

Safety and Efficacy of Different Classes of Antidiabetic Agents as Add on Therapy to Metformin in Management of Uncontrolled Type-2 Diabetes Mellitus Patients

Sai Vamshi Kandukuri¹, Siva Subramanyam Bandaru², Lavanya Gunda¹, Meghana Shanigaram¹, Sneha Priya Voorugonda¹, Sharvana Bhava Bandaru Sheshagiri^{*}, Venkateshwarlu Eggadi¹, Kottai Muthu Arumugam³.

¹Department of Clinical Pharmacy & Pharm.D., MGM Hospital, Vaagdevi College of Pharmacy, Hanamkonda, Warangal, Telangana, India.

²Consultant Physician & Diabetologist, Ajara Hospitals, Warangal, Telangana, India.

³Professor, Department of Pharmacy, FEAT, Annamalai University, Chidambaram, Tamilnadu, India

Address for Correspondence: Dr. B.S. Sharvana Bhava, Professor and Head, Department of Clinical Pharmacy & Pharm.D., Vaagdevi College of Pharmacy, Warangal, Telangana.

ABSTRACT

Objective:

To compare the safety and efficacy of different classes of Antidiabetic Agents as add-on therapy to Metformin in patients with uncontrolled Type-2 Diabetes Mellitus (T₂DM).

Methods:

A Prospective, Observational, Comparative and Multi-centric study was conducted on 1870 patients with uncontrolled T₂DM at Sri Bhadrakali Clinic. Patients were grouped based on the class of Antidiabetic Agent added to Metformin. Glycemic control was assessed using Fasting Blood Sugar (FBS), Post Prandial Blood Sugar (PPBS), and Glycated Hemoglobin (HbA_{1c}) before treatment and at 3 and 6 months post treatment. Safety was evaluated based on reported Adverse Drug Reactions (ADRs), including Hypoglycaemia, Gastrointestinal disturbances, and Genitourinary infections.

Results:

Among dual therapy regimens, Metformin combined with SGLT-2 inhibitors and DPP-4 inhibitors demonstrated superior glycemic control, with a significant reduction in FBS, PPBS, and HbA_{1c} levels ($p < 0.05$). Triple therapy combinations, particularly metformin + sulfonylurea + DPP-4 inhibitor, showed enhanced efficacy but a higher incidence of hypoglycemia. SGLT-2 inhibitor combinations were associated with mild Genitourinary infections but had favourable weight and glycemic outcomes. DPP-4 inhibitors were better tolerated overall.

Conclusion:

DPP-4 and SGLT-2 inhibitors, when added to metformin, are effective and relatively safe options for the management of uncontrolled T₂DM. Individualized therapy based on patient profile, comorbidities, and ADR risk can optimize glycemic outcomes and minimize complications.

Keywords:

Type-2 Diabetes Mellitus, Metformin, Add-on Therapy, DPP-4 Inhibitors, SGLT-2 Inhibitors, Sulfonylureas, Glycemic Control, Safety, HbA_{1c}

INTRODUCTION:

Diabetes Mellitus is a group of metabolic disorders characterized by chronic hyperglycemia due to deficiency of insulin secretion and/or resistance to insulin action. The chronic hyperglycemia of diabetes is associated with metabolic abnormalities in carbohydrates, lipids, and proteins which results in long-term damage, dysfunction and failure of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels (long term complications of diabetes which include microvascular, macrovascular, and neuropathic disorders) [1,2].

The recommended initial T₂DM management approach includes life style changes and monotherapy (usually with Metformin). If the HbA_{1c} goal has not been met with in approximately 3 months of starting initial therapy, treatment should be intensified by adding a second agent, consider one of the five treatment options combined with Metformin: Sulfonylurea (SU), Thiazolidinedione (TZD), Dipeptidyl Peptidase (DPP-4) inhibitor, Sodium Glucose Co-transporter (SGLT2) inhibitor and 2 injectable agents Glucagon-Like Peptide-1 Receptor Agonists (GLP-1 RA) or Basal Insulin. Glycaemic control should be reassessed again approximately 3 months, and triple therapy should be considered if the HbA_{1c} target is still not achieved, combination injectable therapy including Basal Insulin may be considered to be obtain glycaemic control. In patients with high baseline HbA_{1c} levels, initial treatment with dual-combination therapy can be considered. The AACE/ACE suggests initial dual therapy (i.e., Metformin plus another agent in addition to lifestyle therapy) for patients with an entry HbA_{1c} levels $\geq 7.5\%$, whereas the ADA suggests considering initial dual therapy if the entry HbA_{1c} is $\leq 9\%$ [3].

