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ORIGINAL ARTICLE

Comparative Evaluation of Vildagliptin-Metformin Versus Glimepiride-Metformin on Inflammatory Markers and Glycemic Control in Type 2 Diabetes Mellitus: A Randomized, Open-Label Study

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Abstarct

Background: Type 2 Diabetes Mellitus (T2DM) is a chronic disease characterized by the generation of reactive oxygen species, leading to oxidative stress and chronic low-grade inflammation. **Objective:** To evaluate the efficacy of the Vildagliptin-Metformin versus the Glimepiride-Metformin combination in reducing inflammatory markers and improving glycemic control in T2DM patients. **Materials & Methods:** In this randomized, open-label, comparative study, 80 newly diagnosed T2DM patients, above 18 years of age, of either sex, with HbA1c > 6.5% [as per American Diabetes Association (ADA) criteria], were enrolled. They were divided into Group I (Vildagliptin with Metformin) and Group II (Glimepiride with Metformin). Blood samples for biochemical analysis of glycated hemoglobin (HbA1c), fasting blood glucose (FBS), Interleukin-6 (IL-6), high-sensitivity C-reactive protein (hs-CRP), and erythrocyte sedimentation rate (ESR) were collected at baseline and after 12 weeks. **Results:** The study found a significant reduction in hs-CRP levels in the Vildagliptin-Metformin group (41.39%) compared to the Glimepiride-Metformin group (15.69%) (p=0.001), indicating a more effective anti-inflammatory effect while maintaining comparable glycemic control.**Conclusion:** The Vildagliptin-Metformin combination demonstrated superior efficacy in reducing inflammation in T2DM patients, with glycemic control comparable to the Glimepiride-Metformin combination. These findings suggest that Vildagliptin-Metformin could be a more effective therapeutic option for T2DM management, particularly in reducing inflammation.

Key words

Vildagliptin, Glimepiride, Metformin, Type 2 Diabetes Mellitus, Inflammatory Markers

Introduction

Type 2 Diabetes Mellitus (T2DM) is one of the most common chronic diseases [1]. T2DM arises due to insulin resistance and a progressive loss of adequate beta-cell insulin secretion [2]. As a progressive condition, it leads to various micro and macrovascular complications, including cardiovascular and cerebrovascular diseases, if left untreated [3]. Recent studies have shifted the understanding of DM from solely a metabolic disorder to also an inflammatory condition. Current evidence indicates that chronic low-grade inflammation is a component of insulin resistance, contributing to the development of various complications[4,5]. At the cellular level, chronic

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hyperglycemia exposure leads to oxidative stress and endoplasmic reticulum stress (ER-Stress) through the activation of reactive oxygen species (ROS). This inflammatory process increases the production of inflammatory mediators such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and C-reactive protein (CRP)[6].

Patients with raised glycemic levels, despite lifestyle changes, should initiate therapy [7]. Metformin is approved as the first-line therapy[8]. However, early combination therapy with hypoglycemic drugs is sometimes considered to target multiple pathophysiological mechanisms and delay diabetes-related complications[9]. Glimepiride, a second-generation sulfonylurea, is commonly used as monotherapy or in combination with other hypoglycemic agents[10].

Numerous preclinical and clinical studies have demonstrated that hypoglycemic drugs have anti-inflammatory effects, leading to improved outcomes for diabetic patients[5]. Metformin, through the activation of the AMP-activated protein kinase (AMPK) pathway, inhibits cytokine-induced nuclear factor kappa B (NF-κB) activation and pro-inflammatory responses[11]. In contrast, under hyperglycemic conditions, glimepiride suppresses cytokine production from activated macrophages, inhibits the IL-4/IL-13 signaling pathways, and decreases the production of various inflammatory markers (TNF-α, IL-6, hs-CRP)[10]. Similarly, vildagliptin also limits inflammation by suppressing the NF-κB signaling pathway, as indicated by various animal studies[12].

In this context, the current study aims to evaluate the effect of Vildagliptin versus Glimepiride in combination with Metformin on glycemic and inflammatory markers in T2DM patients.

Materials and Methods

This prospective, open-labeled, randomized, comparative study was conducted after receiving approval from the ethical committee and registration with the Clinical Trials Registry of India. All study details were explained to participants before obtaining their informed consent. Patient recruitment and data collection occurred from December 2021 to December 2022.

Inclusion Criteria: Newly diagnosed T2DM subjects above 18 years, of either sex, with HbA1c >6.5% (as per ADA criteria), were recruited from the Medicine department at Guru Gobind Singh Medical College and Hospital, Faridkot.

