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Original Research Article

Comparison of Metformin Plus Modified-Release Gliclazide Versus Metformin Plus Sitagliptin in Patients With Type 2 Diabetes Mellitus and Non-Alcoholic Fatty Liver Disease: A Randomized Controlled Trial

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Abstract: *Type 2 diabetes mellitus (T2DM) commonly coexists with non-alcoholic fatty liver disease (NAFLD), which may complicate glycemic control and therapeutic decision-making. After inadequate response to metformin, sulfonylureas and dipeptidyl peptidase-4 inhibitors are frequently used as add-on therapies.* ***Objective:*** *To compare mean glycated hemoglobin (HbA1c) levels after 12 weeks of treatment with metformin plus modified-release (MR) gliclazide versus metformin plus sitagliptin in patients with T2DM and NAFLD.* ***Methods:*** *This randomized controlled trial included 90 patients with T2DM and NAFLD, who were randomly assigned to two groups. Group A received metformin plus MR gliclazide, while Group B received metformin plus sitagliptin for 12 weeks. HbA1c levels were measured at baseline and at the end of follow-up. This study was conducted at Nishtar Hospital, Multan, from January 2025 to October 2025. Data were analyzed to compare within-group and between-group changes in HbA1c, with p<0.05 considered statistically significant.* ***Results:*** *A total of 90 patients were enrolled, with a slight male predominance (55.5%, n=50). The mean age was 48.2 ± 6.4 years in Group A and 47.9 ± 5.9 years in Group B (p=0.81). In Group A, mean HbA1c decreased from 8.12 ± 0.84% at baseline to 6.91 ± 0.73% after 12 weeks, with a mean reduction of 1.21 ± 0.42% (p<0.001). In Group B, mean HbA1c decreased from 8.05 ± 0.79% to 6.87 ± 0.70%, with a mean reduction of 1.18 ± 0.39% (p<0.001). The difference in mean HbA1c reduction between the two groups was not statistically significant (p=0.62).* ***Conclusion:*** *Metformin combined with either MR gliclazide or sitagliptin significantly improved glycemic control in patients with T2DM and NAFLD over 12 weeks. Both regimens demonstrated comparable efficacy, suggesting that treatment choice may be individualized according to patient profile, safety considerations, and cost.*

Keywords: Metformin, Modified-Release Gliclazide, Sitagliptin, Diabetes

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Introduction

Type 2 diabetes mellitus (T2DM) is a global epidemic, affecting over 500 million individuals worldwide, with projections estimating a rise to 700 million by 2045 (1). Closely intertwined with metabolic syndrome, T2DM is frequently comorbid with non-alcoholic fatty liver disease (NAFLD), now increasingly termed metabolic dysfunction-associated steatotic liver disease (MASLD), which represents the most common chronic liver condition globally (2). NAFLD encompasses a spectrum from simple steatosis to non-alcoholic steatohepatitis (NASH), fibrosis, and cirrhosis, with significant risks of progression to hepatocellular carcinoma and extrahepatic complications such as cardiovascular disease (3). The bidirectional relationship between T2DM and NAFLD is well-established, as insulin resistance, a hallmark of T2DM, promotes hepatic lipid accumulation, while NAFLD exacerbates hyperglycemia and systemic inflammation (4).

Epidemiologically, the global prevalence of NAFLD in the general population is approximately 30–38%, but it surges to 55–70% among individuals with T2DM (1). In patients with T2DM, NAFLD often presents with advanced features; for instance, a prospective study reported a 65% prevalence of NAFLD in adults aged ≥50 years with T2DM, with 14% exhibiting advanced fibrosis (3). Regional variations are notable, with higher rates in South Asia due to rising obesity and urbanization (2). In Pakistan, NAFLD affects about 30% of the general population, escalating to 58% in those with T2DM, underscoring a substantial burden in this demographic (5). Among Pakistani diabetic patients, NAFLD prevalence reaches 71%, strongly associated with elevated body mass index (BMI >25 kg/m²) and poor glycemic control (HbA1c >8.5%) (6).