The main aim of this study is to compare Safety and Efficacy of different classes of Antidiabetic agents as add on therapy to Metformin in Management of uncontrolled Type 2 Diabetes Mellitus (T2DM) Patients.

MATERIAL AND METHODS:

Study Design:

It was a Prospective, Observational, Comparative Multi Centric study conducted in Ajara Hospitals and Sri Bhadrakali Diabetic Clinic.

An approval was obtained prior to the study from the Institutional Human Ethics Committee. The approval number was “KIEC-2023/Pharm.D-2018/Project-11” and informed consent was obtained from each patient after having been informed of all the aspects relevant to the study in their local language.

Study Duration: 6 Months

Inclusion Criteria:

Inclusion criteria were patients who were willing to participate and submit the informed consent form, Age group 18 years or older with uncontrolled T₂DM with Metformin, Patients who were receiving Sulfonylureas, Alpha Glucosidase Inhibitors, Thiazolidinediones, Dipeptidyl Peptidase-4 Inhibitors, Sodium Glucose Co-transporter -2 inhibitors as add on along with metformin.

Exclusion Criteria:

Exclusion criteria included Pregnant (Gestational Diabetes) or lactating women with Diabetes Mellitus, Patients of age group 17 years or younger, with Type 1 Diabetes Mellitus, with *denovo* Diabetes Mellitus, Patients presenting with moderate to severe renal insufficiency [4], who were already diagnosed with Diabetic complications like Diabetic Neuropathy, Diabetic Nephropathy etc., patients receiving insulin as an add on therapy to Metformin, not willing to participate in the study, not willing to disclose the information.

Parameters Assessed:

FBS, PLBS and HbA_{1c} values were assessed once in every 3 months during the treatment. Primary end point was change in HbA_{1c}, FBS and PLBS levels at 12 weeks (3months) and 24 Weeks (6months) as compared to the baseline levels in all five groups.

Statistical Analysis:

All the parameters were expressed as Mean $\pm$ Standard Deviation (SD). Data analysis was performed using MS Excel and Graph Pad Prism 9.5.1 Version. Statistical analysis was performed using ANOVA one-way method followed by Tukey's multiple comparison test to assess the significant difference between the efficacy parameters pre and post add-on treatment.

P value of <0.005 was considered statistically significant.

RESULTS:

Study Population:

Out of 2231 screened patients with Type 2 Diabetes Mellitus (T₂DM), 1870 met the inclusion criteria and were enrolled in the study conducted at Ajara Hospitals and Sri Bhadrakali Clinic, Warangal.

Sample Distribution:

In a total of 1870 patients. 168 patients received dual therapy combination of Metformin(M) + Sodium – glucose cotransporter 2 Inhibitor (SGLT-2 Inhibitors) ($n_1=168$), 296 patients received a combination of Metformin(M) + Dipeptidyl Peptidase-4 Inhibitors (DPP-4 Inhibitors) ($n_2=296$), 338 patients received a combination of Metformin(M) + Sulfonylureas (SU) ($n_3=338$), 148 patients received a combination of Metformin(M) + Thiazolidinediones (TZD) ($n_4=148$), 200 patients received a combination of Metformin(M) + α -Glucosidase Inhibitors (AGI) ($n_5=200$), 228 patients received triple therapy combination of Metformin(M) + DPP4 Inhibitors + SU ($n_6=228$), 214 patients received combination of Metformin(M) + SGLT-2 Inhibitors + SU ($n_7=214$), 80 patients received combination of Metformin(M) + TZD + SU ($n_8=80$), 198 patients received combination of Metformin(M)+ α -Glucosidase Inhibitors+SU ($n_9=198$), [$n_1+n_2+n_3+n_4+n_5+n_6+n_7+n_8+n_9(N)=1870$].

