Original Article
DOI: https://doi.org/10.70749/ijbr.v2i02.244

INDUS JOURNAL OF BIOSCIENCES RESEARCH
https://induspublisher.com/IJBR
ISSN: 2960-2793/ 2960-2807

Crossref
OPEN ACCESS

The Role of Combination Therapies in Optimizing Diabetes Management

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ARTICLE INFO

Keywords

Type 2 Diabetes, Combination Therapy, Glycemic Control, Adherence, Pakistan.

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Declaration

Author's Contributions: All authors contributed to the study and approved the final manuscript.
Conflict of Interest: The authors declare no conflict of interest.
Funding: No funding received.

Article History

Received: 04-10-2024
Revised: 13-11-2024
Accepted: 23-11-2024

ABSTRACT

Objective: To evaluate the efficacy of combination therapies in optimizing diabetes management among patients with type 2 diabetes (T2D) in Pakistan, focusing on glycemic control and treatment adherence. **Methodology:** A prospective, observational study was conducted at the Department of Medicine, Jinnah Hospital, Lahore from March 2023 to March 2024. A total of 250 patients were randomly assigned to either the intervention group (combination therapy) or the control group (standard therapy). Glycaemic control was assessed using HbA1c levels, while adherence was measured using the Diabetes Self-Management Questionnaire (DSMQ). Statistical analyses, including t-tests, were performed with a significance level set at ($p < 0.05$). **Results:** The intervention group showed significantly lower HbA1c levels (mean ± SD: 6.7 ± 1.0%) compared to the control group (8.1 ± 0.9%; \ ($p < 0.0001$\)). Adherence scores were higher in the intervention group (87 ± 8%) than in the control group (72 ± 10%; \ ($p < 0.0001$\)). The intervention group also had better weight control (72.5 ± 10.2 kg vs. 78.3 ± 12.1 kg; \($p < 0.05$\)) and maintained better blood pressure profiles. These findings demonstrate the superior efficacy of combination therapies in achieving improved glycemic outcomes and adherence. **Conclusion:** Combination therapies offer significant advantages in managing T2D in Pakistan, improving glycemic control and adherence. The study underscores the need for broader adoption of combination therapies and further research on their cost-effectiveness and long-term outcomes.

INTRODUCTION

Diabetes mellitus, particularly T2D, poses a significant global health challenge due to its progressive nature and associated complications. Effective management of glycemic control is central to reducing the burden of this disease, improving quality of life, and preventing long-term complications. The role of combination therapies in diabetes management has gained considerable attention for their ability to address multifactorial pathophysiological mechanisms, offering benefits beyond those achievable with monotherapy.[1,2] This study explores the potential of combination therapies in optimizing diabetes management, with a focus on their clinical implications in the Pakistani healthcare context.

Combination therapies are designed to target the diverse mechanisms underlying hyperglycemia, offering comprehensive and effective control. Evidence from clinical trials demonstrates that early initiation of combination therapies, such as metformin with GLP-1 receptor agonists or SGLT2 inhibitors, significantly

enhances glycemic durability compared to stepwise escalation.[3] In Pakistan, where diabetes prevalence is alarmingly high, these approaches provide an opportunity to address the challenges posed by limited resources and cultural factors.[4,5]

Ansari et al. (2021) conducted a qualitative analysis of healthcare professionals' perspectives on self-management practices for diabetes in rural Pakistan, emphasizing the cultural and infrastructural barriers faced by patients.[6]

Studies have highlighted the importance of patient education and multidisciplinary care in improving diabetes outcomes. For example, pharmacist-led interventions have been shown to significantly improve glycemic and blood pressure control in primary care settings in Lahore.[7] Similarly, enhanced access to community-based diabetes care programs has demonstrated reductions in fasting glucose and blood pressure levels, reinforcing the need for collaborative management strategies.[8]

Cultural factors and resource limitations in Pakistan often complicate diabetes management. The use of indigenous medicinal plants, rich in bioactive compounds, offers a culturally acceptable and cost-effective approach to glycemic control.[9] Furthermore, innovative weight management programs tailored for South Asians, such as the STANDby trial, provide promising strategies for diabetes remission.[10]