Exclusion Criteria: Subjects with diabetes other than T2DM, conditions where inflammatory markers are raised (such as inflammatory bowel disease, systemic lupus erythematosus, rheumatoid arthritis), hepatic or renal impairment, malignancy, and those on anti-inflammatory or immunomodulatory drugs were excluded.

Group Allocation: The first 80 consecutive eligible subjects were randomized into two groups (40 in each group) using a computer-generated random number table.

Group I (n=40): Subjects were administered Vildagliptin (50-100 mg) plus Metformin (500-2000 mg) per oral tablets.

Group II (n=40): Subjects were administered Glimepiride (1-6 mg) plus Metformin (500-2000 mg) per oral tablets.

Dosage Adjustments: The minimum and maximum daily doses of the study drugs were adjusted and titrated based on the patient's plasma glucose level and clinical condition by the treating physician. After screening, subjects were examined and evaluated at baseline (at 0 week) and then at 12 weeks for blood investigations, including FBS, HbA1c, IL-6, hs-CRP, and ESR.

Follow-up: All subjects were followed every two weeks to assess the adequacy of drug dosage and the need for titration.

Statistical analysis

The data were entered as a data matrix in Microsoft® Excel® and analyzed using IBM® SPSS® version 20.0.0.1. Descriptive statistics for categorical variables were presented as frequency and percentage, and for continuous variables as mean and standard deviation. Median and interquartile range were reported for non-normal continuous data. The difference in non-normal continuous data across two groups was explored using the Mann-Whitney U test, and the difference in non-normal continuous data across paired observations was tested using the Wilcoxon test. A p-value of <0.05 was considered statistically significant for the purpose of this study.

Results

Clinical Characteristics: Initial screening identified 118 patients, of which 80 newly diagnosed T2DM patients met the inclusion criteria. Group I comprised 24 females and 16 males, and Group II had 18 females and 22 males. The mean ages were 54.0±8.5 years in Group I and 53.4±10.04 years in Group II. Out of the 80 patients, 40 in Group I and 39 in Group II completed the study. One patient in Group II discontinued the therapy for herbal

medicine alternatives [*Fig-1*]. The demographic and clinical characteristics, including gender distribution, mean age, and baseline levels of FBG, HbA1c, IL-6, hs-CRP, and ESR, are detailed in *Table-1*, showing homogeneity between the groups at baseline.

Changes in Glycemic Level: Both treatment groups showed significant decreases in FBS over the 12-week study period. However, no significant difference in FBS was observed between the two groups at the end of therapy [*Table-2*]. Similarly, both groups exhibited significant reductions in HbA1c from baseline, with no significant difference between the groups at the end of the study [*Table-2*].

Change in Inflammatory Markers: The baseline and post-treatment levels of inflammatory markers (IL-6, hs-CRP, ESR) for both groups are presented in Table-

Table 1 : Baseline Demographic and Clinical Characteristics for Both Study Groups

Variables	Group I (n=40) mean±SD (median)	Group II (n=40) mean±SD (median)	p-value	Statistical Test Used
Gender(male/female)	16/24	22/18	0.336	Chi-Square Test
Mean age (Years)±SD	54.0±8.5	53.4±10.04	0.788	Independent t-test
FBG (mg/dl)	163.0±11 (166.0)	166.0±12 (164.0)	0.511	Mann-Whitney U Test
HbA1c (%)	8.5±0.6 (8.4)	8.6±0.9 (8.6)	0.239	Mann-Whitney U Test
IL-6 (pg/ml)	4.01±1.17 (3.70)	4.59±1.70 (4.69)	0.076	Mann-Whitney U Test
hs-CRP (mg/l)	2.15±0.44 (2.04)	2.23±0.79 (2.25)	0.513	Mann-Whitney U Test
ESR (mm/h)	34.0±1 (34.0)	35.0±2 (35.0)	0.068	Mann-Whitney U Test

p-values indicate significance levels with p<0.05 to 0.01 as significant, p<0.001 as highly significant, and p>0.05 as non-significant. Data is presented as mean±SD (Standard Deviation) ± median and Range.

Table 2 : Comparison of Study Groups at the End of 12 Weeks

Variables	Group I (n=40) mean±SD (median)	Group II (n=39) mean±SD (median)	p-value	Statistical Test Used
FBG (mg/dl)	134±8 (133)	130±10 (131)	0.126	Mann-Whitney U Test
HbA1c (%)	7.6±0.5 (7.4)	7.8±0.8 (7.5)	0.379	Mann-Whitney U Test
IL-6 (pg/ml)	1.83±0.78 (1.55)	2.43±1.32 (1.76)	0.063	Mann-Whitney U Test
hs-CRP (mg/l)	1.26±0.24 (1.19)	1.88±0.73 (1.59)	0.001	Mann-Whitney U Test
ESR (mm/h)	28±1 (28)	30±2 (30)	0.001	Mann-Whitney U Test

p-values indicate significance levels with p<0.05 to 0.01 as significant, p<0.001 as highly significant, and p>0.05 as non-significant. Data is presented as mean±SD (Standard Deviation) ± median and Range.