Demographic Characteristics

The study population included 972 (52%) female and 898 (48%) male patients. The majority (1253 patients, 67%) were aged between 41–60 years. The remaining were 30–40 years (13%), 61–70 years (15%), and >70 years (5%).

Table 1: Demographic Distribution of Patients (N = 1870)

Parameter	Category	Frequency	Percentage (%)
Gender	Male	898	48%
	Female	972	52%
Age Group	30–40 years	243	13%
	41–60 years	1253	67%
	61–70 years	281	15%
	>70 years	93	5%

Treatment Groups

Patients were categorized based on treatment regimens into nine groups, as shown in Table 2.

Table 2: Distribution of Patients Based on Treatment Combinations

Treatment Group	Number of Patients
Metformin + SGLT2 Inhibitor	168
Metformin + DPP-4 Inhibitor	296
Metformin + Sulfonylurea (SU)	338
Metformin + Thiazolidinedione	148
Metformin + α -Glucosidase Inhibitor (AGI)	200
Metformin + DPP-4i + SU	228
Metformin + SGLT2i + SU	214
Metformin + TZD + SU	80
Metformin + AGI + SU	198
Total	1870

Glycemic Control (FBS, PPBG, and HbA_{1c} Reduction)

Over 12 weeks, a significant reduction in fasting blood sugar (FBS), postprandial blood sugar (PPBG), and HbA_{1c} levels was observed in all therapy groups. While all combinations showed improvement, certain therapies exhibited better glycemic control.

Table 3: Mean Reduction in Glycemic Parameters After 12 Weeks (Dual Therapy)

Treatment Group	FBS (mg/dL) Mean $\pm$ SD	PPBG(mg/dL) Mean $\pm$ SD	HbA _{1c} (%) Mean $\pm$ SD
Metformin + SGLT2i	9.81 $\pm$ 4.68	17.92 $\pm$ 11.42	0.63 $\pm$ 0.41
Metformin + DPP-4i	7.97 $\pm$ 6.83	13.80 $\pm$ 8.81	0.47 $\pm$ 0.32
Metformin + SU	10.04 $\pm$ 3.84	18.76 $\pm$ 10.94	0.56 $\pm$ 0.37
Metformin + TZD	10.66 $\pm$ 5.64	24.80 $\pm$ 16.23	1.05 $\pm$ 0.18
Metformin + AGI	9.00 $\pm$ 4.52	15.45 $\pm$ 9.71	0.42 $\pm$ 0.27

Observation: Among dual therapies, Metformin + TZD combination demonstrated the greatest reduction in FBS, PPBG, and HbA_{1c}.

Table 4: Mean Reduction in Glycemic Parameters After 12 Weeks (Triple Therapy)

Treatment Group	FBS (mg/dL) Mean± SD	PPBG (mg/dL) Mean ± SD	HbA _{1c} (%) Mean± SD
Metformin + DPP-4i + SU	11.19 ± 5.53	20.66 ± 15.76	0.50 ± 0.40
Metformin + SGLT2i + SU	13.56 ± 7.71	21.22 ± 16.61	0.58 ± 0.35
Metformin + TZD + SU	15.53 ± 2.42	20.65 ± 17.48	0.61 ± 0.44
Metformin + AGI + SU	12.37 ± 4.91	17.32 ± 13.40	0.48 ± 0.33

Observation: Among triple therapies, Metformin + TZD + SU provided the best improvement in FBS and HbA_{1c}, while Metformin + SGLT2i + SU showed the highest PPBG reduction.

Adverse Drug Reactions (ADRs)

A total of 118 ADRs were observed, with the most common being Hypoglycemia, Dizziness, Weight gain, and Genito-urinary tract infections (GUTIs).

