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Glycemic Control and Cardiovascular Risk in Type 2 Diabetics Using Metformin vs. Combination Therapy

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Abstract

Introduction: Type 2 diabetes mellitus (T2DM) is a growing public health concern worldwide. While metformin is the first-line therapy, many patients require additional oral antidiabetic drugs (OADs) to achieve glycemic targets.
Objective: To determine which is better at controlling blood sugar and lowering the risk of heart disease in people with type 2 diabetes: metformin monotherapy or combination treatment.
Methodology: The Department of Endocrinology at Jinnah Hospital in Lahore carried out a descriptive, cross-sectional research between February 2023 and January 2024. A total of 132 T2DM patients were enrolled using convenience sampling and divided into two groups: Group A (metformin only; n=62) and Group B (metformin plus OADs; n=70). Fasting blood glucose, HbA1c, blood pressure, and lipid profile were assessed. Independent samples t-tests were used to compare means between groups, with $p<0.05$ considered statistically significant.
Results: Group B patients had far better blood sugar management than Group A patients. Their fasting blood sugar levels were 134.6 mg/dL compared to 144.2 mg/dL ($p = 0.047$), and their mean HbA1c levels were 7.36% compared to 7.94% ($p = 0.002$). Group B included 36 patients (51.43%) who were able to regulate their blood sugar levels (HbA1c <7%), whereas Group A had 18 patients (29.03%) who were able to do the same. In Group A, 39 patients (62.90%) and in Group B, 34 patients (48.57%) had dyslipidemia. There were 28 patients (45.16%) with high blood pressure in Group A and 29 patients (41.43%) in Group B.
Conclusion: Combination therapy with metformin and other OADs was associated with better glycemic control compared to metformin monotherapy. However, no significant reduction in cardiovascular risk factors was observed. Further longitudinal studies are needed to explore long-term outcomes and safety, including hypoglycemia risk.
Keywords: Type 2 diabetes mellitus, metformin, combination therapy, glycemic control, cardiovascular risk, HbA1c.

Introduction

The chronic metabolic disease known as type 2 diabetes mellitus (T2DM) is characterised by insulin resistance and decreased insulin production, which results in chronic hyperglycemia [1,2]. It makes up the great majority of diabetes cases globally, and because of its increasing incidence and strong correlation with morbidity and death, it has emerged as a serious public health problem [3].

Cardiovascular disease (CVD), which continues to be the primary cause of mortality for diabetic patients, is one of the most serious side effects of type 2 diabetes [4]. Chronic hyperglycemia raises the risk of cardiovascular disease by promoting the development of atherosclerosis, endothelial dysfunction, and systemic inflammation [5]. Therefore, maintaining proper glycaemic management is essential for reducing long-term cardiovascular outcomes as well as avoiding microvascular consequences such retinopathy and nephropathy [6].

Due to its effectiveness, safety record, and cardiovascular advantages, metformin has long been the mainstay of pharmacological treatment for type 2 diabetes [7]. Metformin, when used alone, lowers hepatic glucose synthesis and increases insulin sensitivity without producing hypoglycemia or weight gain. To reach ideal glycaemic goals, many patients ultimately need additional medications [8]. As a result, combination therapy combining medications such SGLT2 inhibitors, DPP-4 inhibitors, sulfonylureas, and GLP-1 receptor agonists are now widely used [9]. These

substances differ not only in how they work but also in how they affect cardiovascular risk variables such as body weight, lipid profiles, and blood pressure [10]. International guidelines, including those from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD), recommend adding combination therapy when HbA1c is more than 1.5% above target.

Even while combination treatment is becoming more and more popular, there is still debate over whether it is as successful as metformin monotherapy, especially in actual clinical situations. Results may also be impacted by variations in patient adherence, medication tolerance, and cost. Furthermore, few studies have directly compared the cardiovascular risks and glycaemic control of metformin monotherapy and certain medication combinations, despite the fact that several clinical trials have assessed the cardiovascular effects of various antidiabetic medications. This cross-sectional study aims to evaluate the association between metformin monotherapy and combination therapy (metformin plus other oral antidiabetic drugs) in terms of glycaemic control and cardiovascular risk profiles.

