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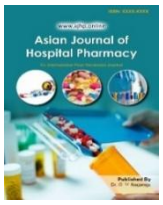

A PROSPECTIVE OBSERVATIONAL STUDY ON SAFETY AND EFFICACY OF METFORMIN IN COMBINATION WITH DPP4 INHIBITORS IN TYPE 2 DIABETES MELLITUS

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Abstract

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by insulin resistance and impaired insulin secretion, leading to persistent hyperglycemia and various complications. Effective glycemic control is essential to prevent disease progression and associated complications. Metformin is widely used as a first-line antidiabetic agent, while DPP-4 inhibitors such as Sitagliptin improve glycemic control by enhancing incretin hormone activity. The present prospective observational study was conducted to evaluate the safety and efficacy of metformin in combination with DPP-4 inhibitors in patients with T2DM. A total of 80 patients were enrolled and observed over a period of six months. Patient demographics, family history, BMI, comorbidities, prescription patterns, and adverse drug reactions were recorded. Efficacy was assessed by comparing fasting plasma glucose (FPG) and random blood sugar (RBS) levels before and after treatment. The results demonstrated a significant reduction in FPG from 170.8 mg/dL to 120.6 mg/dL, indicating improved glycemic control. RBS levels also showed notable improvement following therapy. Safety evaluation revealed that only 5% of patients experienced mild adverse effects, with no serious complications reported. The study concludes that metformin in combination with DPP-4 inhibitors is an effective and well-tolerated therapeutic approach for managing T2DM, offering better glycemic control and improved patient outcomes in routine clinical practice.

Keywords: *Type 2 Diabetes Mellitus, Metformin, DPP-4 Inhibitors, Glycemic Control, Safety, Efficacy, Hyperglycemia.*

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from insulin resistance and progressive pancreatic β-cell dysfunction [1]. It is one of the most common non-communicable diseases worldwide and poses a major burden on healthcare systems. According to the International Diabetes Federation, approximately 537 million adults were living with diabetes globally in 2021, and this number is expected to increase to 783 million by 2045, with T2DM accounting for nearly 90–95% of all diabetes cases [2]. In India, the prevalence of diabetes is rapidly increasing due to urbanization, sedentary lifestyles, obesity, and dietary changes, making it a significant public health concern [3].Metformin is widely recommended as the first-line oral antidiabetic agent because of its proven efficacy, safety, and cost-effectiveness in lowering blood glucose levels. It primarily acts by reducing hepatic glucose production, improving peripheral insulin sensitivity, and enhancing glucose uptake [4]. Additionally, metformin has beneficial effects on body weight and cardiovascular risk factors, making it an ideal initial therapy for T2DM patients [5]. However, due to the progressive nature of the disease, monotherapy with metformin often becomes insufficient over time, necessitating the addition of other antidiabetic agents to maintain glycemic targets [6].

Dipeptidyl peptidase-4 (DPP-4) inhibitors have emerged as an important class of oral hypoglycemic agents for combination therapy in T2DM. These drugs act by inhibiting the DPP-4 enzyme responsible for the degradation of

incretin hormones such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), thereby prolonging their action [7]. This mechanism enhances glucose-dependent insulin secretion, suppresses glucagon release, and improves both fasting and postprandial blood glucose levels [8]. Commonly used DPP-4 inhibitors include Sitagliptin, Vildagliptin, Linagliptin, and Teneligliptin.The combination of metformin and DPP-4 inhibitors has gained significant clinical importance due to their complementary mechanisms of action. While metformin primarily targets insulin resistance and hepatic glucose output, DPP-4 inhibitors improve β-cell function and incretin-mediated glucose regulation [9]. This combination has been shown to provide better glycemic control compared to monotherapy, with a lower risk of hypoglycemia and minimal impact on body weight [10-15].

Despite the increasing prescription of metformin in combination with DPP-4 inhibitors, there is limited real-world evidence regarding their safety and efficacy in routine clinical settings. Prospective observational studies play an important role in evaluating treatment outcomes, adverse drug reactions, and patient adherence under actual clinical practice conditions. Therefore, the present study was designed to assess the safety and efficacy of metformin in combination with DPP-4 inhibitors in patients with Type 2 Diabetes Mellitus, with a focus on glycemic outcomes and adverse effects.

