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Research Article

Anti-Inflammatory Effects of Metformin and Saxagliptin in Patients with Type 2 Diabetes Mellitus

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Abstract

Introduction: Type 2 diabetes mellitus (T2DM) is a chronic condition characterized by hyperglycemia, insulin resistance, and low-grade inflammation, contributing to complications like cardiovascular disease. Elevated inflammatory biomarkers, such as CRP and IL-6, worsen disease progression and outcomes. Metformin, a first-line therapy for T2DM, and saxagliptin, a DPP-4 inhibitor, are known for their glycaemic benefits and potential anti-inflammatory effects. This study investigates the impact of metformin monotherapy and metformin-saxagliptin combination therapy on inflammatory biomarkers in T2DM to inform more comprehensive treatment strategies.

Materials and Methods: A prospective observational study enrolled 100 newly diagnosed T2DM patients (aged 18–60) from Osmania Medical College, Hyderabad. Participants were divided into two groups: Group A (metformin monotherapy, n=50) and Group B (metformin-saxagliptin, n=50). Serum CRP and IL-6 levels were measured at baseline, 6 months, and 12 months. Statistical analyses included paired t-tests, independent t-tests, and ANOVA, with a significance level of $p < 0.05$.

Results: CRP levels declined significantly in both groups (Group A: 4.66 ± 0.39 to 2.77 ± 0.23; Group B: 4.68 ± 0.37 to 2.78 ± 0.22; p=0.795). IL-6 levels also decreased in both groups, with a greater reduction observed in Group B (32.19 ± 1.26 vs. 28.42 ± 0.65; $p<0.0001$). These findings indicate that both treatments effectively reduce inflammation, but the combination therapy showed superior IL-6 modulation.

Conclusion: Both metformin monotherapy and combination therapy with saxagliptin reduce inflammation in T2DM. Sitagliptin's enhanced effect on IL-6 underscores its potential for optimizing inflammatory and metabolic management.

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1. INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic metabolic condition marked by persistent hyperglycemia and insulin resistance. [1] Beyond its direct metabolic consequences, T2DM is closely associated with chronic low-grade inflammation, which significantly contributes to the development of complications such as cardiovascular disease, nephropathy, and retinopathy. [2,3] Elevated levels of inflammatory biomarkers like C-reactive protein (CRP) and interleukin-6 (IL-6) are often observed in patients with T2DM, as predictors of adverse outcomes. These inflammatory processes worsen glucose metabolism and complicate disease management, making the

study of inflammation in T2DM a crucial aspect of advancing therapeutic approaches. [4]

Metformin and saxagliptin are two commonly prescribed medications for managing T2DM. Metformin, a first-line therapy, primarily reduces hepatic glucose production and improves insulin sensitivity. Saxagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, complements metformin by enhancing glucose-dependent insulin secretion and reducing glucagon levels. Recent research indicates that these drugs may extend their benefits beyond glycaemic control by exerting anti-inflammatory effects. Despite these insights, the mechanisms through which they influence inflammatory biomarkers such as CRP and IL-6 remain insufficiently explored, necessitating further investigation into their potential role in modulating the inflammatory milieu of T2DM. [5,6]

Understanding how metformin and saxagliptin impact inflammatory biomarkers can provide critical insights into the interplay between glycaemic control and inflammation in T2DM. [7] This study aims to assess and compare the effects of metformin alone and with saxagliptin on serum levels of CRP and IL-6. By elucidating these effects, the research seeks to contribute to developing more comprehensive treatment strategies that address both metabolic and inflammatory aspects of T2DM. This dual approach could improve patient outcomes, reduce complication risks, and enhance the quality of life for individuals with this multifaceted condition.

2. MATERIALS AND METHODS

An open-labeled, prospective observational study, "Exploring the Anti-Inflammatory Effects of Metformin and Saxagliptin in Patients with Type 2 Diabetes Mellitus" was conducted at Osmania Medical College, Hyderabad. The study spanned one year, beginning in January 2023, and included newly diagnosed (de novo) T2DM patients attending the outpatient block of the Department of Endocrinology. Inclusion criteria specified patients aged 18–60 years, of either sex, with de novo T2DM and no comorbidities listed in the exclusion criteria. Exclusion criteria included cancer, cardiovascular disease, autoimmune diseases, pulmonary diseases (e.g., COPD), neurodegenerative diseases (e.g., ALS), oral diseases (e.g., periodontitis), fever of unknown origin (FUO), and pregnancy. Institutional Ethics Committee approval was obtained before study initiation.

