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Original Research Article

A Comparative Study of Metformin Monotherapy versus Combination Therapy in Newly Diagnosed Type 2 Diabetes Mellitus Patients

Mohd. Atif Khan[1], Shams Rizwan[2]

[1]Junior Resident, Department of Urology, AIIMS, Raebareli, UP, India
[2]Deputy District Tuberculosis officer. District Tuberculosis Center, District Hospital Raebareli, UP, India

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Corresponding author: Dr. Shams Rizwan
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Abstract

Introduction: Type 2 diabetes mellitus (T2DM) is a progressive metabolic disorder often requiring pharmacological intervention for glycemic control. While metformin is the first-line therapy, early combination with other oral antidiabetic drugs may offer superior glycemic outcomes. This study aimed to compare the efficacy and safety of metformin monotherapy versus metformin-based combination therapy in newly diagnosed T2DM patients.

Materials and Method: A prospective, observational study was conducted on 200 newly diagnosed T2DM patients aged 30–65 years at a tertiary care hospital. Patients were divided into two equal groups: Group A received metformin monotherapy, and Group B received metformin plus another oral antidiabetic agent (e.g., sulfonylurea, DPP-4 inhibitor, or SGLT2 inhibitor). Glycemic parameters—HbA1c, fasting plasma glucose (FPG), and postprandial plasma glucose (PPG)—were recorded at baseline and after six months. Adverse drug reactions (ADRs) were monitored, and data were statistically analysed using appropriate tests.

Results: Both groups showed significant improvement in glycemic control after six months. The combination group showed a greater reduction in HbA1c (1.64 ± 0.55% vs. 1.28 ± 0.52%; p = 0.002), FPG (52.7 ± 22.1 vs. 38.2 ± 20.5 mg/dL; p = 0.001), and PPG (84.9 ± 30.7 vs. 68.6 ± 28.3 mg/dL; p = 0.003). A higher proportion of patients in Group B achieved HbA1c <7% (72% vs. 56%; p = 0.01). Hypoglycemia occurred only in the combination group (6%; p = 0.03).

Conclusion: Early combination therapy provides superior glycemic control compared to metformin alone but carries a higher risk of hypoglycemia, necessitating individualized treatment planning.

Keywords: Type 2 diabetes mellitus, Metformin, Combination therapy, Glycemic control, Hypoglycemia, Oral antidiabetic drugs.

Introduction

Type 2 diabetes mellitus (T2DM) is a chronic, progressive metabolic disorder characterized by persistent hyperglycemia resulting from insulin resistance, impaired insulin secretion, or both. It has emerged as a global health challenge, with the International Diabetes Federation (IDF) estimating that more than 500 million adults worldwide are currently living with diabetes, with projections of approximately 643 million cases by 2030 [1].

The burden is particularly high in Asia, which contributes to over 60% of the global diabetic population, and India is often referred to as the "diabetes capital of the world" due to its rapidly increasing prevalence [2]. The disease is associated with significant morbidity and mortality, largely because of long-term complications affecting cardiovascular, renal, neurological, and ocular systems, which also pose a substantial socioeconomic burden. The cornerstone of T2DM management remains lifestyle modification, including dietary regulation, weight control, and physical activity. However, for most patients, pharmacological therapy becomes necessary to achieve and maintain glycemic targets [3]. Metformin, a biguanide, is universally recommended as the first-line oral antihyperglycemic agent owing to its proven efficacy, favorable safety profile, weight neutrality, low risk of hypoglycemia, and possible cardiovascular benefits [3,4].

Both the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) endorse metformin monotherapy as the initial treatment in drug-naïve patients without contraindications [3]. Nevertheless, the progressive nature of T2DM leads to declining β-

cell function and worsening insulin resistance, causing many patients to fail to achieve or sustain glycemic control with metformin monotherapy alone [5]. Traditionally, therapy has followed a stepwise approach, with additional agents introduced only after monotherapy failure. However, this strategy may delay optimal glycemic control and allow for glycemic burden that contributes to early onset of complications [6]. Consequently, there has been growing interest in the concept of initiating early combination therapy, in which metformin is started alongside another oral antidiabetic drug with a complementary mechanism of action [6,7].