MATERIALS AND METHODS

Study Site

The present study was conducted at Gleneagles Global Hospital, Lakdikapul, Hyderabad, Telangana, India, a tertiary care multispecialty hospital providing specialised diabetic care.

Study Design

A prospective observational study was carried out to evaluate the safety and efficacy of Metformin in combination with DPP-4 inhibitors in patients diagnosed with Type 2 Diabetes Mellitus.

Study Duration

The study was conducted over a period of six months.

Study Population and Sample Size

A total of 80 patients diagnosed with Type 2 Diabetes Mellitus and receiving metformin in combination with DPP-4 inhibitors were enrolled in the study.

Eligibility Criteria

Inclusion Criteria

- Patients aged between 30 and 80 years.
- Both male and female patients.
- Patients with previously diagnosed or newly diagnosed Type 2 Diabetes Mellitus.
- Conscious and cooperative patients.
- Patients willing to provide written informed consent.

Exclusion Criteria

- Pregnant and lactating women.
- Non-cooperative patients.
- Patients with psychiatric disorders.
- Patients diagnosed with Type 1 Diabetes Mellitus.
- Patients with post-acute pancreatitis.

Data Collection Sources

Data were collected from the following sources:

- Physician progress notes
- Inpatient and outpatient prescriptions
- Clinical laboratory reports
- Diabetes medication charts
- Patient interviews
- Informed consent forms

Data Analysis

Demographic characteristics such as age, gender, body mass index (BMI), family history, and comorbidities were recorded. Safety assessment was carried out by documenting adverse drug reactions and side effects during the study period. Efficacy was evaluated based on glycemic parameters including fasting plasma glucose (FPG) and random blood sugar (RBS) before and after treatment. Prescription patterns of metformin and DPP-4 inhibitor combinations were also analyzed. The influence of comorbidities such as hypertension, coronary artery disease, hypothyroidism, myocardial infarction, diabetic retinopathy, and nephropathy on treatment outcomes was assessed[16-19].

Ethical Approval

The study protocol was approved by the Institutional Ethics Committee of Gleneagles Global Hospital prior to initiation of the study.

Statistical Analysis

The collected data were analyzed using appropriate statistical methods and results were expressed as mean, percentage, and standard deviation. Comparative analysis was performed using suitable statistical tools to determine significance.

RESULTS AND DISCUSSION

Demographic Characteristics

A total of 80 patients diagnosed with Type 2 Diabetes Mellitus (T2DM) and prescribed Metformin in combination with DPP-4 inhibitors were included in this prospective observational study. The demographic and clinical profile of the study population was evaluated to determine the safety and efficacy of the prescribed therapy.

Gender Distribution

The gender-wise distribution revealed that 49 patients (61.25%) were female and 31 patients (38.75%) were male, as shown in Table 01. The higher female predominance in this study may indicate increased disease burden or better treatment-seeking behavior among women.

Table 01: Gender-wise distribution of patients receiving metformin in combination with DPP-4 inhibitors.

Gender	Number of Patients	Percentage (%)
Male	31	38.75
Female	49	61.25

Age Distribution

The age distribution of the study population is presented in Table 02 and Figure 01. The majority of patients belonged to the 51–60 years age group (37.5%), followed by 41–50 years (22.5%) and 61–70 years (22.5%). This suggests that T2DM is more prevalent in middle-aged and elderly individuals.

Table 02: Age-wise distribution of the study population prescribed metformin with DPP-4 inhibitors.

Age Group (Years)	Number of Patients	Percentage (%)
30–40	8	10.0
41–50	18	22.5
51–60	30	37.5
61–70	18	22.5
71–80	6	7.5

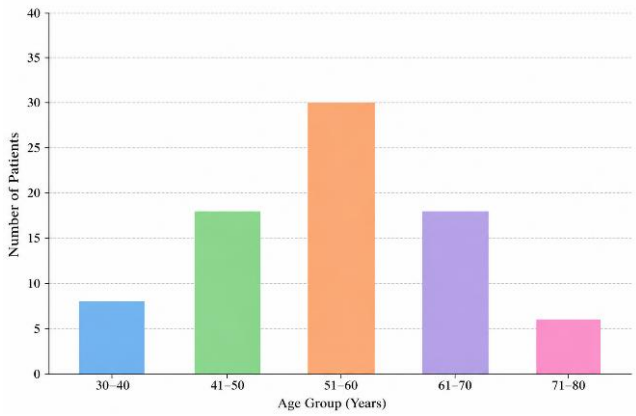

Figure 01: Age-wise distribution of study subjects

Family History

As shown in Table 3, 58.75% (47 patients) had a positive family history of diabetes, while 41.25% (33 patients) had no family history. This finding supports the hereditary influence in T2DM progression.