Research Objective

The purpose of this research is to evaluate how well metformin monotherapy and combination medication work to lower cardiovascular risk and achieve glycemic control in people with type 2 diabetes mellitus.

Materials and methods

Study Design and Setting

The Department of Endocrinology at Jinnah Hospital Lahore did a descriptive, cross-sectional research. The research was place over the course of a year, from February 2023 to January 2024. This study was designed to assess associations, not causal relationships, due to its cross-sectional nature.

Inclusion and Exclusion Criteria

Participants in the research were to be adults between the ages of 30 and 70 who had been diagnosed with type 2 diabetes mellitus for at least six months and who had been taking metformin on a consistent basis for at least three months, either by alone or in conjunction with another oral antidiabetic medication. In order to participate, patients had to provide their informed permission. Type 1 diabetes, gestational diabetes, insulin treatment, severe cardiovascular events during the previous six months, substantial renal impairment (eGFR < 30 mL/min/1.73 m2), hepatic dysfunction, malignancy, or insufficient medical records were among the exclusion criteria.

Sample Size

A total of 132 patients were enrolled using convenience sampling from the outpatient endocrinology clinic. The single-center design and the objective of enrolling all eligible patients during a one-year period led to the selection of this approach. The sample size is consistent with prior observational studies on type 2 diabetes, although no formal power calculation was conducted to determine whether the sample size was sufficient to detect statistically or clinically meaningful differences [11,12]. This limitation is addressed in the discussion section.

Data Collection

The data was collected using a pre-made, structured proforma. The demographic information that was recorded included age, gender, body mass index (BMI), smoking status, family history of diabetes, and duration of disease. Clinical factors included systolic and diastolic blood pressure, whereas laboratory data included glycated hemoglobin (HbA1c), fasting blood glucose, and lipid profile (total cholesterol, LDL, HDL, and triglycerides). The kind and quantity of medications were recorded using patient prescriptions, and hospital records were consulted for verification. Patients in Group B were using metformin in addition to another oral drug, whereas patients in Group A were taking metformin only. Lifestyle interventions such as diet and physical activity were not standardized or controlled, which may have influenced glycaemic and cardiovascular outcomes. Baseline comorbidities such as obesity and chronic kidney disease (CKD) were noted through clinical records, but medication adherence was not formally assessed.

Metformin Dosage (According to FDA Guidelines)

According to the U.S. Food and Drug Administration (FDA), people with type 2 diabetes often begin taking 500 mg twice day or 850 mg once daily with meals to minimize gastrointestinal adverse effects. The dosage may be gradually changed based on patient response and tolerance, with immediate-release formulations having a maximum daily dose of 2,550 mg and extended-release formulations having a maximum dose of 2,500 mg. Metformin monotherapy patients in Group A of this experiment received daily doses of 1,000–2,000 mg of the medication, often 500 mg twice daily, 850 mg twice daily, or 1,000 mg twice daily. Patients in Group B (metformin plus another oral antidiabetic medicine) were receiving similar doses of metformin together with either a sulfonylurea, DPP-4 inhibitor, or SGLT2 inhibitor depending on their individual glycaemic profiles and treatment tolerance.

Statistical Analysis

We used SPSS version 26.0 to enter and look at the data. We utilized the independent samples t-test to compare the two groups' continuous variables, which we showed as mean ± standard deviation. The assumption of normality was tested using the Shapiro-Wilk test before applying t-tests. It was thought that p-values below 0.05 were statistically significant. If data were found to be non-normally distributed, non-parametric alternatives (e.g., Mann-Whitney U test) were considered.

Ethical Approval

The Department of Endocrinology at Jinnah Hospital in Lahore's Institutional Review Board (IRB) granted clearance for this research under approval number IRB/DE/JHL/2023-022. All subjects provided written informed permission prior to data collection.

Throughout the research, patient confidentiality and anonymity were rigorously maintained in compliance with the Declaration of Helsinki's ethical guidelines.