100 participants meeting the eligibility criteria were recruited and segregated into two groups: Group A (n=50) received metformin monotherapy, while Group B (n=50) received a combination of metformin and saxagliptin. After obtaining informed consent, participants underwent a detailed clinical examination and baseline laboratory investigations, including measurements of serum CRP and IL-6 levels. Venous blood samples were collected at three intervals: baseline (at diagnosis), six months, and 12 months. The study ensured meticulous follow-up to monitor the effects of treatment over time on inflammatory biomarkers.

Statistical analysis was performed using Microsoft Excel, with results expressed as mean ± standard deviation (SD). Paired Student's t-tests were used for within-group comparisons before and after treatment, while independent sample t-tests were applied to analyse differences between the groups. Further, analysis of variance (ANOVA) with post-hoc testing was conducted to evaluate changes across the three intervals. A p-value of less than 0.05 was considered statistically significant. This methodological framework comprehensively assessed the anti-inflammatory effects of metformin and saxagliptin in patients with T2DM.

3. RESULTS

The study included 100 newly diagnosed patients with type 2 diabetes mellitus (T2DM), equally divided into Group A (metformin monotherapy) and Group B (metformin with saxagliptin). The age distribution showed distinct patterns, with Group A skewed younger, having the most significant proportion (34%) in the 20–30 age range, while Group B had the highest concentration (36%) in the 31–40 age range. Gender distribution showed 24 males and 26 females in Group A, while Group B comprised 27 males and 23 females, indicating a slightly higher male proportion in Group B.

C-reactive protein (CRP) levels at baseline were similar between the groups (Group A: 4.66 ± 0.39; Group B: 4.68 ± 0.37, $p = 0.7949$). Both groups consistently declined over time, reaching 2.77 ± 0.23 in Group A and 2.78 ± 0.22 in Group B by 12 months ($p = 0.795$), with no statistically significant differences. This indicates a steady reduction in systemic inflammation in both treatment groups.

Interleukin-6 (IL-6) levels also showed a comparable baseline (Group A: 38.03 ± 1.49; Group B: 38.42 ± 0.88, $p = 0.118$). However, Group B demonstrated a more substantial decline, reaching 28.42 ± 0.65 by 12 months, compared to 32.19 ± 1.26 in Group A ($p < 0.0001$). These findings suggest that while both treatments effectively reduced inflammation, the combination of metformin with saxagliptin significantly impacted lowering IL-6 levels, highlighting its potential as a more effective anti-inflammatory regimen.

4. DISCUSSION

This randomized prospective observational study evaluated the effects of metformin monotherapy and metformin combined with saxagliptin on inflammatory biomarkers in patients with T2DM. The study population was carefully balanced, with 50 participants in each group, ensuring robust comparisons. The baseline characteristics, including age and gender distribution, were consistent with other studies like those by Derosa G *et al.*, [8] and Al Hussona AM *et al.*, [9], highlighting the generalizability of our findings. Baseline inflammatory markers, CRP and IL-6, were comparable across groups, underscoring a uniform starting point for assessing treatment effects.

CRP levels showed a significant decline in both groups over 12 months, demonstrating the anti-inflammatory properties of both interventions. However, our findings aligned with Mansour M *et al.*, [10] in observing no statistically significant differences in CRP levels between groups at follow-up. The consistency of CRP reduction between groups suggests similar efficacy for the two treatments in reducing systemic inflammation. Conversely, IL-6

levels declined more prominently in the metformin-saxagliptin group, a pattern also observed in the Al Hussona AM *et al.,* [9] study. This finding underscores the superior anti-inflammatory potential of the combination therapy, particularly in reducing IL-6, a critical marker in chronic inflammation associated with diabetes. The results indicate that both treatments effectively reduce systemic inflammation, with saxagliptin providing an added benefit in modulating IL-6 levels. These findings align with prior research, bolstering the evidence for the role of DPP-4 inhibitors in managing inflammation in T2DM. The study's balanced design and consistent methodology enhance its reliability, though variations in absolute biomarker levels across studies highlight the influence of population-specific factors. Future research should focus on long-term clinical outcomes and personalized approaches to optimize treatment strategies for managing inflammation in diabetes.

5. CONCLUSION

This study highlights the anti-inflammatory effects of metformin monotherapy and metformin-saxagliptin combination therapy in patients with type 2 diabetes mellitus, as evidenced by significant reductions in CRP and IL-6 levels over 12 months. While both treatments effectively reduced inflammation, the combination therapy demonstrated a more significant impact on IL-6 levels, suggesting enhanced efficacy in modulating inflammatory markers. These findings support the potential benefits of adding saxagliptin to metformin in managing inflammation in T2DM and underscore the need for further research to assess long-term clinical outcomes and develop personalized treatment strategies.

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