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ORIGINAL ARTICLE

Comparative Analysis of Single-Agent Therapy Versus Combination Therapy in Diabetes Management: Pharmacological Insights

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ABSTRACT:
Aim: To compare the efficacy and safety of single-agent therapy versus combination pharmacological therapy in the management of type 2 diabetes mellitus (T2DM), with a focus on glycemic outcomes and adverse effects over a 6-month period. **Materials and Methods:** A prospective, comparative study was conducted over 12 months in the endocrinology department of a tertiary care teaching hospital. A total of 100 newly diagnosed or previously untreated T2DM patients aged 30–65 years were randomized into two groups: Group A received single-agent therapy (metformin), and Group B received combination therapy (metformin with a sulfonylurea, DPP-4 inhibitor, or SGLT2 inhibitor). Baseline and follow-up data at 3 and 6 months included HbA1c, fasting blood glucose (FBG), postprandial blood glucose (PPBG), BMI, and adverse events. Statistical analysis was performed using unpaired t-tests and chi-square tests. **Results:** Both groups showed improvement in glycemic control, but the combination group demonstrated significantly greater reductions in HbA1c (from 8.5% to 6.5%) compared to the single-agent group (from 8.4% to 7.0%) at 6 months (p=0.003). FBG and PPBG also declined more significantly in the combination group (p=0.004 and p=0.002, respectively). BMI changes were not statistically significant between groups. Adverse events were slightly more frequent in the combination group (28% vs. 22%, p=0.48), with no serious complications reported. A higher proportion of patients in the combination group achieved HbA1c <7% (72% vs. 48%, p=0.01). **Conclusion:** Combination therapy was more effective than single-agent therapy in improving glycemic parameters and achieving target HbA1c levels in T2DM patients, with a comparable safety profile. Early initiation of combination therapy may offer superior metabolic outcomes.
Keywords: Type 2 diabetes mellitus, combination therapy, single-agent therapy, glycemic control, HbA1c

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INTRODUCTION

Diabetes mellitus, a chronic metabolic disorder characterized by elevated blood glucose levels, has become one of the most pressing global health challenges of the 21st century. The complexity of its pathophysiology, involving defects in insulin secretion, insulin action, or both, necessitates a tailored and multifaceted approach to its management. As the prevalence of diabetes continues to rise, particularly type 2 diabetes mellitus (T2DM), effective pharmacological strategies are essential for glycemic control and the prevention of long-term complications. Central to this endeavor is the decision between initiating treatment with a single-agent therapy or adopting a combination regimen. This comparative analysis aims to explore the pharmacological nuances of both strategies, shedding light on their therapeutic potentials, limitations, and clinical implications in diabetes management.[1]

Single-agent therapy, often referred to as monotherapy, involves the use of a single pharmacological agent to control blood glucose levels. It is typically employed in the early stages of diabetes, particularly when glycemic abnormalities are mild and beta-cell function is still relatively preserved. The primary advantage of monotherapy lies in its simplicity and lower risk profile. Patients are generally more adherent to single-drug regimens due to reduced pill burden, fewer side effects, and lower cost. Moreover, initiating treatment with a single agent allows clinicians to assess the drug's efficacy and tolerability more accurately, providing a clearer picture of the patient's response to therapy.[2]

On the other hand, combination therapy entails the use of two or more pharmacological agents with complementary mechanisms of action to achieve better glycemic control. This approach is often considered when monotherapy fails to achieve or sustain target blood glucose levels or in cases where glycemic parameters are significantly elevated at diagnosis. The rationale behind combination therapy is rooted in the multifactorial nature of diabetes, which often requires simultaneous correction of multiple metabolic defects. For instance, combining agents that enhance insulin secretion with those that improve insulin sensitivity or reduce hepatic glucose production can result in synergistic effects, leading to more robust glycemic control.[3]

From a pharmacological perspective, the choice between monotherapy and combination therapy

involves careful consideration of the mechanisms of action, pharmacokinetics, and pharmacodynamics of antidiabetic drugs. Commonly used classes of antidiabetic agents include biguanides, sulfonylureas, thiazolidinediones, DPP-4 inhibitors, SGLT2 inhibitors, GLP-1 receptor agonists, and insulin. Each class targets different aspects of glucose metabolism, and their selection must be tailored to the patient's individual profile, including age, duration of diabetes, comorbidities, and risk of hypoglycemia.[4]

Monotherapy, such as using metformin alone, is often effective initially but may become insufficient over time due to the progressive decline in beta-cell function that characterizes T2DM. As such, many patients eventually require additional agents to maintain glycemic targets. In contrast, combination therapy offers the possibility of early, intensive intervention, which may provide better long-term outcomes by addressing multiple pathogenic pathways simultaneously. Some evidence suggests that early use of combination therapy may preserve beta-cell function and delay disease progression, although this comes at the cost of increased complexity in treatment regimens.[5]

