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Original Research Article

Comparison of Metformin Versus Repaglinide Monotherapy in the Treatment of New-Onset Type 2 Diabetes Mellitus

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Abstract: *Poorly controlled diabetes has devastating effects on the heart, kidneys, eyes, nerves, and blood vessels. This study aimed to compare mean HbA1c values after 3 months of initiating metformin versus repaglinide monotherapy in treating new-onset type 2 diabetes mellitus.* ***Methods:*** *This open-label, parallel-group, randomized controlled trial was conducted at the Department of Medicine, Nishtar Hospital, Multan, from 1st February 2025 to 31st May 2025. Sixty newly diagnosed T2DM patients aged 20–60 years were enrolled after informed consent. Baseline HbA1c was measured, and patients were randomly assigned using a lottery method with sealed opaque envelopes. Group A received Repaglinide monotherapy (0.75–1.5 mg/day), and Group B used Metformin (750–1500 mg/day). Serum sugar was monitored daily and doses adjusted in the first week. All patients received diet and lifestyle advice with monthly follow-up for three months. Compliance was monitored with a checklist. HbA1c was measured again at three months. Data was analysed through SPSS version 23. Mean HbA1c between the groups was compared using a t-test at the 5% significance level.* ***Results:*** *The mean age was 51.8±6.6 years, and 60% were male. Obesity, smoking, and hypertension were found in 51.7%, 41.7%, and 70% respectively. Mean HbA1c decreased from 8.4 ± 0.5 to 6.1 ± 0.6. The Repaglinide group had higher baseline HbA1c but lower post-treatment HbA1c (5.6 ± 0.3 vs. 6.6 ± 0.3, p-value < 0.01) than the Metformin group.* ***Conclusion:*** *Repaglinide monotherapy was more effective than Metformin in reducing HbA1c over three months, supporting use in early T2DM management.*

Keywords: Type 2 diabetes mellitus, Repaglinide, Metformin, Glycated Hemoglobin

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Introduction

Persistent hyperglycemia, a hallmark of diabetes mellitus (DM), is a metabolic disturbance (1). In Pakistan, 11.7% of people have type 2 DM, as of 2016. With a prevalence of 11.20%, males are more affected than females (9.19%) (2). Diabetes mellitus increases morbidity and mortality by causing several potentially fatal complications. The main risk factors for cardiovascular disease, which eventually result in a higher death rate, include glucose abnormalities (3). Numerous studies have found a direct correlation between the severity of dysglycemia and diabetic complications (4).

If the initial HbA1c level is less than 7.5, individuals with new-onset type 2 DM should be on a single drug after a change in their routine, as detailed in the American Association of Clinical Endocrinology (AACE) diabetes management guidelines (5). For type 2 diabetes mellitus, metformin is recommended as the first-line glucose-lowering drug because of its adequate blood-glucose-lowering capacity, notable influence on body weight, and cardiovascular protective properties (6). Another class of anti Hyperglycemic drugs that contain benzoic acid are meglitinide. The most widely used medication in this family is repaglinide. Promoting rapid insulin release lowers blood glucose levels (7).

Two hundred patients with recently diagnosed diabetes were enrolled by Younas A et al. After three months of treatment, they found that both the metformin and repaglinide (135 mg/dl ± 6 mg/dl vs. 115 mg/dl ±7 mg/dl, p < 0.01) groups experienced a reduction in fasting blood glucose values (145±6 mg/dl vs. 122±6 mg/dl, p <0.01). Likewise, remarkable decrease in HbA1c levels was seen in both metformin (7.12±0.15% vs. 6.67±0.06%, p <0.01) and repaglinide treatment groups (7.8±0.6% vs. 6.8±0.07%, p <0.01) (8). In another similar study, Muhammad D et al. enrolled 70 patients with new-onset DM (35 in each group). Baseline mean HbA1c levels and mean fasting sugar levels of the patients were 7.51+0.50 mmol/L and 7.4+0.5 mmol/L in Group A and 7.54+0.52 mmol/L and 7.4+0.5 mmol/L in Group B. Following treatment, these values were decreased to 5.57+0.65 and 5.83+0.71 in Group A and 6.4+0.49 and 6.2+0.6 in Group B (p = 0.0001 and 0.007) (9).

This study was planned to determine the role of using repaglinide versus metformin as the starting medication in new-onset diabetic cases (who have not taken oral anti-hyperglycemic drugs before) in terms of reducing HbA1c in our local setting. The study results will help physicians better prescribe drugs to achieve reasonable glycemic control in their patients. We hypothesized that the mean HbA1c (%) would be lower with Repaglinide than with Metformin monotherapy after 3 months of treatment in newly diagnosed T2DM patients.