Results

Table 1 shows that the average age of the 132 patients was 54.2 ± 8.6 years in Group A (62 on metformin monotherapy) and 55.7 ± 9.1 years in Group B (70 on combination therapy). There were 34 men (54.84%) and 28 women (45.16%) in Group A. In Group B, 38 were men (54.29%) and 32 were women (45.71%) (p = 0.946). The average BMI in Group A (27.8 ± 3.5 kg/m²) was slightly lower than in Group B (28.6 ± 3.2 kg/m²; p = 0.137). Smoking prevalence was 19.35% in Group A and 24.29% in Group B (p = 0.409). A family history of diabetes was present in 62.90% of Group A and 65.71% of Group B (p = 0.691). Diabetes duration distribution showed no significant group difference (p = 0.057), although more patients in Group B had diabetes for over 10 years.

Table 1: Demographic and Baseline Characteristics of Patients (n = 132)

Category	Characteristic	Group A (n = 62)	Group B (n = 70)	p-value
Demographics (n;%)	Age (mean ± SD)	54.2 ± 8.6 years	55.7 ± 9.1 years	0.281
	Male	34 (54.84)	38 (54.29)	0.946
	Female	28 (45.16)	32 (45.71)	
	BMI (mean ± SD)	27.8 ± 3.5 kg/m²	28.6 ± 3.2 kg/m²	0.137
Lifestyle Factors (n;%)	Smoker	12 (19.35)	17 (24.29)	0.409
	Non-smoker	50 (80.65)	53 (75.71)	
Family History of Diabetes Mellitus (n;%)	Positive	39 (62.90)	46 (65.71)	0.691
	Negative	23 (37.10)	24 (34.29)	
Disease Duration (n;%)	Less than 5 years	24 (38.71)	21 (30.00)	0.057
	Between 5 to 10 years	27 (43.55)	31 (44.29)	
	Above 10 years	11 (17.74)	18 (25.71)	

Group B exhibited significantly better glycemic and lipid outcomes (table 2). The average fasting blood glucose was 144.2 ± 28.5 mg/dL in Group A and 134.6 ± 24.7 mg/dL in Group B (p = 0.047). Mean HbA1c was significantly lower in Group B (7.36 ± 0.71%) compared to Group A (7.94 ± 0.78%; p = 0.002). Similarly, Group B had lower total cholesterol (188.2 ± 29.6 mg/dL vs. 201.3 ± 33.7 mg/dL; p = 0.014) and LDL (113.5 ± 24.9 mg/dL vs. 123.7 ± 27.2 mg/dL; p = 0.028). Differences in HDL, triglycerides, systolic, and diastolic BP were not statistically significant.

Table 2: Clinical and Laboratory Parameters Comparison

Parameter	Group A (n = 62)	Group B (n = 70)	p-value
Systolic BP (mmHg)	132.6 ± 12.4	129.1 ± 13.2	0.113
Diastolic BP (mmHg)	82.1 ± 7.6	80.4 ± 8.2	0.183
Fasting Blood Glucose (mg/dL)	144.2 ± 28.5	134.6 ± 24.7	0.047*
HbA1c (%)	7.94 ± 0.78	7.36 ± 0.71	0.002*
Total Cholesterol (mg/dL)	201.3 ± 33.7	188.2 ± 29.6	0.014*
LDL (mg/dL)	123.7 ± 27.2	113.5 ± 24.9	0.028*
HDL (mg/dL)	40.9 ± 6.3	43.2 ± 5.9	0.062
Triglycerides (mg/dL)	174.5 ± 40.8	163.6 ± 38.4	0.119

In terms of glycemic control, 18 out of 62 patients in Group A (29.03%) achieved target HbA1c levels (<7%), while 44 (70.97%) remained uncontrolled (HbA1c ≥7%), shown in figure 1. In Group B, 36 out of 70 patients (51.43%) achieved controlled HbA1c levels, whereas 34 (48.57%) had uncontrolled levels. Thus, glycemic control was significantly better in the combination therapy group.