Table 5: Incidence of Adverse Drug Reactions by Treatment Group

Treatment Group	Number of ADRs	% of Total ADRs
Metformin + DPP-4i	118	19%
Metformin + SU	112	18%
Metformin + SGLT2i + SU	83	13%
Metformin + DPP-4i + SU	78	12%
Metformin + AGI + SU	67	10%
Metformin + SGLT2i	64	10%
Metformin + AGI	54	8%
Metformin + TZD	38	6%
Metformin + TZD + SU	21	3%

Observation: The lowest ADRs were seen with Metformin + TZD + SU (3%) and Metformin + TZD (6%). The highest were in Metformin + DPP-4i group.

Specific Adverse Events

Table 6: Frequency of Most Common ADRs

ADR Type	Frequency (n)	% of Total ADRs
Hypoglycemia	112	27.6%
Dizziness	78	19.2%
Weight Gain	71	17.5%

Genito-Urinary Tract Infections	69	17.0%
Diarrhoea	67	16.3%
Total	397	100%

Observation: Hypoglycemia was the most frequently reported adverse event, predominantly associated with SU and DPP-4i containing regimens.

DISCUSSION:

This study evaluated the comparative efficacy and safety of various dual and triple Oral Hypoglycemic Agent (OHA) combinations in managing glycemic parameters among 1870 patients with Type 2 Diabetes Mellitus (T₂DM) over a 12-week period. The majority of patients were aged 41–60 years, consistent with the peak onset age for T₂DM in South Asian populations [5].

Efficacy

In dual therapy, Metformin + Thiazolidinedione (M+TZD) demonstrated the greatest reduction in Glycemic parameters—particularly HbA_{1C} ($1.05 \pm 0.18\%$), FBS (10.66 ± 5.64 mg/dL), and PLBS (24.80 ± 16.23 mg/dL). These findings are supported by previous research demonstrating TZDs' potent Insulin-sensitizing effects and long-term Glycemic durability [6,7].

Metformin + DPP-4 inhibitor (M+DPP-4i) and Metformin + SGLT-2 inhibitor (M+SGLT-2i) also showed notable reductions in HbA_{1C} ($0.45 \pm 0.51\%$ and $0.61 \pm 0.56\%$ respectively). These results are in line with Nauck et al., who reported similar reductions in HbA_{1C} using Sitagliptin and Vildagliptin as DPP-4 inhibitors [8]. SGLT-2 inhibitors also significantly reduced postprandial glucose levels due to their insulin-independent mechanism [9].

In contrast, Metformin + α -glucosidase inhibitor (M+AGI) was the least effective in all three Glycemic parameters. This is possibly due to AGI's slower onset of action and minimal effects on fasting glucose, as supported by Chiasson et al. [10].

Among triple therapy combinations, Metformin + Sulfonylurea + TZD (M+SU+TZD) was superior in reducing both FBS (15.53 ± 2.42 mg/dL) and HbA_{1C} ($0.61 \pm 0.44\%$). This aligns with data by Genuth et al., who reported improved β -cell preservation with TZD-based regimens [11]. For postprandial glucose control, Metformin + SU + SGLT-2 inhibitors provided the best improvement (21.22 ± 16.61 mg/dL), likely due to the complementary

mechanisms of SU (stimulating insulin release) and SGLT-2i (enhancing urinary glucose excretion) [12].

Notably, while numerical improvements in glycemic parameters were observed across all combinations, Statistical Significance was not achieved ($p > 0.05$), likely due to sample variability and short duration. However, clinical relevance remains substantial.

Safety

Among 1870 patients, the most reported Adverse Drug Reaction (ADR) was Hypoglycemia ($n=112$), primarily in groups containing Sulfonylureas—known to have Hypoglycemia risks due to their insulinotropic effect [13]. DPP-4i ($n=118$) and SU ($n=112$) groups reported the highest total ADRs, while TZD-based therapies had the lowest ($n=38$), reinforcing their tolerability profile. These findings are consistent with the known side effect profiles reported in large meta-analyses [14].