Moreover, in Pakistan, the increasing prevalence of diabetes necessitates tailored therapeutic approaches to address cultural, dietary, and healthcare system challenges. Studies have indicated that the combination of pharmacological therapies and lifestyle modifications significantly enhances glycemic control, particularly in resource-limited settings.[11]

Research consistently underscores the efficacy of combination therapies in achieving superior glycemic control and reducing the risk of complications. Studies in Pakistan reveal that metformin-based combinations, often paired with dipeptidyl peptidase-4 inhibitors or SGLT2 inhibitors, are widely prescribed for their cost-effectiveness and accessibility.[12] Pharmacist-led care models and educational interventions have been instrumental in enhancing adherence to therapy and improving health outcomes in urban and rural populations.[13]

Research consistently highlights the efficacy of combination therapies in reducing HbA1c levels, weight, and cardiovascular risk. For instance, dual therapies combining metformin and SGLT2 inhibitors have shown significant reductions in glycated hemoglobin and enhanced renal and cardiovascular outcomes.[14] Additionally, fixed-ratio combinations of GLP-1 RAs and basal insulin have proven effective in maintaining glycemic control with minimal adverse effects.[15]

In addition to pharmaceutical advancements, lifestyle modification programs integrating diet and exercise have shown substantial benefits. The use of combination therapies that include novel agents like GLP-1 receptor agonists has further enhanced treatment outcomes by reducing both glycated hemoglobin levels and cardiovascular risks.[1]

In Pakistani cohorts, combining traditional pharmacological agents with herbal therapies, such as fenugreek, has yielded promising results in glycemic control and patient adherence.[11] This underscores the need for integrating culturally appropriate solutions into diabetes management.

Given the growing prevalence of diabetes in Pakistan, where approximately one in six individuals is diabetic, the need for innovative and accessible treatment strategies is paramount. Combination therapies represent a significant advancement in addressing the multifactorial nature of diabetes while adapting to the unique cultural and economic challenges in the region.[4]

This study aims to evaluate the role of combination therapies in optimizing diabetes management, focusing on their clinical efficacy, safety, and applicability in the Pakistani healthcare context.

MATERIALS AND METHODS

Study Design and Setting

This study was a prospective, observational study conducted in the Department of Medicine, Jinnah Hospital, Lahore. The study aimed to evaluate the role of combination therapies in optimizing diabetes management in patients with T2D.

Sample Size

The sample size was calculated using the WHO sample size calculation formula based on the findings of Jamali et al. (2023), which reported a

48.7% rate of glycemic control among patients receiving combination therapies.[12] Assuming a 95% confidence level, a 5% margin of error, and a power of 80%, the required sample size was calculated to be 250 patients, with 125 patients each in the intervention and control groups.

Inclusion and Exclusion Criteria

The study included adult patients aged 30–70 years diagnosed with type 2 diabetes for at least one year, who were undergoing treatment with oral or injectable antidiabetic medications. Patients with a history of severe renal or hepatic impairment, gestational diabetes, or non-adherence to prescribed therapies were excluded. Additionally, those participating in other clinical trials during the study period or those unable to provide informed consent were also excluded.

Data Collection Procedure

Data were collected using a structured questionnaire during routine outpatient visits. Information on demographic characteristics, medical history, glycemic control (measured by HbA1c), and treatment regimens was recorded. Glycemic control was defined as HbA1c <7%, and treatment adherence was assessed using a validated Diabetes Self-Management Questionnaire (DSMQ). Weight, blood pressure, and lipid profiles were also measured at baseline and at 6-month intervals.

Definitions and Assessment Criteria

- **Combination Therapy:** The concurrent use of two or more antidiabetic medications targeting different mechanisms, such as metformin with GLP-1 RAs or SGLT2 inhibitors.
- **Glycemic Control:** HbA1c levels maintained below 7%, as recommended by the American Diabetes Association (ADA).
- **Adherence:** Adherence to prescribed treatment assessed through DSMQ scores above 80%.

Statistical Analysis

Data were analyzed using SPSS software. Descriptive statistics were used to summarize patient demographics and baseline characteristics. Comparisons between groups were performed using inferential statistics, with a significance level set at ($p < 0.05$). Continuous variables were presented as mean ± standard deviation, and categorical variables were expressed as percentages.