Management of T2DM in the context of NAFLD prioritizes lifestyle interventions and pharmacotherapy to improve glycemic control and mitigate hepatic injury. Metformin remains the first-line agent, demonstrating modest benefits in reducing hepatic steatosis through improved insulin sensitivity, though its effects on advanced fibrosis are limited (7). When metformin monotherapy is insufficient, second-line options include sulfonylureas (e.g., modified-release gliclazide) or dipeptidyl peptidase-4 inhibitors (DPP-4i, e.g., sitagliptin). Sulfonylureas enhance insulin secretion but are linked to weight gain and hypoglycemia, potentially worsening NAFLD progression (8). In contrast, DPP-4i, such as sitagliptin, offer weight-neutral effects and may attenuate hepatic inflammation, with clinical trials showing reductions in liver enzymes and fibrosis scores in NAFLD patients (4). Direct comparisons, however, reveal mixed outcomes; for example, adding sitagliptin to metformin in T2DM with NAFLD led to greater improvements in fasting blood sugar (mean reduction: 20 mg/dL), triglycerides (mean reduction: 30 mg/dL), and alanine aminotransferase (mean reduction: 15 U/L) compared to metformin alone (9). Yet, evidence on sulfonylureas versus DPP-4i in NAFLD-specific cohorts remains sparse, with some reviews indicating neutral cardiovascular effects for DPP-4i but potential risks with sulfonylureas (10).

Despite these therapeutic options, gaps persist in optimizing regimens for comorbid T2DM and NAFLD, particularly in resource-limited settings where advanced diagnostics are unavailable. Randomized controlled trials comparing combination therapies are therefore essential to guide evidence-based practice and align with international recommendations that emphasize individualized treatment targeting both glycemic control and hepatic outcomes.

The rationale for conducting this study in the Pakistani population arises from the high dual burden of T2DM and NAFLD, driven by genetic predispositions, dietary patterns rich in refined carbohydrates, and increasingly sedentary lifestyles in urban settings. With NAFLD prevalence among Pakistani diabetic patients ranging from 58% to 71% and limited access to newer pharmacological agents such as GLP-1 receptor agonists or SGLT2 inhibitors, evaluating cost-effective and widely available therapeutic combinations is particularly relevant (5,6). Comparing metformin combined with modified-release gliclazide versus metformin combined with sitagliptin may therefore help identify practical treatment strategies that can improve glycemic control while potentially reducing the progression of liver-related complications in this high-risk population.

Methodology

This randomized controlled trial was conducted at Nishtar Hospital, Multan, from January 2025 to October 2025. Ninety eligible patients aged 30–60 years with T2DM and NAFLD were randomized into two groups (n=45 each). Sample size was calculated using the WHO calculator for comparing two means, assuming mean HbA1c values of 6.5% and 6.4%, a pooled standard deviation of 0.16, 80% power, and a 5% significance level. The calculated sample size was 90 patients (45 per group). All patients aged 30–60 years of either sex with T2DM (FBS ≥126 mg/dL, RBS ≥200 mg/dL, or HbA1c ≥6.5%), confirmed NAFLD having HbA1c between 6.5% and 11% on metformin 1000 mg/day were included in our study while patients with major cardiovascular events, AST/ALT >2.5× upper limit, renal impairment, Insulin therapy, recent corticosteroid use and pregnant women were excluded. These patients were randomly divided into 2 groups using computer-generated random tables. Group A received metformin 1000 mg/day plus MR gliclazide 60 mg/day, and Group B received metformin 1000 mg/day plus sitagliptin 100 mg/day for 12 weeks. The primary outcome was the change in HbA1c. Statistical analysis was performed using SPSS version 25. Paired sample t-test was applied to compare mean HbA1c values at baseline and 12 weeks after treatment within the same groups. In contrast, the independent-samples t-test was used to compare post-treatment mean HbA1c values between the 2 groups, with a 95 CI (using ≤0.05 as the level of significance).