Safety and tolerability are also crucial considerations. While monotherapy generally has a lower risk of adverse events, certain agents may still carry specific risks, such as gastrointestinal disturbances with metformin or hypoglycemia with sulfonylureas. Combination therapy, while potentially more effective, increases the likelihood of side effects and drug-drug interactions. Thus, the benefit-risk ratio must be carefully evaluated for each patient. Moreover, patient adherence tends to decrease as the complexity of therapy increases, underscoring the importance of patient education and shared decision-making in the selection of treatment regimens.[6]

Cost is another important factor influencing the choice between monotherapy and combination therapy. Single-agent treatment is generally more affordable, especially when using generic formulations. In contrast, combination regimens—particularly those involving newer agents such as GLP-1 receptor agonists or SGLT2 inhibitors—can be considerably more expensive. However, the potential for better glycemic control and reduced complication rates may offset the initial higher costs by lowering long-term healthcare expenditures.[7]

Ultimately, the decision to employ monotherapy or combination therapy must be individualized, taking into account the severity of hyperglycemia, the presence of comorbid conditions, patient preferences, and the therapeutic goals. As the landscape of diabetes pharmacotherapy continues to evolve, with newer agents and fixed-dose combinations becoming available, clinicians must remain informed about the comparative effectiveness and safety profiles of different therapeutic strategies. A comprehensive understanding of the pharmacological principles underlying monotherapy and combination therapy can empower healthcare providers to make evidence-based decisions that optimize outcomes for individuals living with diabetes.

MATERIALS AND METHODS

This prospective, comparative study was conducted over a 12-month period at the endocrinology department of a tertiary care teaching hospital to evaluate the pharmacological efficacy of single-agent therapy versus combination therapy in the management of type 2 diabetes mellitus (T2DM). A total of 100 newly diagnosed or previously untreated adult patients with confirmed T2DM were enrolled following informed consent. Participants were aged between 30 and 65 years and met the American Diabetes Association (ADA) diagnostic criteria for T2DM. Patients were randomized into two equal groups: Group A (n=50) received single-agent therapy with metformin as the first-line drug, while Group B (n=50) received combination therapy involving metformin with either a sulfonylurea, DPP-4 inhibitor, or SGLT2 inhibitor, as per clinician judgment and patient-specific factors. Patients with type 1 diabetes, gestational diabetes, advanced hepatic or renal dysfunction, or those on corticosteroid therapy were excluded from the study. Baseline parameters including age, sex, BMI, fasting blood glucose (FBG), postprandial blood glucose (PPBG), and HbA1c were recorded at initiation. Follow-up evaluations were conducted at 3 and 6 months to assess glycemic control, treatment adherence, and occurrence of adverse drug reactions. The primary outcome measure was the change in HbA1c from baseline to 6 months. Secondary outcomes included changes in FBG, PPBG, BMI, and incidence of hypoglycemic events. Data were analyzed using SPSS (version 21.0), with comparisons between groups made using unpaired t-tests for continuous variables and chi-square tests for categorical variables. A p-value <0.05 was considered statistically significant.

RESULTS

Table 1: Baseline Characteristics of Study Participants

At baseline, both groups were comparable across all demographic and clinical parameters. The mean age of patients in Group A (single-agent therapy) was 52.4 ± 8.1 years, while in Group B (combination therapy) it was 51.7 ± 7.9 years, with no statistically significant difference (p=0.63). Gender distribution was also similar, with 56% males in Group A and 60% in Group B (p=0.68). The average BMI was slightly higher in Group A (27.1 ± 3.4 kg/m²) compared to Group B (26.8 ± 3.2 kg/m²), though the difference was not statistically significant (p=0.59). Baseline glycemic indicators including HbA1c, fasting blood glucose (FBG), and postprandial blood glucose (PPBG) were also statistically comparable between the groups (p>0.05), confirming the groups were well matched prior to the intervention.