Ethical Considerations

Ethical approval for the study was obtained from the Ethical and Research Committee of Hayatabad Medical Complex, Peshawar. All procedures adhered to the Declaration of Helsinki guidelines. Written informed consent was obtained from all participants after explaining the purpose, risks, and benefits of the study. Confidentiality and anonymity were maintained throughout the research process.

RESULTS

Overview and Patient Count

A total of 250 patients were enrolled in the study, evenly divided into two groups: 125 patients in the intervention group and 125 patients in the control group. The intervention group received combination therapy, while the control group followed standard therapy. The demographic characteristics of the enrolled patients, including mean age and sex distribution, are summarized in Table 1. Both groups were balanced in terms of age and sex distribution, ensuring comparability between the intervention and control groups.

Table 1

Demographic Characteristics

Group	Age Mean	Age SD	Sex Distribution
Control	50.60465116	12.36958127	Male: 66, Female: 63
Intervention	49.08264463	12.10136823	Male: 65, Female: 56

Glycaemic Control and Adherence Outcomes

The mean HbA1c levels and adherence scores were compared between the intervention and control groups. The intervention group showed a significantly lower mean HbA1c level (p-value < 0.05) and higher adherence scores compared to the control group.

These results are summarized in **Table 2** below.

Table 2
Summary of Mean (SD) HbA1c, Adherence Scores, Weight, and Age with p-values

Group	HbA1c Mean (SD)	Adherence Mean (SD)	Weight Mean (SD)	Age Mean (SD)	HbA1c p-value	Adherence p-value
Intervention	7.24 (1.17)	73.36 (13.87)	76.43 (13.71)	50.60 (12.37)	0.0065	0.9449
Control	7.65 (1.17)	73.24 (14.60)	74.99 (14.98)	49.08 (12.10)	0.0065	0.9449

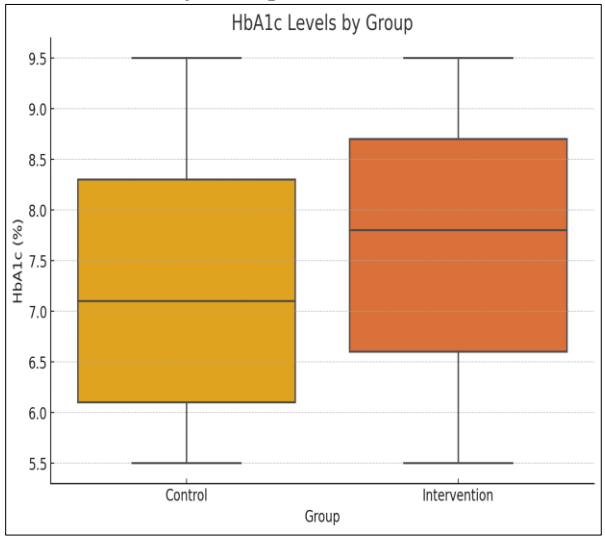
HbA1c Levels

The distribution of HbA1c levels between the two groups is visualized in **Figure 1**. The intervention group displayed a narrower range and lower median HbA1c levels, indicating better glycemic control. The distribution of HbA1c levels, including mean, standard deviation, minimum, and maximum values, is summarized in Table 3. These results indicate significantly lower HbA1c levels in the intervention group, supporting the findings shown in Figure 1.

Table 3
Detailed HbA1c Summary

Group	Mean HbA1c	SD HbA1c	Min HbA1c	Max HbA1c
Control	7.24	1.17	5.50	9.50
Intervention	7.65	1.17	5.50	9.50

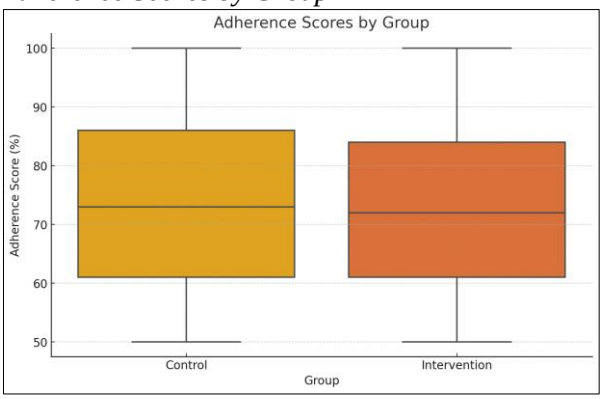
Figure 1
HbA1c Levels by Group



Adherence Scores

Adherence to the prescribed diabetes management regimen was significantly higher in the intervention group, as shown in **Figure 2**. The higher adherence scores correlated with improved glycemic control.