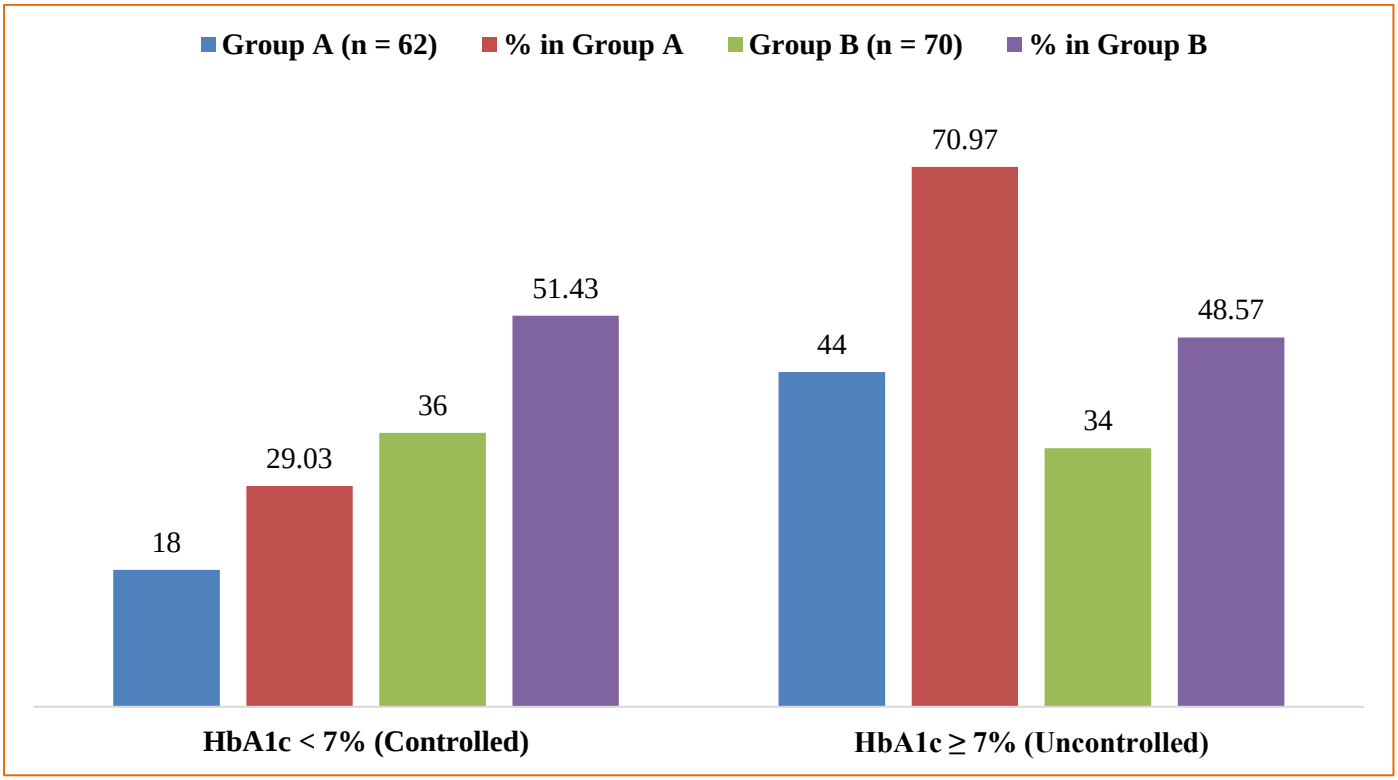

Figure 1: Glycemic Control Achievement (HbA1c < 7%)

Table 3 shows cardiovascular risk factors. Hypertension was present in 45.16% of Group A and 41.43% of Group B (p = 0.669). Dyslipidemia was more common in Group A (62.90%) than in Group B (48.57%), though not statistically significant (p = 0.097). Combined risk (both hypertension and dyslipidemia) was similar in both groups (p = 0.958).

