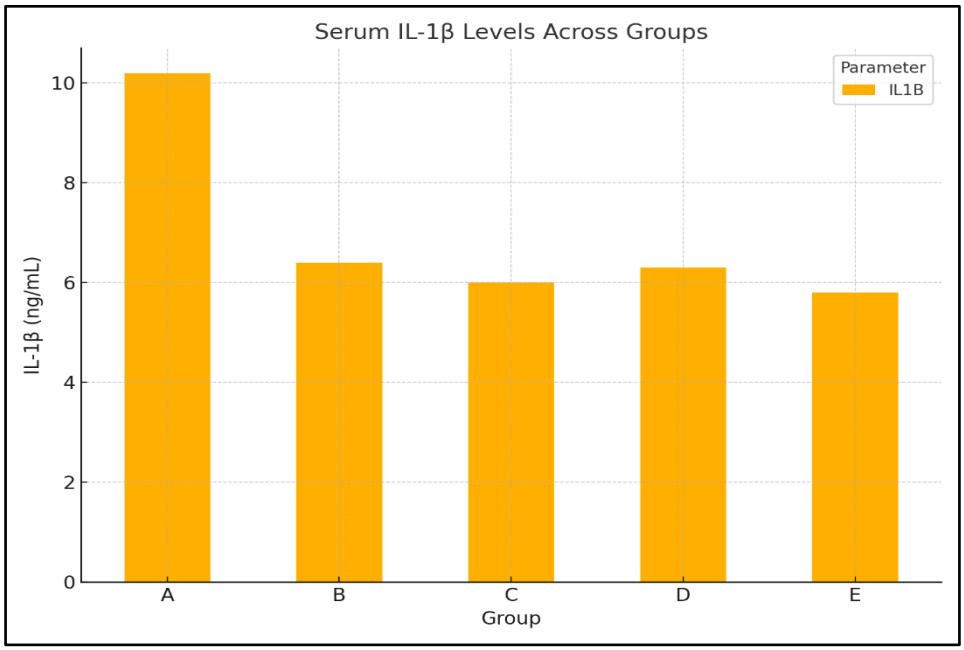


**Figure (7): Serum IL-1β Levels among Study Groups**

**Figure 8** shows that there was no significant difference between the three COPD groups regarding MMRC.

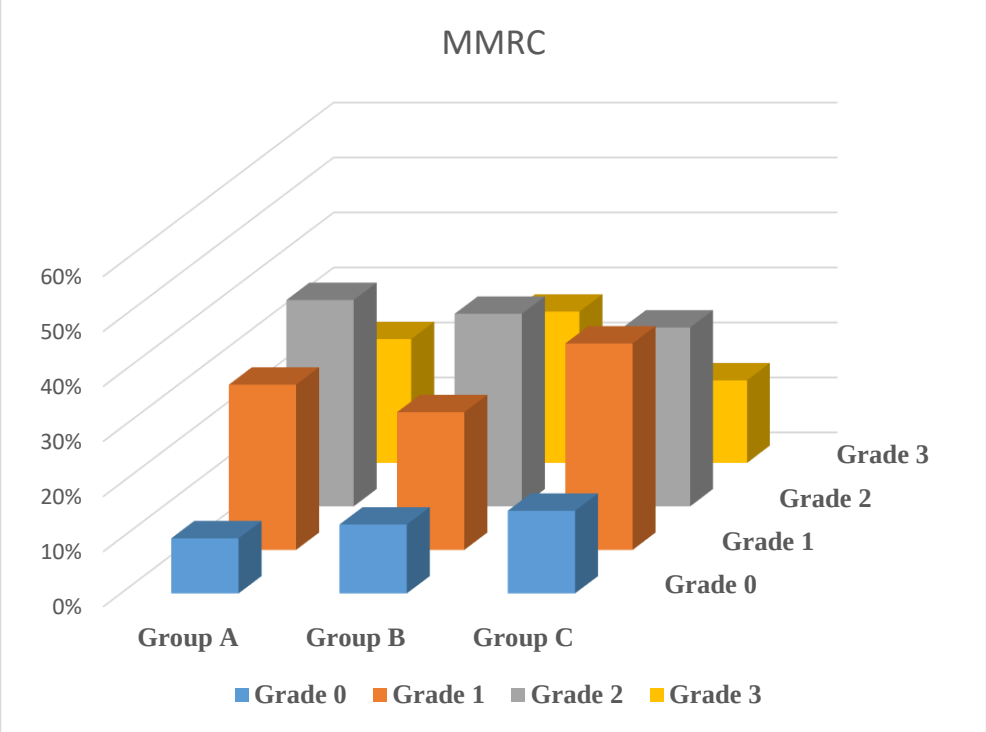


**Figure (8): Comparing MMRC between the Groups A, B, and C.**

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## DISCUSSION

Chronic obstructive pulmonary disease (COPD) remains a major global health problem, affecting an estimated 380 million people and contributing substantially to morbidity and mortality worldwide[10]. Characterized by persistent airflow limitation and chronic airway inflammation, COPD frequently coexists with systemic manifestations and comorbidities [11]. Type 2 diabetes mellitus (T2DM) is a particularly common comorbidity, linked to shared risk factors such as systemic inflammation, oxidative stress, aging, and corticosteroid exposure [12].