Results

A total of 90 participants with type 2 diabetes mellitus were included in the study and randomly allocated into two equal groups (Group A: n = 45; Group B: n = 45). The baseline demographic and clinical characteristics of the participants were comparable between the two groups. The mean age of participants in Group A was 48.2 ± 6.4 years, while in Group B it was 47.9 ± 5.9 years, with no statistically significant difference between the groups (p = 0.81). Male participants constituted 57.8% (n = 26) of Group A and 53.3% (n = 24) of Group B (p = 0.67). The mean body mass index (BMI) was 29.4 ± 3.1 kg/m² in Group A and 29.1 ± 3.3 kg/m² in Group B (p = 0.72). Similarly, baseline glycemic status was comparable, with mean HbA1c values of 8.12 ± 0.84% in Group A and 8.05 ± 0.79% in Group B (p = 0.69). These findings indicate that both groups were well matched at baseline with respect to demographic and clinical characteristics (Table 1). After 12 weeks of treatment, both groups showed a significant reduction in HbA1c levels compared with baseline. In Group A, the mean HbA1c decreased from 8.12 ± 0.84% at baseline to 6.91 ± 0.73% after 12 weeks, representing a mean reduction of 1.21 ± 0.42% (p < 0.001). Similarly, Group B showed a decrease in HbA1c from 8.05 ± 0.79% to 6.87 ± 0.70%, corresponding to a mean reduction of 1.18 ± 0.39% (p < 0.001).

Although both treatment approaches resulted in statistically significant improvements in glycemic control within each group, the difference in mean HbA1c reduction between Group A and Group B was not statistically significant (p = 0.62), suggesting comparable efficacy of the two interventions over the 12-week study period (Table 2).

Table 1: Baseline Characteristics

Variable	Group A (n=45)	Group B (n=45)	p-value
Age (years)	48.2 ± 6.4	47.9 ± 5.9	0.81
Male, n (%)	26 (57.8%)	24 (53.3%)	0.67
BMI (kg/m²)	29.4 ± 3.1	29.1 ± 3.3	0.72
Baseline HbA1c (%)	8.12 ± 0.84	8.05 ± 0.79	0.69

Table 2: HbA1c Comparison After 12 Weeks

Group	Baseline HbA1c	12 Weeks HbA1c	Mean Reduction	p-value (within group)
Group A	8.12 ± 0.84	6.91 ± 0.73	1.21 ± 0.42	<0.001
Group B	8.05 ± 0.79	6.87 ± 0.70	1.18 ± 0.39	<0.001

Between-group comparison of mean HbA1c reduction: p = 0.62

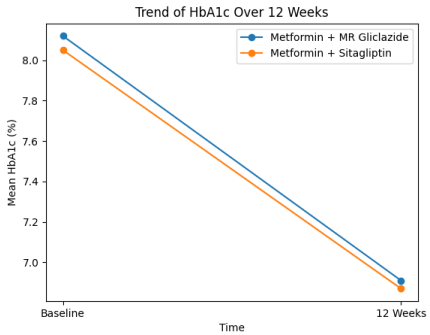

Figure 1: Line graph showing reduction in mean HbA1c from baseline to 12 weeks in both groups.

Discussion

The present randomized controlled trial compared the efficacy of metformin combined with modified-release gliclazide (Group A) versus metformin combined with sitagliptin (Group B) in patients with type 2 diabetes mellitus (T2DM) and non-alcoholic fatty liver disease (NAFLD) over 12 weeks. Both regimens demonstrated significant within-group reductions in HbA1c levels (1.21% in Group A and 1.18% in Group B, both $p < 0.001$), yet no statistically significant difference between groups was observed ($p = 0.62$). These findings indicate comparable glycemic efficacy of the two combinations in this comorbid population, aligning with the need for tailored therapies that address both hyperglycemia and hepatic steatosis without exacerbating liver burden.

Our results corroborate recent evidence from noninferiority trials evaluating these agents in the management of T2DM. For instance, a single-center prospective study in treatment-naïve T2DM patients with glucotoxicity reported similar HbA1c reductions after 12 weeks: 4.03% with sitagliptin plus metformin versus 4.13% with gliclazide plus metformin, confirming noninferiority (mean difference: -0.097%, 95% CI: -0.648 to 0.453) (11). While that trial reported faster target achievement and greater weight loss with sitagliptin, our study found no intergroup differences in HbA1c reduction, possibly because our study focused on patients with established NAFLD, where baseline insulin resistance may modulate responses. Similarly, a network meta-analysis of 21 RCTs involving 1,717 T2DM patients with metabolic dysfunction-associated steatotic liver disease (MASLD, formerly NAFLD) ranked sitagliptin lower for HbA1c reduction than agents such as ertugliflozin or pioglitazone, while gliclazide was among the least effective for fasting plasma glucose (FPG) lowering (12). In our cohort, both combinations achieved robust improvements in HbA1c, suggesting that, in real-world settings with NAFLD comorbidity, these affordable options maintain parity in glycemic control. However, neither excelled in hepatic-specific outcomes based on the provided data.