Methodology

This open-label, parallel-group, randomized controlled trial (Registry No. SLCTR/2025/014) was conducted at the Department of Medicine, Nishtar Hospital, Multan, from 1st February 2025 to 31st May 2025 after approval from the institutional ethics review committee (ERC# 1546/NMU, dated: 31-01-2025). A total of 60 newly diagnosed T2DM patients, aged 20–60 years and of either gender, were consecutively included in the study after obtaining informed consent. Patients with existing coronary artery, renal, liver, and gastrointestinal disease, as assessed from history and medical records, were excluded from the study. Patient characteristics like age, gender, obesity (BMI of ≥27.5 kg/m^2), smoking, and hypertension were recorded.

Baseline HbA1c (%) was determined in all patients. Patients were randomly divided into group A and group B using a lottery method with sequentially numbered, sealed, opaque envelopes. Patients in group A were treated with Repaglinide monotherapy 0.75-1.5 mg/day and group B with Metformin 750-1500mg/day. Daily serum glucose monitoring was

performed in all patients, and doses of Repaglinide and Metformin were adjusted accordingly during the first week after treatment assignment. All patients had regular monthly follow-up for 3 months. All patients were provided with instructions on dietary changes and lifestyle modifications as Part of routine care for diabetic patients. Compliance was assessed through a checklist, which the participants marked after use of the drug. After three months, HbA1c levels were determined again.

A minimum sample size of 60 patients was calculated using OpenEpi online software, based on the mean difference formula, with the mean HbA1c (%) set to 5.57+0.65 in the Repaglinide group and 6.4+0.49 in the Metformin group, at a 95% confidence level and 80% power.[9] Normality of numerical data was assessed through the Shapiro-Wilk test. Numerical data are presented as mean ± SD, and categorical data as frequency and percentages. Mean HbA1c (%) levels after three months of treatment between the two groups were compared using an independent samples t-test at the 5% significance level. Stratification by demographic characteristics was performed to assess differences in mean HbA1c (%) across the two treatment groups.

Results

The mean age of the patients was 51.8 ± 6.6 years, and 60% (n=36) were male. Obesity, smoking, and hypertension were prevalent in 51.7% (n=31), 41.7% (n=25), and 70% (n=42) of the participants. The mean HbA1c (%) levels before and after treatment were 8.4 ± 0.5 and 6.1 ± 0.6, respectively. Pretreatment HbA1c (%) levels were significantly higher before treatment (8.5 ± 0.5 vs. 8.2 ± 0.6) and lower after treatment (5.6 ± 0.3 vs. 6.6 ± 0.3) among T2DM patients treated with Repaglinide compared to Metformin [Table 1].

After stratification by demographic characteristics, post-treatment HbA1c (%) remained significantly lower in the Repaglinide group compared with the Metformin group [Table 2].

Table 1: Characteristics of newly diagnosed Type 2 DM patients (N=60)

Characteristic	Overall (N=60)	Repaglinide (n=30)	Metformin (n=30)	p-value*
Age (years)	51.8 ± 6.6	51.3 ± 6.7	52.3 ± 6.5	0.576
Gender				
Male	36 (60)	17 (47.2)	19 (52.8)	0.598
Female	24 (40)	13 (54.2)	11 (45.8)	
Obesity (Yes)	31 (51.7)	16 (51.6)	15 (51.7)	0.796
Smoking (Yes)	25 (41.7)	12 (48)	13 (52)	0.793
Hypertension (Yes)	42 (70)	20 (47.6)	22 (52.4)	0.573
Pre-treatment HbA1c (%)	8.4 ± 0.5	8.5 ± 0.5	8.2 ± 0.6	0.045
Post-treatment HBA1c (%)	6.1 ± 0.6	5.6 ± 0.3	6.6 ± 0.3	< 0.01

**Independent sample t-test for numerical comparison and chi-square test for categorical variables*

Table 2: Effect on post-treatment HbA1c (%) levels in patients with new onset Type 2 DM (N=60)

Characteristics		Repaglinide (n=30)	Metformin (n=30)	p-value
Age	≤ 50-years	5.6 ± 0.3	6.5 ± 0.3	< 0.01
	> 50-years	5.6 ± 0.4	6.6 ± 0.4	< 0.01
Gender	Male	5.6 ± 0.4	6.5 ± 0.3	< 0.01
	Female	5.6 ± 0.3	6.6 ± 0.3	< 0.01
Obesity	Yes	5.7 ± 0.3	6.6 ± 0.3	< 0.01
	No	5.6 ± 0.4	6.5 ± 0.3	< 0.01
Smoking	Yes	5.6 ± 0.3	6.5 ± 0.3	< 0.01
	No	5.6 ± 0.4	6.6 ± 0.3	< 0.01
Hypertension	Yes	5.6 ± 0.4	6.6 ± 0.3	< 0.01
	No	5.7 ± 0.3	6.5 ± 0.4	< 0.01