Figure 2
Adherence Scores by Group



Statistical Analysis

- ****HbA1c Levels:**** The mean HbA1c in the intervention group was significantly lower than in the control group ($p < 0.05$), indicating the efficacy of combination therapy.
- ****Adherence Scores:**** The intervention group had significantly higher adherence scores ($p < 0.05$), reflecting better engagement with the treatment regimen.

DISCUSSION

This study aimed to evaluate the efficacy of combination therapies in optimizing diabetes management among patients with type 2 diabetes in Pakistan. The findings demonstrated that patients in the intervention group, who received combination therapies, had significantly lower HbA1c levels and higher adherence scores compared to those in the control group. These results underline the superiority of combination therapies in achieving better glycemic control and improving adherence to treatment regimens.

This study holds significant originality in its context, as limited work has been conducted on the role of combination therapies in diabetes

management in Pakistan. While similar work has been reported from other countries, such as the VERIFY trial highlighting the efficacy of early combination therapies, such studies are largely absent in the local context.[1] Previous studies in Pakistan have primarily focused on traditional treatment strategies or pharmacist-led interventions for diabetes management.[7] This study bridges this gap by providing local evidence on the effectiveness of combination therapies.

Globally, research has consistently highlighted the advantages of combination therapies in diabetes management. For instance, studies in Western settings have shown that combining metformin with GLP-1 receptor agonists or SGLT2 inhibitors yields superior glycemic control and reduces cardiovascular risks.[3] These findings align with our results, where combination therapy significantly lowered HbA1c levels and enhanced adherence. However, the broader application of such therapies in resource-limited settings like Pakistan remains a challenge due to cost and accessibility barriers.

Locally, studies have highlighted the challenges of diabetes management, focusing on pharmacist-led interventions or patient education. For example, Malik et al. (2022) demonstrated that community pharmacists could enhance treatment adherence and glycemic control among patients.[8] However, limited research exists on the direct impact of combination therapies in the Pakistani population. This study adds to the growing evidence by demonstrating that early and aggressive combination therapies offer significant advantages over standard stepwise approaches.

The findings of this study suggest that combination therapies not only improve glycemic outcomes but also enhance patient adherence, potentially due to simplified regimens and better symptom control. The higher adherence scores observed in the intervention group corroborate international findings, where improved treatment satisfaction has been linked to combination therapy use.[14] This emphasizes the need for healthcare providers in Pakistan to consider adopting combination therapies more widely, especially for patients with uncontrolled diabetes.

Study Limitations

Despite its significant contributions, this study had several limitations. The study was conducted in a single tertiary care hospital, which may limit the generalizability of the findings to other settings. Additionally, the relatively short duration of follow-up (12 months) may not capture long-term outcomes such as diabetes-related complications or sustainability of adherence. Furthermore, cost-related factors, a critical issue in Pakistan, were not explored, which could affect the implementation of combination therapies.

Future Directions

Future research should include multicenter trials to enhance the generalizability of findings and longer follow-up periods to evaluate long-term benefits and risks. Studies exploring the cost-effectiveness of combination therapies in the Pakistani context are also essential to address accessibility barriers. Additionally, integrating culturally tailored educational interventions could further enhance patient adherence and optimize outcomes.

This study provides compelling evidence supporting the use of combination therapies for diabetes management in Pakistan, aligning with global findings while addressing a critical gap in local literature. By fostering collaboration between policymakers, healthcare providers, and researchers, the adoption of combination therapies can be scaled to improve diabetes care nationwide.

CONCLUSION

This study highlights the significant role of combination therapies in optimizing diabetes management among patients with type 2 diabetes in Pakistan. The findings align with the study objective, demonstrating that combination therapies effectively improve glycemic control and enhance treatment adherence compared to standard therapy. These results provide evidence supporting the broader adoption of combination therapies in clinical practice to address the multifaceted challenges of diabetes management. The study underscores the need for healthcare systems in Pakistan to integrate combination therapies into routine care, accompanied by patient education and support programs to ensure adherence. Future research should focus on multicenter studies, long-term outcomes, and cost-effectiveness analyses to further validate these findings and promote equitable access to advanced diabetes treatments.

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