Table 3: Cardiovascular Risk Profile (Hypertension & Dyslipidemia)

Risk Factor	Group A (n = 62)	Group B (n = 70)	p-value
Hypertension	28 (45.16%)	29 (41.43%)	0.669
Dyslipidemia	39 (62.90%)	34 (48.57%)	0.097
Both Present	21 (33.87%)	24 (34.29%)	0.958

Detailed statistical comparisons revealed significantly better outcomes in Group B for several parameters (table 4). Fasting blood glucose was significantly lower in Group B (134.6 ± 24.7 mg/dL) compared to Group A (144.2 ± 28.5 mg/dL; t=2.00; p=0.047). HbA1c was also lower (7.36% vs. 7.94%; t=3.22; p=0.002). Lipid profile parameters were more favorable in Group B, including total cholesterol (188.2 vs. 201.3 mg/dL; p=0.014) and LDL (113.5 vs. 123.7 mg/dL; p=0.028). HDL and triglyceride levels, though slightly better in Group B, were not significantly different. Systolic and diastolic blood pressures were also not significantly different between groups.

Table 4: Independent Samples t-Test Comparison of Clinical and Laboratory Parameters between Group A and Group B

Variable	Group A (Metformin only; *n = 62)*	Group B (Metformin + OADs; *n = 70)*	t-value	p-value
Systolic BP (mmHg)	132.6 ± 12.4	129.1 ± 13.2	1.61	0.113
Diastolic BP (mmHg)	82.1 ± 7.6	80.4 ± 8.2	1.34	0.183
Fasting Blood Glucose (mg/dL)	144.2 ± 28.5	134.6 ± 24.7	2.00	0.047
HbA1c (%)	7.94 ± 0.78	7.36 ± 0.71	3.22	0.002
Total Cholesterol (mg/dL)	201.3 ± 33.7	188.2 ± 29.6	2.48	0.014
LDL (mg/dL)	123.7 ± 27.2	113.5 ± 24.9	2.22	0.028
HDL (mg/dL)	40.9 ± 6.3	43.2 ± 5.9	-1.89	0.062
Triglycerides (mg/dL)	174.5 ± 40.8	163.6 ± 38.4	1.57	0.119

Discussion

This study compared the effectiveness of metformin monotherapy versus combination oral antidiabetic therapy in improving glycaemic control and

cardiovascular risk profiles in patients with type 2 diabetes mellitus (T2DM). Combination therapy, primarily involving metformin plus either sulfonylureas or DPP-4 inhibitors, was associated with significantly better glycaemic outcomes. With 36 out of 70 patients (51.43%) in Group B reaching goal HbA1c levels (<7%), compared to only 18 out of 62 patients (29.03%) in Group A, our results showed that combination treatment was associated with considerably improved glycaemic control ($p < 0.05$). This is consistent with earlier research showing better glycaemic results when metformin is used with other oral antidiabetic medications, especially sulfonylureas or DPP-4 inhibitors, which have complementary modes of action and stronger benefits on decreasing blood sugar [13].

Additionally, Group B's mean HbA1c levels were considerably lower (7.36 0.71%) than Group A's (7.94 0.78%), which is in line with earlier research that shown that using metformin in conjunction with other treatments reduced HbA1c by 0.6% to 1.0% more than using it alone [14]. Additionally, Group B's fasting blood glucose was considerably lower (134.6 ± 24.7 mg/dL) than Group A's (144.2 ± 28.5 mg/dL), which supports the combination therapy's improved glycaemic management.

Patients in Group B exhibited better lipid profiles with regard to cardiovascular risk factors, albeit these differences should be interpreted cautiously, as they were modest despite being statistically significant. Group B had lower LDL levels (113.5 ± 24.9 mg/dL vs. 123.7 ± 27.2 mg/dL; $p = 0.028$) and lower total cholesterol (188.2 ± 29.6 mg/dL) than Group A (201.3 ± 33.7 mg/dL; $p = 0.014$). These results are consistent with other studies that shown that better cholesterol management and glycaemic control are linked to fewer cardiovascular events in diabetes individuals [15]. However, since cardiovascular outcomes were not directly assessed and the observed lipid differences may not be clinically significant, any conclusions about cardiovascular risk reduction must be considered speculative.