In NAFLD-specific contexts, adding sitagliptin to metformin has shown benefits beyond glycemia. A double-blind RCT in 66 T2DM patients with NAFLD reported greater improvements in fasting blood sugar (FBS), triglycerides, alanine aminotransferase (ALT), and vitamin D3 with sitagliptin plus metformin versus metformin alone after 12 weeks (e.g., ALT reduction: $p < 0.05$) (9). Although our trial did not directly measure liver enzymes or steatosis, the comparable HbA1c reductions imply potential indirect hepatic benefits, as sustained glycemic control mitigates lipotoxicity in NAFLD. In contrast, a triple-blind RCT in 120 non-diabetic NAFLD patients found that sitagliptin (50 mg daily) significantly reduced fibrosis scores ($p = 0.001$) and liver enzymes (AST: $p < 0.001$; ALT: $p = 0.036$) over 56 weeks, with effects more pronounced in non-obese individuals (13). Our obese-predominant cohort (mean BMI ~29 kg/m²) may explain the lack of intergroup differences, highlighting BMI as a modifier of DPP-4 inhibitor efficacy in NAFLD.

Narrative reviews further contextualize these findings. One analysis of anti-diabetic drugs in NAFLD reported contradictory results for metformin and DPP-4 inhibitors like sitagliptin, with pioglitazone showing consistent improvements in NASH, but emphasized sitagliptin's potential to reduce inflammation without weight gain (4). In our study, the absence of significant differences between groups supports the use of either regimen in resource-constrained settings, where gliclazide's lower cost may favor it over sitagliptin. Another review positioned gliclazide modified-release as a safe second-line option post-metformin, citing real-world data showing superior initial HbA1c reductions compared to sitagliptin (HR 1.35 for HbA1c <7.0%), though with similar durability (14). This aligns with our equivalent efficacy, but underscores gliclazide's role in rapid control, which could benefit NAFLD progression by reducing glucotoxicity.

Broader meta-analyses reinforce these observations. A network meta-analysis of diabetes medications in NAFLD (49 trials, 3,836 patients) ranked DPP-4 inhibitors, such as sitagliptin, highest for AST reduction (WMD = -6.89, 95% CI = -11.72 to -2.07), while sulfonylureas were less prominent (15). However, in a head-to-head RCT comparing sitagliptin, dapagliflozin, and lobeglitazone as add-ons to metformin-sulfonylurea in uncontrolled T2DM, all three showed good glucose-lowering effects (HbA1c reductions of ~0.8–1.0%). Still, sitagliptin lacked the favorable changes in body composition observed with others (16). Our trial's comparable outcomes suggest that in NAFLD-T2DM, the choice between gliclazide and sitagliptin may hinge on patient-specific factors like hypoglycemia risk (lower with sitagliptin) or cost.

These comparisons highlight strengths and limitations. Both regimens' efficacy in our study supports their use in NAFLD-T2DM, where glycemic control is pivotal to halt fibrosis. However, the lack of NAFLD-specific endpoints (e.g., ALT, steatosis via imaging) limits direct hepatic comparisons; future analyses should incorporate these. The 12-week duration may underestimate long-term differences, as reviews indicate sustained benefits with DPP-4 inhibitors in fibrosis (4). Our well-matched baseline characteristics (e.g., HbA1c ~8.1%, BMI ~29 kg/m²) enhance internal validity, but generalizability to non-Pakistani populations is uncertain.

In the Pakistani context, where T2DM prevalence exceeds 17%, and NAFLD affects 58–71% of diabetics, driven by urbanization and high-carbohydrate diets, affordable therapies like metformin-gliclazide are crucial amid limited access to GLP-1 agonists or SGLT2 inhibitors (12,14). Our findings advocate for these combinations to optimize glycemic control, potentially delaying NAFLD progression in this high-burden setting.

Conclusion

Our study results show that both treatment regimens demonstrate comparable efficacy in terms of glycemic control, as the difference in mean reduction in HbA1c between the groups was insignificant. However, Metformin combined with either MR gliclazide or sitagliptin significantly improves glycemic control in patients with T2DM and NAFLD. Clinicians treating these patients can employ these regimens, and treatment selection should be individualized based on the patient's profile, safety, and affordability.

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-MMUN-025-02-24)

Consent for publication
Approved

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Conflict of interest

The authors declared no conflict of interest.

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