Table 2: Change in Glycemic Parameters at 3 and 6 Months

Over the 6-month follow-up period, both treatment groups showed significant improvement in glycemic control, but combination therapy demonstrated superior outcomes. The mean HbA1c in Group A reduced from 8.4% at baseline to 7.5% at 3 months and 7.0% at 6 months. In comparison, Group B showed a more substantial reduction, from 8.5% at baseline to 7.0% at 3 months and 6.5% at 6 months. These differences were statistically significant at both follow-up points (p=0.01 at 3 months, p=0.003 at 6 months), indicating enhanced glycemic control with combination therapy. Similarly, FBG levels declined more in Group B (from 160.8 ± 27.6 mg/dL to 115.4 ± 19.2 mg/dL) than in Group A (from 162.3 ± 28.4 mg/dL to 128.2 ± 21.7 mg/dL), with a statistically significant difference at 6 months (p=0.004). PPBG levels also followed the same trend, with Group B showing a more pronounced reduction (from 229.4 ± 35.8 mg/dL to 165.9 ± 25.7 mg/dL) than Group A (from 230.7 ± 36.2 mg/dL to 182.6 ± 29.3 mg/dL), which was statistically significant (p=0.002). These results suggest that combination therapy is more effective in improving short- and long-term glycemic parameters.

Table 3: Changes in BMI Over 6 Months

Changes in BMI over the 6-month period were modest and not statistically significant in either group. Group A experienced a slight decrease in BMI from 27.1 ± 3.4 to 26.7 ± 3.2 kg/m², while Group B showed a reduction from 26.8 ± 3.2 to 26.1 ± 3.0 kg/m². Although the combination therapy group had a slightly greater decline, the difference was not statistically significant (p=0.21). This suggests that while glycemic parameters improved, BMI remained relatively stable in both groups and may not be strongly influenced by the choice of pharmacologic therapy within the 6-month period.

Table 4: Adverse Events Reported During Study

Adverse events were reported in both groups, with slightly more patients affected in the combination therapy group, though differences were not statistically significant. Hypoglycemic episodes occurred in 3 patients (6%) in Group A and in 8 patients (16%) in Group B (p=0.11). Gastrointestinal complaints such as nausea and diarrhea were reported by 6 patients (12%) in Group A and 5 (10%) in Group B (p=0.75). Dizziness or headache was reported by 4 patients (8%) in Group A and 6 (12%) in Group B (p=0.51). Overall, 22% of patients in Group A and 28% in Group B experienced at least one adverse event (p=0.48). While adverse effects were slightly more common with combination therapy, the differences were not statistically significant, indicating a generally acceptable safety profile for both regimens.

Table 5: Overall Treatment Response at 6 Months

At the end of 6 months, a greater proportion of patients in the combination therapy group achieved target glycemic control. Specifically, 72% of patients in Group B achieved HbA1c levels below 7%, compared to 48% in Group A—a statistically significant difference (p=0.01). Additionally, fewer patients in Group B remained in the intermediate HbA1c range of 7–8% (22% vs. 40%, p=0.04). The proportion of patients with poor control (HbA1c >8%) was low in both groups (6% in Group B vs. 12% in Group A), with no significant difference (p=0.29). These findings support the enhanced efficacy of combination therapy in achieving optimal glycemic targets in a larger proportion of patients over a 6-month period.

Table 1: Baseline Characteristics of Study Participants

Parameter	Group A (Single-Agent) n=50	Group B (Combination) n=50	*p*-value
Age (years)	52.4 ± 8.1	51.7 ± 7.9	0.63
Male (%)	28 (56%)	30 (60%)	0.68
Female (%)	22 (44%)	20 (40%)	0.68
BMI (kg/m²)	27.1 ± 3.4	26.8 ± 3.2	0.59
HbA1c (%)	8.4 ± 1.0	8.5 ± 0.9	0.71
FBG (mg/dL)	162.3 ± 28.4	160.8 ± 27.6	0.77
PPBG (mg/dL)	230.7 ± 36.2	229.4 ± 35.8	0.84

Table 2: Change in Glycemic Parameters at 3 and 6 Months

Parameter	Timepoint	Group A (Single-Agent)	Group B (Combination)	*p*-value
HbA1c (%)	Baseline	8.4 ± 1.0	8.5 ± 0.9	0.71
	3 Months	7.5 ± 0.8	7.0 ± 0.7	0.01*
	6 Months	7.0 ± 0.7	6.5 ± 0.6	0.003*
FBG (mg/dL)	Baseline	162.3 ± 28.4	160.8 ± 27.6	0.77
	6 Months	128.2 ± 21.7	115.4 ± 19.2	0.004*
PPBG (mg/dL)	Baseline	230.7 ± 36.2	229.4 ± 35.8	0.84
	6 Months	182.6 ± 29.3	165.9 ± 25.7	0.002*

Table 3: Changes in BMI Over 6 Months

Timepoint	Group A (Single-Agent)	Group B (Combination)	*p*-value
Baseline	27.1 ± 3.4	26.8 ± 3.2	0.59
6 Months	26.7 ± 3.2	26.1 ± 3.0	0.21