Evidence supporting this approach has emerged from clinical experience and utilization studies demonstrating that newer oral antidiabetic drugs, when combined with metformin, may improve long-term glycemic outcomes [7]. Despite these advantages, early combination therapy is not uniformly adopted due to factors such as drug costs, safety concerns, accessibility, physician preference, and patient adherence.

In regions such as India, where diabetes prevalence is high and healthcare resources are often limited, it is particularly important to identify therapeutic strategies that optimize glycemic outcomes while balancing cost-effectiveness and safety.

Against this background, the present study was designed to compare the efficacy and safety of metformin monotherapy versus metformin-based combination therapy in newly diagnosed T2DM patients. By evaluating glycemic outcomes, treatment tolerability, and adverse effects, this study aims to provide evidence that can guide individualized treatment strategies and improve long-term diabetes care.

Materials and Methods

This was a prospective, comparative, observational study conducted in the Department of Medicine at , a tertiary care teaching hospital. The study aimed to evaluate and compare the efficacy and safety of metformin monotherapy versus metformin-based combination therapy in newly diagnosed type 2 diabetes mellitus (T2DM) patients.

A total of 200 patients with newly diagnosed T2DM were enrolled. Diagnosis was made according to the American Diabetes Association (ADA) criteria: fasting plasma glucose (FPG) ≥126 mg/dL, or 2-hour plasma glucose ≥200 mg/dL during an oral glucose tolerance test, or glycated hemoglobin (HbA1c) ≥6.5%, or a random plasma glucose ≥200 mg/dL in the presence of classic symptoms of hyperglycemia.

Inclusion Criteria

- Age between 30–65 years.
- Newly diagnosed cases of T2DM (diagnosis within the past 6 months).
- Drug-naïve patients who had not received prior antidiabetic pharmacotherapy.
- Patients willing to provide written informed consent.

Exclusion Criteria

- Type 1 diabetes mellitus or secondary diabetes.
- Patients with severe hepatic, renal, or cardiac dysfunction.
- Pregnant or lactating women.
- Patients already on insulin or with contraindications to metformin.
- Known hypersensitivity to study drugs.

Sample Size

A total of 200 patients were included in the study. They were allocated into two groups of 100 patients each:

- **Group A (Monotherapy group):** Patients received metformin monotherapy at standard doses (initial 500 mg twice daily, titrated as tolerated).
- **Group B (Combination therapy group):** Patients received metformin in combination with another oral antidiabetic agent (such as sulfonylurea, DPP-4 inhibitor, or SGLT2 inhibitor), based on physician discretion and patient profile.

Study Procedure

At baseline, detailed demographic, clinical, and laboratory data were collected, including age, sex, body mass index (BMI), blood pressure, fasting plasma glucose (FPG), postprandial plasma glucose (PPG), HbA1c, and lipid profile. Patients were counseled on lifestyle modification and dietary management.

Follow-up visits were scheduled at 1 month, 3 months, and 6 months. At each visit, patients were evaluated for glycemic parameters (FPG, PPG, HbA1c), treatment adherence, and adverse drug reactions (ADRs). HbA1c was assessed at baseline and at 6 months. ADRs were recorded and classified according to WHO-UMC causality categories.

Outcome Measures

- **Primary outcome:** Change in glycemic control (HbA1c, FPG, PPG) between baseline and 6 months.
- **Secondary outcomes:** Incidence of adverse drug reactions, weight changes, and treatment tolerability in the two groups.

Statistical Analysis

Data were analyzed using Statistical Package for the Social Sciences (SPSS) version [21].

Continuous variables were expressed as mean ± standard deviation (SD) and compared using Student's t-test or Mann–Whitney U test, depending on data distribution. Categorical variables were presented as frequencies and percentages, and compared using Chi-square or Fisher's exact test. A p-value <0.05 was considered statistically significant.