Table 03: Distribution based on family history

Family History	Number of Patients	Percentage (%)
Yes	47	58.75

No	33	41.25

Body Mass Index (BMI)

The BMI analysis showed that 37 patients (46.25%) were overweight and 24 patients (30%) were obese, as summarised in Table 04 and Figure 02. Increased BMI is a significant contributing factor for insulin resistance and poor glycemic control.

Table 04: Distribution based on body mass index

Category	BMI Range	Number of Patients
Underweight	<18.4	0
Normal weight	18.5–24.9	19
Overweight	25–29.9	37
Obese	30–40	24

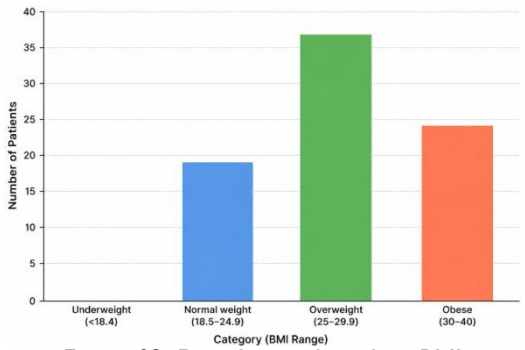

Figure 02: Distribution based on BMI

Comorbidity Profile

The comorbidity assessment showed that hypertension (95%) was the most common associated condition, followed by CAD (25%) and hypothyroidism (21.25%), as shown in Table 05 and Figure 03. This indicates the significant burden of cardiovascular and endocrine disorders in diabetic patients.

Table 05: Distribution based on comorbidities

Disease	Total Cases
CAD + DM	20
LV Dysfunction + DM	6
Retinopathy + DM	5
Diabetic Foot Ulcer + DM	10
HTN + DM	76
MI + DM	4
Hypothyroidism + DM	17

Multiple Comorbidities

Multiple comorbidities were frequently observed. The most common combination was HTN + CAD + DM (22 cases), as shown in Table 06 and Figure 03. The presence of multiple comorbid conditions may increase disease complexity and influence therapeutic outcomes.

Table 06: Distribution based on multiple comorbidities

Disease Combination	Number of Cases
HTN + Cervical Spondylitis + DM	1
HTN + CAD + DM	22
HTN + LV Dysfunction + DM	1
HTN + Retinopathy + DM	1
Diabetic Foot Ulcer + DM + HTN	3
HTN + Nephropathy + DM	3

HTN + Hypothyroidism + DM	7

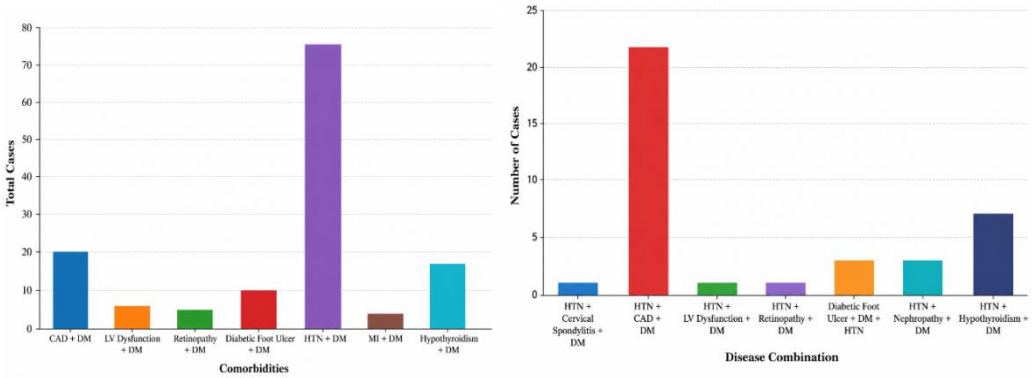

Figure 03: Distribution based on comorbidities and multiple comorbidities

Prescription Pattern

The prescription pattern analysis revealed that Istamet (26.25%) was the most commonly prescribed brand, followed by Janumet (23.75%) and Sitara-M (20%), as shown in Table 07 and Figure 04.