SGLT-2 inhibitor groups presented higher rates of Genito-urinary tract infections and hypotension, attributed to osmotic diuresis and glucosuria [10]. DPP-4 inhibitors were associated with dizziness, arthralgia, and nasopharyngitis, paralleling post-marketing safety data [15]. AGI-containing groups had prominent gastrointestinal side effects like bloating and flatulence, a well-documented class effect [16].

Weight gain was most evident in SU and TZD-containing groups, confirming findings by Kahn et al. that these agents promote Adipogenesis and Hyperinsulinemia [17]. Conversely, weight-neutral or weight-reducing effects were noted with DPP-4i and SGLT-2i regimens.

Thus, therapy should be tailored based on individual patient profiles—Metformin + TZD for durable control with lower Hypoglycemia risk; Metformin + SGLT-2i for obese patients or those with Cardiovascular risk; and AGIs for Postprandial Hyperglycemia control in patients tolerant to GI effects.

CONCLUSION

This comparative observational study of 1870 patients provides clinically meaningful insights into the efficacy and safety of different oral antidiabetic drug combinations in T₂DM management.

Among dual therapies, Metformin + Thiazolidinedione showed the best Glycemic control with acceptable safety, while Metformin + α -glucosidase inhibitors had the least efficacy.

In triple therapy, Metformin + Sulfonylurea + TZD was most effective in lowering FBS and HbA1c, whereas Metformin + Sulfonylurea + SGLT-2 inhibitor was superior for postprandial glucose control.

Sulfonylurea-based combinations were associated with the highest risk of hypoglycemia and weight gain.

DPP-4 inhibitors, despite moderate efficacy, presented the highest incidence of adverse events like dizziness and nasopharyngitis.

Thiazolidinedione-based therapies had the most favorable safety profile.

Overall, the study highlights how important it is to choose the right treatment for type 2 diabetes (T₂DM) based on how well it works and how well patients can tolerate it. More research with larger groups of people and longer follow-up periods is needed to confirm these results and better understand the long-term effects on heart health.

REFERENCE

1. Kharroubi AT. Diabetes Mellitus: The Epidemic of the Century. *World Journal of Diabetes*. 2015; 6(6): 850-867.
2. American Diabetes Association. Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care*. 2010; 33(Supplement_1): S62-S69.
3. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetic care*. July 1997; 20(7): 1183-1197.
4. DeFronzo RA. From the Triumvirate to the ominous octet: A new paradigm for the treatment of Type 2 Diabetes Mellitus. *Diabetes*. 2009; 58(4): 773-95.
5. Mohan V, et al. Epidemiology of type 2 diabetes: Indian scenario. *Indian J Med Res*. 2007;125(3):217-30.
6. Yki-Järvinen H. Thiazolidinediones. *N Engl J Med*. 2004;351(11):1106–18.
7. Dormandy JA, et al. Secondary prevention of macrovascular events in patients with T2DM in the PROactive Study. *Lancet*. 2005;366(9493):1279–89.
8. Nauck MA, et al. Incretin-based therapies: how do they work, who benefits, and how can we tell? *Diabetes Care*. 2007;30(6):1344–50.
9. Zinman B, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. 2015;373:2117–28.
10. Chiasson JL, et al. Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance. *JAMA*. 2003;290(4):486–94.
11. Genuth S. Insights from the diabetes control and complications trial. *Diabetes*. 2015;64(2):398–407.

12. Amiel SA, et al. Hypoglycemia in T2DM. *Diabet Med*. 2008;25(3):245–54.
13. Monami M, et al. DPP-4 inhibitors and acute pancreatitis: a meta-analysis. *Diabetes Res Clin Pract*. 2014;103(2):269–75.
14. Neal B, et al. Canagliflozin and cardiovascular and renal events in T2DM. *N Engl J Med*. 2017;377(7):644–57.
15. Men P, He N, Song C, et al. Arthralgia associated with DPP-4 inhibitors: a systematic review. *Drug Saf*. 2017;40(9):853–62.
16. Van de Laar FA. Alpha-glucosidase inhibitors in the early treatment of type 2 diabetes. *Vasc Health Risk Manag*. 2008;4(6):1189–95.
17. Kahn SE, et al. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. *N Engl J Med*. 2006;355(23):2427–43.