Results

The study included a total of 200 patients, with 100 patients each in the monotherapy group (Group A) and the combination therapy group (Group B). The mean age was comparable between the two groups, being 49.2 ± 10.1 years in Group A and 50.0 ± 9.6 years in Group B (p = 0.42). The gender distribution was also similar, with a male-to-female ratio of 58:42 in Group A and 55:45 in Group B (p = 0.68). The mean BMI was 26.4 ± 3.2 kg/m² in Group A and 26.7 ± 3.0 kg/m² in Group B (p = 0.58). Baseline fasting plasma glucose (FPG), postprandial plasma glucose (PPG), and HbA1c values did not differ significantly between the groups, confirming the homogeneity of the study population at baseline (Table 1). At the end of six months, both groups showed significant improvement in glycemic control, but the combination therapy group demonstrated superior outcomes. The mean reduction in HbA1c was greater in Group B (1.64 ± 0.55%) compared to Group A (1.28 ± 0.52%), and this difference was statistically significant (p = 0.002). Similarly, FPG reduction was higher in the combination group (52.7 ± 22.1 mg/dL) compared to the monotherapy group (38.2 ± 20.5 mg/dL) (p = 0.001). Postprandial glucose reduction followed the same trend, with Group B achieving a greater reduction (84.9 ± 30.7 mg/dL) compared to Group A (68.6 ± 28.3 mg/dL) (p = 0.003). Furthermore, a significantly higher proportion of patients in Group B (72%) achieved target HbA1c levels of less than 7% compared to Group A (56%) (p = 0.01) (Table 2). Adverse drug reactions (ADRs) were observed in both groups, but with some notable differences. Gastrointestinal intolerance was reported in 12% of patients in Group A and 10% in Group B, showing no significant difference (p = 0.65). Hypoglycemia, however, occurred exclusively in the combination therapy group, with 6% of patients affected, while none were reported in the monotherapy group, and this difference was statistically significant (p = 0.03). Other adverse events, such as headache and fatigue, were reported in 2% of patients in both groups (p = 1.00). The overall incidence of ADRs was 14% in Group A and 18% in Group B, with no significant difference (p = 0.42) (Table 3).

Table 1. Baseline characteristics of the study population

Parameter	Group A (Monotherapy) (n = 100)	Group B (Combination) (n = 100)	p-value
Age (years, mean ± SD)	49.2 ± 10.1	50.0 ± 9.6	0.42
Male: Female (%)	58 : 42	55 : 45	0.68
BMI (kg/m², mean ± SD)	26.4 ± 3.2	26.7 ± 3.0	0.58
FPG (mg/dL, mean ± SD)	161.5 ± 32.1	163.7 ± 31.4	0.64
PPG (mg/dL, mean ± SD)	245.4 ± 45.8	248.9 ± 47.3	0.57
HbA1c (% , mean ± SD)	8.62 ± 0.71	8.58 ± 0.68	0.71

Table 2. Glycemic control outcomes after 6 months of therapy

Parameter	Group A (Monotherapy) (n = 100)	Group B (Combination) (n = 100)	p-value
HbA1c reduction (%)	1.28 ± 0.52	1.64 ± 0.55	0.002
FPG reduction (mg/dL)	38.2 ± 20.5	52.7 ± 22.1	0.001
PPG reduction (mg/dL)	68.6 ± 28.3	84.9 ± 30.7	0.003
Patients achieving HbA1c <7% (%)	56 (56%)	72 (72%)	0.01

Table 3. Adverse drug reactions (ADRs) observed in the study population

Adverse Drug Reaction	Group A (Monotherapy) (n = 100)	Group B (Combination) (n = 100)	p-value
Gastrointestinal intolerance (%)	12 (12%)	10 (10%)	0.65
Hypoglycemia (%)	0 (0%)	6 (6%)	0.03
Others (headache, fatigue) (%)	2 (2%)	2 (2%)	1.00
Total ADRs (%)	14 (14%)	18 (18%)	0.42