T2DM itself is a chronic metabolic disorder characterized by hyperglycemia due to insulin resistance and/or inadequate insulin secretion. The coexistence of COPD and T2DM may amplify inflammatory responses, impair pulmonary function, and influence prognosis [13,14]. Beyond its role in glycemic control, metformin—the first-line oral agent for T2DM—has been shown to exert pleiotropic anti-inflammatory and antioxidant effects, with potential benefits in respiratory diseases [15,16]. These include attenuation of cytokine production, modulation of immune cell activation, and reduction of oxidative stress [17].

Recent studies have suggested that antidiabetic therapy, particularly metformin, may impact COPD outcomes through both direct immunomodulation and indirect effects via improved metabolic control [18,19]. However, there is limited clinical evidence on whether metformin alone or in combination with other oral antidiabetic agents alters inflammatory status, hematologic parameters, or symptom burden in stable COPD patients. Our study addressed this gap by evaluating COPD patients—with or without T2DM—comparing those on metformin monotherapy to those on combination therapy, and assessing associations with key clinical and biochemical parameters.

In the present study, no significant differences were observed in mean age or gender distribution across the five study groups, and the majority of participants resided in urban areas. This aligns with previous reports indicating that COPD prevalence and severity are not consistently influenced by age or sex distribution when patients are matched for disease stage and treatment background [20,21]. Similarly, urban predominance in COPD and T2DM patients has been linked to higher exposure to environmental pollutants and sedentary lifestyles, which may act as shared risk factors for both conditions [10,22].

The mean duration of COPD in groups with and without T2DM was comparable, with no statistically significant differences. Likewise, the duration of T2DM did not differ significantly between diabetic groups, regardless of whether patients were on metformin alone or in combination therapy. These findings are in line with prior evidence that disease chronicity in COPD and T2DM often overlaps due to shared pathophysiological pathways such as systemic inflammation and oxidative stress, but duration alone may not be a determinant of inflammatory burden when patients are clinically stable [23,24].

No significant differences in fasting blood glucose or fasting serum insulin levels were observed among the studied groups. This could be attributed to adequate glycemic control under current therapeutic regimens, as

all diabetic participants were on stable oral antidiabetic therapy for at least six months. Similar outcomes have been reported in controlled T2DM populations, where both metformin monotherapy and combination regimens maintained comparable fasting glucose and insulin levels [15,25]. Moreover, the absence of marked glycemic variation reduces the potential confounding effect of hyperglycemia on inflammatory marker interpretation in COPD [9].

Total WBC counts, neutrophil counts, and lymphocyte counts did not differ significantly between COPD patients with or without T2DM, nor between those on metformin alone versus combination therapy. Prior studies suggest that hematological indices in stable COPD are less influenced by comorbid T2DM when patients are free from acute exacerbations, as acute inflammatory surges predominantly drive leukocytosis and neutrophilia [26,27].

The stability of leukocyte profiles in our cohort supports the selection of a clinically stable population, thereby isolating chronic low-grade inflammation from acute responses.

Serum IL-1β was significantly higher in COPD patients without T2DM compared to all other groups, while diabetic patients (with or without COPD) had lower IL-1β levels. Both metformin monotherapy and combination therapy groups showed comparably reduced IL-1β. These findings support previous evidence of metformin's anti-inflammatory role, where suppression of IL-1β production has been demonstrated in both clinical and experimental models [28,29]. The attenuation of IL-1β in diabetic COPD patients could reflect the immunomodulatory effect of metformin, possibly mediated through AMPK activation and NF-κB inhibition [17,30].

The mMRC dyspnea scale scores did not differ significantly among COPD groups, regardless of T2DM status or antidiabetic regimen. This is consistent with findings that symptom burden in stable COPD is primarily driven by airflow limitation rather than glycemic status when both diseases are under control [31]. Similarly, no significant differences in pulmonary artery pressure were detected, suggesting that neither T2DM nor metformin therapy exerted a measurable influence on pulmonary hemodynamics in the stable disease state.

Collectively, our results indicate that in stable COPD patients with or without T2DM metformin alone or in combination with other oral antidiabetics does not significantly alter demographic distribution, disease duration, glycemic control, hematological indices, or symptom burden, but is associated with a notable reduction in IL-1β levels. This supports the potential anti-inflammatory benefit of metformin in COPD patients with T2DM, consistent with prior literature, and warrants further longitudinal studies to determine whether these effects translate into reduced exacerbation risk or slower disease progression.

## CONCLUSION

This study demonstrated that metformin, whether administered alone or in combination with other oral antidiabetic agents, was associated with a significant reduction in IL-1β levels in COPD patients with coexisting T2DM, while other inflammatory markers, hematological parameters, and clinical measures such as MMRC dyspnea score, pulmonary artery pressure, and lung function remained comparable across groups. These findings suggest that metformin may exert targeted anti-inflammatory effects in this patient population, potentially contributing to better disease modulation. However, as this was a cross-sectional study without longitudinal follow-up, further prospective research is warranted to confirm these effects and to evaluate the impact of metformin-based regimens on COPD exacerbations and long-term clinical outcomes.

**Conflict of interest:** The authors declared no conflicts of interest.
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