Table 07: Different brands of metformin with DPP-4 inhibitors are prescribed

Brand Name	Number of Patients	Percentage (%)
Glavusmet	12	15.0
Teneglip-M	2	2.5
Istamet	21	26.25
Zildaglip-M	1	1.25
Janumet	19	23.75
Vildacad-M	4	5.0
Sitara-M	16	20.0
Vilda-Met	5	6.25

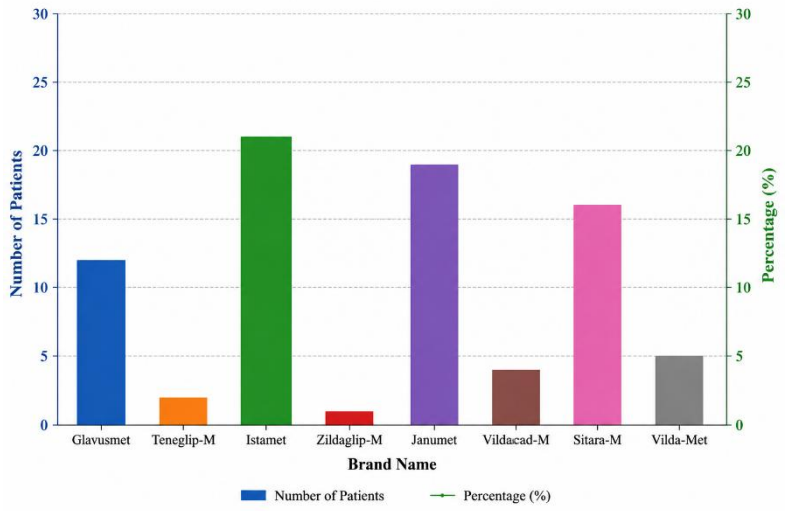

Figure 07: Prescription pattern of metformin and DPP-4 inhibitor combinations

Safety Assessment

The safety evaluation showed that 75 patients (93.75%) experienced no adverse effects. Only 5 patients (6.25%) reported mild adverse effects such as ketoacidosis, UTI, and hypoglycemia.

Efficacy Assessment

Fasting Plasma Glucose (FPG)

The mean FPG significantly reduced from 170.8 mg/dL before treatment to 120.6 mg/dL after treatment. This reduction confirms the effectiveness of the combination therapy in improving fasting glycemic levels.

Random Blood Sugar (RBS)
Similarly, the mean RBS decreased from 230.1 mg/dL to 143.2 mg/dL. The significant reduction in RBS indicates better postprandial glucose control.

Prescription Accuracy
The evaluation of prescription accuracy demonstrated that all 80 prescriptions were found to be appropriate and in accordance with the clinical indication for Type 2 Diabetes Mellitus treatment. No inappropriate prescriptions were identified during the study period. Similarly, dosing assessment revealed that all patients received the correct therapeutic dose, with no cases of overdose or underdose observed. These findings indicate a high level of adherence to standard treatment guidelines and reflect rational prescribing practices by clinicians. Proper indication and dose selection play a crucial role in achieving optimal therapeutic outcomes and minimising the risk of adverse drug reactions.

CONCLUSION
The present study concluded that the combination therapy of Metformin and DPP-4 inhibitors is an effective and safe treatment option for patients with Type 2 Diabetes Mellitus. The therapy showed significant improvement in glycemic control by reducing fasting plasma glucose and random blood sugar levels over the study period. The combination was well tolerated, with only minimal adverse effects reported and no serious complications observed. These findings support the use of metformin with DPP-4 inhibitors as a reliable therapeutic approach for achieving better diabetes management and improving patient outcomes.

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Nil

CONFLICT OF INTEREST
The authors declare that there are no conflicts of interest regarding the publication of this paper.

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AUTHOR CONTRIBUTIONS
K. Chandana, M. Abhinaya, P. Akhila, and P. Swetha contributed to the study conceptualization, data collection, patient interviews, data analysis, and manuscript preparation. Dr. B. Manjula supervised the study, reviewed the manuscript critically, and approved the final version for submission. All authors have read and approved the final manuscript.

ETHICAL STATEMENT
The ethical committee clearance was obtained from Gleneagles Global Hospital before initiating the study. Reference number: AIPS/ 04/ IEC/05

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