Discussion

In our study, the mean age was 49.2 ± 10.1 years in the monotherapy group and 50.0 ± 9.6 years in the combination group (p = 0.42), with a nearly equal gender distribution (male-to-female ratio 58:42 vs. 55:45). The mean BMI was similar in both groups (26.4 ± 3.2 vs. 26.7 ± 3.0 kg/m²; p = 0.58). These

results confirmed the homogeneity of the study groups.Comparable demographic findings were reported by Asiimwe et al. (2020) [8], who studied elderly patients aged 45–80 years in Uganda and found a T2DM prevalence of 15.2%, with higher risk in overweight individuals. Similarly, Scavini et al. (2003) [9] reported that in Zuni Indians, the prevalence of diabetes was higher among females (20.4%) compared to males (15.1%). In contrast, our study did not show significant gender differences, possibly reflecting regional and lifestyle variations.We observed that HbA1c reduction was greater in the combination group (1.64 ± 0.55%) compared to the monotherapy group (1.28 ± 0.52%; p = 0.002). Similarly, FPG reduction was higher in Group B (52.7 ± 22.1 mg/dL) compared to Group A (38.2 ± 20.5 mg/dL; p = 0.001). PPG reduction was also greater with combination therapy (84.9 ± 30.7 mg/dL vs. 68.6 ± 28.3 mg/dL; p = 0.003). Importantly, 72% of patients in Group B achieved HbA1c < 7% compared to 56% in Group A (p = 0.01).

These findings are consistent with Rosenstock et al. (2015) [10], who evaluated dual add-on therapy with saxagliptin and dapagliflozin in patients poorly controlled on metformin. They reported a mean HbA1c reduction of –1.5% with dual therapy compared to –1.2% with dapagliflozin alone and –0.9% with saxagliptin alone, clearly demonstrating the superiority of combination therapy.

Likewise, Nishanth et al. (2018) [11] compared metformin-glimepiride with metformin-teneligliptin and found mean HbA1c reductions of 1.4% and 1.3%, respectively, over 24 weeks, both being significant. Guideline recommendations also support our findings. Oliver (2013) [12] emphasized individualized therapy, starting with metformin but advocating early combination when monotherapy is insufficient. Pippitt et al. (2016) [13] further noted that patients with higher baseline HbA1c are unlikely to reach glycemic targets with monotherapy, favouring early dual therapy. Thus, our results corroborate both evidence from clinical trials and expert consensus.

In our study, gastrointestinal intolerance was reported in 12% of monotherapy patients and 10% of combination therapy patients (p = 0.65). Hypoglycemia occurred exclusively in the combination group (6% vs. 0%; p = 0.03), mainly in sulfonylurea users. Other mild events such as headache and fatigue were reported equally in both groups (2%).

Overall ADR incidence was 14% in Group A and 18% in Group B (p = 0.42).Deb et al. (2017) [14] studied ADRs in T2DM patients on oral agents and found gastrointestinal intolerance to be the most common ADR (15.7%), followed by hypoglycemia in 12% of patients, particularly among those receiving sulfonylureas. This is consistent with our findings, where hypoglycemia was observed only in the combination group. Similarly, Sultana et al. (2010) [15] observed that sulfonylureas accounted for the majority of hypoglycemia cases, whereas DPP-4 inhibitor combinations were better tolerated. In another study, Rani & Reddy (2015) [16] highlighted that sulfonylurea-based combinations carried a greater risk of hypoglycemia compared to other drug classes. Our results mirror these findings, showing higher hypoglycemia incidence only in the combination group.

Conclusion

Both metformin monotherapy and combination therapy significantly improved glycemic control in newly diagnosed T2DM patients. Combination therapy led to greater reductions in HbA1c, FPG, and PPG, with more patients achieving target HbA1c <7%. However, hypoglycemia was observed only in the combination group. Thus, while more effective, combination therapy warrants careful monitoring.

Limitations of the Study

This study was conducted at a single tertiary care center, which may limit the generalizability of the findings. The duration of follow-up was limited to six months, preventing assessment of long-term glycemic control and complication rates. The choice of combination agent was not standardized and depended on physician discretion, introducing variability. Additionally, lifestyle factors and adherence were self-reported, which may have led to reporting bias.

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