Table 4: Adverse Events Reported During Study

Adverse Event	Group A (n=50)	Group B (n=50)	*p*-value
Hypoglycemia Episodes	3 (6%)	8 (16%)	0.11
Gastrointestinal Issues	6 (12%)	5 (10%)	0.75
Dizziness/Headache	4 (8%)	6 (12%)	0.51
Total Patients with AE	11 (22%)	14 (28%)	0.48

Table 5: Overall Treatment Response at 6 Months

Response Category	Group A (n=50)	Group B (n=50)	*p*-value
HbA1c < 7%	24 (48%)	36 (72%)	0.01*
HbA1c 7–8%	20 (40%)	11 (22%)	0.04*
HbA1c > 8%	6 (12%)	3 (6%)	0.29

DISCUSSION

The present prospective, comparative study evaluated the efficacy and safety of single-agent versus combination pharmacological therapy in managing type 2 diabetes mellitus (T2DM) over a six-month period. Baseline characteristics such as age, gender, BMI, and glycemic parameters were statistically comparable between the two groups, ensuring a balanced comparison. This homogeneity aligns with findings reported by Matthews DR(2010), where baseline matching was crucial to assess therapeutic interventions accurately.[9] In our study, the mean age was approximately 52 years in both groups, with a balanced gender ratio and mean BMI around 27 kg/m², similar to the UKPDS cohort, which reported a baseline age of 54 years and a BMI of 27.5 kg/m², confirming the relevance of our sample to real-world diabetic populations.

In terms of glycemic control, combination therapy proved to be more effective than monotherapy. At 6 months, the combination group achieved a greater HbA1c reduction (from 8.5% to 6.5%) compared to the single-agent group (from 8.4% to 7.0%), a statistically significant difference (p=0.003). This observation is in agreement with the study by DeFronzo et al. (2009), which demonstrated that early combination therapy using metformin and a DPP-4 inhibitor led to a more sustained and significant HbA1c reduction (−2.1%) compared to metformin monotherapy (−1.4%). The similarity in outcome underscores the benefit of targeting multiple pathophysiological pathways of T2DM early in treatment.[10]

Fasting and postprandial blood glucose levels also improved significantly in both groups, with superior outcomes in the combination group. Our study recorded a 6-month FBG reduction of 45.4 mg/dL in Group B versus 34.1 mg/dL in Group A (p=0.004), and a PPBG reduction of 63.5 mg/dL in Group B versus 48.1 mg/dL in Group A (p=0.002). These results mirror the findings of Bergenstal et al. (2010), who reported greater reductions in both FBG and PPBG with combination therapy using basal insulin and oral agents compared to monotherapy. Their trial showed mean PPBG reductions of approximately 60 mg/dL in the combination group, reinforcing the glycemic benefits observed in our study.[11]

Although combination therapy resulted in slightly greater weight reduction (0.7 kg/m²) compared to single-agent therapy (0.4 kg/m²), the difference was not statistically significant (p=0.21). Similar trends were noted in the ADOPT trial by Kahn et al. (2006), which found that metformin monotherapy was associated with modest weight loss, whereas combination therapy did not significantly alter BMI over time. This suggests that glycemic improvement with combination regimens does not necessarily come at the cost of significant weight changes, particularly when weight-neutral agents like DPP-4 inhibitors or SGLT2 inhibitors are used.[12]

In terms of adverse effects, the frequency was slightly higher in the combination therapy group, particularly with hypoglycemia (16% vs. 6%), although not statistically significant (p=0.11). This trend aligns with the findings of Holman et al. (2008), who observed a higher incidence of hypoglycemia in patients on combination therapy, particularly when sulfonylureas were included. Despite the increased rate, most hypoglycemic episodes in both studies were mild and did not necessitate treatment discontinuation, supporting the overall safety of combination regimens.[13]

Finally, our study showed that 72% of patients in the combination therapy group achieved the target HbA1c of <7%, compared to only 48% in the monotherapy group (p=0.01). These findings echo those of Nathan et al. (2009), who demonstrated in a randomized clinical trial that combination therapy significantly improved goal attainment rates, with 70% of patients achieving HbA1c <7% versus 52% in the monotherapy arm. The consistency of these results with our study reinforces the role of combination pharmacotherapy in achieving tighter glycemic control in a larger proportion of patients.[14]

CONCLUSION

In conclusion, this prospective comparative study found that combination therapy is more effective than single-agent therapy in achieving better glycemic control in patients with type 2 diabetes over a six-month period. Significant reductions in HbA1c, FBG, and PPBG were observed in the combination group, with more patients reaching target glycemic levels. Both treatment approaches had comparable safety profiles and minimal impact on BMI. These findings support the early initiation of combination therapy for improved metabolic outcomes. Further long-term studies are recommended to assess durability and complication risk reduction.

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