1 and *Table-2*. While both groups showed decreases in IL-6 levels, the difference between the groups was not significant. However, significant differences were observed in the mean percentage changes of hs-CRP and ESR between Group I and Group II at 12 weeks [*Table-2*].

Discussion

Silent or subclinical inflammation, often not clinically manifest, is a critical concern in diabetic patients. It contributes to various micro and macrovascular complications, imposing a significant clinical and economic burden on the healthcare system. Detecting this silent inflammation is essential, with inflammatory markers such as IL-6, hs-CRP, and ESR playing a vital role in identifying cellular - level inflammation.

Numerous studies suggest that hypoglycemic drugs may have anti-inflammatory effects, potentially improving outcomes for diabetic patients. Our present study aimed to assess the glycemic and anti-inflammatory effects of these drugs in patients with T2DM.

Effect on Glycemic Level: In our study, both Group I (Vildagliptin-Metformin) and Group II (Glimepiride-Metformin) showed reductions in HbA1c and FBS. No statistically significant difference in glycemic levels was observed between the two groups at the end of the 12-week study period, indicating equal efficacy in glycemic management. These results are in line with findings from Kumar *et al*.[13] and Jeon *et al*.[14], which demonstrated comparable efficacy of these drug combinations.

Effect on Inflammatory Markers: Significant reductions in inflammatory markers, including ESR, hs-CRP and IL-6, were observed in both groups. Existing literature suggests that DPP-4 inhibitors, like Vildagliptin, have the potential for anti-inflammatory effects. Vildagliptin can limit inflammation by suppressing the NF-κβ signaling pathway and pro-inflammatory agents such as TNF-α, IL-1β, and IL-6[15]. Above finding aligns with the study by Rizzo *et al*.[16] and Younis *et al*.[17], which reported significant decreases in these inflammatory markers with DPP-4 inhibitors.

However, the mechanism behind Glimepiride's reduction of inflammation is not fully understood, but it may involve actions on ATP-sensitive potassium channels in monocytes/macrophages, reducing inflammation through MAPKs/NF-κα-dependent pathways[10], as indicated in the study by Shrestha *et al*.[18] Our results on the reduction of IL-6, hs-CRP, and ESR levels by Glimepiride-Metformin treatment are consistent with these reports.

Furthermore, our study demonstrated that the addition of Vildagliptin to Metformin for 12 weeks significantly reduced hs-CRP and ESR levels compared to the Glimepiride-Metformin treated group [$p<0.001$], echoing the findings of Derosa *et al*.[19] The combination of Metformin and Vildagliptin may offer a synergistic effect in reducing inflammation, potentially reducing microvascular and macrovascular complications in T2DM patients.

Conclusion

The study demonstrates that the combination of Vildagliptin and Metformin leads to a significant reduction in inflammatory markers, specifically hs-CRP and ESR, compared to the Glimepiride-Metformin combination (41.39% vs. 15.69% and 17.64% vs. 14.28%, respectively, with $p=0.001$ for both). Although both treatments improved glycemic levels, the Vildagliptin-Metformin combination exhibited a superior anti-inflammatory effect. These findings suggest that combining Vildagliptin with Metformin could be a more effective option in the management of T2DM, especially for patients where inflammation is a significant concern.

Future Recommendations: Given the observed paradoxical effects of Vildagliptin, there is a need to further explore its impact on inflammation in patients with Type 2 diabetes. Consequently, future clinical studies with larger sample sizes are essential to resolve this ambiguity. Additionally, other inflammatory and oxidative markers should be considered to comprehensively assess its effects.

Strengths: This study successfully demonstrated the additive anti-inflammatory effect of Vildagliptin, a drug that is increasingly popular, cost-effective, and commonly prescribed for T2DM management. The pronounced anti-inflammatory properties of Vildagliptin, particularly when combined with Metformin, suggest that this combination could be beneficial in the initial therapy of T2DM patients. This may potentially prevent the progression of various macro- and microvascular complications.

Limitations: The study faced several limitations. The short duration of the study may have significantly impacted the results, and the small sample size could limit the generalizability of the findings. Furthermore, the study did not evaluate whether the beneficial effects of the drugs were sustained post-therapy.

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Conflicts of Interest
There are no conflict of Interest

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