It's interesting to note that both groups had comparable rates of dyslipidaemia and hypertension. 45.16% of Group A and 41.43% of Group B had hypertension, while 62.90% and 48.57% of Group B had dyslipidaemia, respectively. Similar results were seen in the earlier trial, where despite variations in glycaemic control, blood pressure outcomes did not vary substantially between groups receiving monotherapy and combination medication [16].

The lack of control for lifestyle interventions such as diet and physical activity, which are known to affect glycaemic and lipid outcomes, limits the internal validity of the study. Additionally, baseline comorbidities such as obesity, chronic kidney disease (CKD), and medication adherence were not recorded or adjusted for, which may have introduced confounding. Group sizes were slightly imbalanced (62 vs. 70), and no power calculation was performed to assess whether the sample size was sufficient to detect clinically meaningful differences. Although t-tests were used to compare means, no confirmation of normality was reported, which may affect the appropriateness of parametric statistical tests.

Comprehensive risk reduction initiatives are necessary, as shown by the relatively high burden of combined cardiovascular risk factors in both groups (33.87% in Group A vs. 34.29% in Group B). This is consistent with previous real-world cohort studies and supports the multifaceted strategy to managing type 2 diabetes [17]. Nevertheless, this study's cross-sectional design limits any inference of causality, and findings should be interpreted as associations rather than direct effects of combination therapy. Prospective studies with randomized sampling, adequate power, and adjustment for confounders are needed to validate these findings and explore long-term outcomes.

Strengths and Limitations

This study's real-world clinical setting represents a key strength, as it enhances the applicability of the findings to routine outpatient diabetes management in Pakistan. A valid comparison between metformin monotherapy and combination therapy was facilitated by the inclusion of a well-defined cohort with comparable baseline characteristics across both groups. Furthermore, the assessment of both glycaemic and cardiovascular biomarkers provided a comprehensive evaluation of therapeutic effectiveness.

However, several limitations should be acknowledged. The cross-sectional design limits the ability to assess long-term outcomes or establish causal relationships. Convenience sampling may have introduced selection bias, and the generalizability of the results is restricted due to the relatively small sample size (n = 132) drawn from a single center. Moreover, lifestyle factors such as diet and physical activity were not standardized or controlled, potentially confounding the results. Lastly, although treatment groups were clearly defined, the specific classes of adjunct oral antidiabetic drugs (e.g., sulfonylureas, DPP-4 inhibitors, SGLT2 inhibitors) were not categorized or analyzed separately, which could influence both glycaemic and cardiovascular outcomes differently.

Conclusion

This study suggests that individuals with type 2 diabetes mellitus may achieve better glycaemic control with a combination of metformin and another oral antidiabetic agent compared to metformin alone. Patients in the combination therapy group demonstrated significantly lower fasting blood glucose levels (134.6 mg/dL vs. 144.2 mg/dL, $p = 0.047$) and HbA1c values (7.36% vs. 7.94%, $p = 0.002$), along with modest improvements in lipid profiles. However, the high and comparable prevalence of dyslipidemia and hypertension in both groups highlights the persistent cardiovascular risk in this population. These findings underscore the need for individualized and multimodal management strategies in T2DM to optimize both metabolic and cardiovascular outcomes. Future longitudinal or interventional studies

are warranted to confirm these associations and to evaluate the differential impact of specific drug combinations.

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Conflict of interest
The authors state no conflict of interest.

Author Contributions
Sehrish Jabeen: Conceptualization, Literature Review, Data Analysis, Drafting of the Manuscript
Dr. Anam: Clinical Supervision, Data Collection, Methodology
Fatima Abass: Patient Recruitment, Data Entry, Statistical Analysis
Syeda Aisha: Study Design, Manuscript Writing, Final Review and Correspondence
Saba Khalid: Interpretation of Results, Critical Revision, Reference Management

All authors read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

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