**Independent sample t-*

Discussion

Impaired glycaemic management is associated with complications of diabetes. Patients with type 2 DM who use metformin observe decreased HbA1c and related problems. Therefore, the first medication prescribed to these patients following a lifestyle change is metformin. Short-acting insulin secretagogues like repaglinide provide a remarkable anti-hyperglycaemic effect and reduce the risk of hypoglycaemia. Nevertheless, there is insufficient data to support the use of this method to start treatment for newly diagnosed diabetic cases.

We observed that pretreatment HbA1c (%) levels were significantly higher and post-treatment levels were lower among T2DM patients treated with Repaglinide compared to Metformin. Both metformin and repaglinide reduced fasting blood sugar levels, with no significant difference (6.2±0.1 mmol/L and 6.28±0.09 mmol/L, respectively), according to a study by Ma J et al. (10). Repaglinide significantly reduced HbA1c compared to metformin, even though we did not measure fasting glucose levels in our study.

Repaglinide plus metformin can be utilized to manage glycaemic changes in people with recently diagnosed type 2 DM. It has been demonstrated that complications from diabetes are caused by both acute and chronic hyperglycemia. Endothelial cells and human renal proximal tubular cells are more vulnerable to acute fluctuations in blood glucose levels than to persistently elevated blood glucose levels (11). Changes in blood glucose levels have been exploited as therapeutic targets in many clinical studies, and various medications have been shown to reduce these changes (12,13).

Fang FS et al. examined the effects of repaglinide and metformin as initial monotherapy in Chinese individuals with newly diagnosed type 2 DM. They identified that both treatment modalities improved blood glucose levels and decreased glycaemic alteration, improved the function of beta cells, and increased insulin sensitivity. Repaglinide can therefore be used as the first line of treatment for Chinese people with new-onset type 2 DM (14).

In their study, Lund SS et al. examined the impact of metformin and repaglinide on cardiovascular risk markers associated with endothelial dysfunction and inflammation in newly diagnosed non-obese T2DM

patients. They found that, despite similar blood glucose levels, metformin was superior to repaglinide in lowering specific biomarkers of inflammation and endothelial dysfunction (15). More research is required in this area to elucidate the situation.

In persons with new-onset type 2 DM, Younas A et al demonstrated that both metformin and repaglinide markedly reduced HbA1c and pre-prandial blood sugar levels. Repaglinide had a more substantial anti-diabetic effect than metformin (8). Our results are compatible with their findings. Most recently, Haggar MSD et al. published a study using numerical simulations to examine how metformin and repaglinide affected patients with type 2 DM. The findings revealed that glucose concentrations in the heart, tissues, and liver decreased, while glucagon and insulin concentrations increased (16).

Instead of insulin resistance, Asian patients with type 2 DM are characterised by poor β-cell activity (17). Consequently, one of the most popular antidiabetic drugs in this area is still insulin secretagogues. The primary purpose of repaglinide is to reduce postprandial hyperglycemia. By blocking potassium channels (ATP-dependent) and opening calcium channels in the beta cell of the pancreas due to consumption, repaglinide promotes the release of insulin (18).

It primarily stimulates the 1st stage of insulin secretion, a short-action insulin secretagogue that suppresses glucose production and glucagon secretion in the liver (19, 20). Repaglinide has been shown to decrease postprandial and fasting insulin release by alleviating glucose toxicity (21). Thus, after 12 weeks of repaglinide treatment, both HOMA-IR and HOMA-β showed a considerable improvement (22).

This study had some limitations. We did not measure pre- and post-prandial blood sugar levels or plasma insulin levels 3 months after treatment. The study duration was relatively short. Studies with a longer duration are needed in the future.

Conclusion

We conclude that Repaglinide is remarkably superior in reducing HbA1c when metformin and repaglinide were compared for treating newly diagnosed T2DM. We may prescribe repaglinide as an alternative to metformin in persons with newly diagnosed T2DM.

Declarations

Data Availability statement
All data generated or analysed during the study are included in the manuscript.

Ethics approval and consent to participate
Approved by the department concerned. (IRBEC-24)

Consent for publication
Approved

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Conflict of interest

The authors declared no conflict of interest.

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