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COMPARING EFFICACY OF COMBINATION THERAPY (METFORMIN PLUS SULFONLYUREAS VS METFORMIN PLUS DPP-4 INHIBITORS) IN TYPE II DIABETES MELLITUS AT TERTIARY CARE HOSPITAL

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Abstract

Hypothesis: *The aim of the study was to compare efficacy of combination therapy (metformin plus sulfonylureas vs metformin plus DPP-4 inhibitors) in type II diabetes mellitus at tertiary care hospital*

Design of the Study: *Randomized control trial*

Study Duration: *06 months, November 2024 to April 2025*

Location of Study: *Department of Medicine, CMH Lahore*

Methods: *148 adults with Type 2 diabetes undergoing unstable metformin therapy and with poor glycemic control were randomized 1:1 to Metformin+Sulfonylurea and Metformin+DPP-4 inhibitor groups. Participants were followed at Weeks 4, 12 and 24 and eligible (age 30-75 years, BMI 18.5 - 40 kg/m 2). The main outcome was the change in HbA1c at the 24 weeks; the secondary ones were FPG, weight/BMI, hypoglycemia, adverse events and lipids. Proper statistical tests were conducted on the intention-to-treat analysis of data.*

Results: *One hundred and forty-eight patients were recruited and 138 of them attended the 24 weeks study. There was no significant difference in baseline characteristics between (Met+SU) and (Met+DPP-4). Both groups demonstrated indicating substantial declines in HbA1c and FPG with a non-significantly higher but insignificant decline in HbA1c of Met+SU (−1.46) compared to Met+DPP-4 (−1.31) at 24 weeks. The 59.4% and 54.3% of HbA1c were below 7% each (p= 0.49). Met +SU (+1.2 kg) and Met +DPP-4 (-0.4 kg, p<0.001) led to weight gain and weight loss, respectively. Met+SU exhibited more Hypoglycemia (17.5% vs. 4.1%), whereas other adverse events and lipid changes were similar.*

Conclusion: *The combinations of Metformin+Sulfonylurea and Metformin+DPP-4 inhibitors showed a significant glycemic control rate in 24 weeks. However, Met+DPP-4 exhibited obvious safety benefits, such as reduced hypoglycemia and a slight loss of weight.*

INTRODUCTION

T2DM is a chronic metabolic disease that is associated with insulin resistance, insulin secretion impairment, and the elevated production of hepatic glucose, which results in chronic hyperglycemia. It is a large global public health issue, and causes over 90 percent of all

diabetes cases and contributes greatly to morbidity and mortality due to microvascular and macrovascular comorbidities including nephropathy, retinopathy, neuropathy and cardiovascular disease. Proper glycemic control is still the key to the success of diabetes management in order to avoid these complications and enhance patient outcomes.[1]

Metformin is commonly known as the first-line pharmacological agent used in the treatment of T2DM because of its effects, safety characteristics, weight impartiality, and its impact on the cardiovascular system. Nonetheless, in the course of the disease, majority of the patients ultimately need the use of supplementary agents in order to attain optimal glycemic control. Out of the options available, two types of frequently used classes of medications are sulfonylureas (SUs) and dipeptidyl peptidase-4 (DPP-4) inhibitors, which are prescribed alongside metformin. Sulfonylureas include glimepiride and gliclazide which works by stimulating the β-cells in the pancreas to secrete more insulin and hence lowers the blood glucose levels but increase the chances of hypoglycemia and weight gain. By comparison, DPP-4 inhibitors, including sitagliptin and linagliptin, act by augmenting incretin activity, with an enhancing effect on insulin secretion and glucagon suppression glucose-dependently, and have a more desirable safety profile.[2,3]

Contrasting literature has demonstrated inconsistent outcomes with respect to the effectiveness and safety of these combination therapies. Hence, the proposed study will evaluate the effectiveness of metformin and sulfonylureas versus metformin and DPP-4 inhibitors in patients with Type II Diabetes Mellitus in a tertiary care hospital with respect to glycemic control, adverse effects, and the overall outcomes of the treatment.

Methodology

The study was a prospective, parallel-group, randomized, open-label controlled trial, which was carried out in the Department of Medicine at the Tertiary Care Hospital Lahore between Nov 24 and Feb 25. The research questions are as follows: 1) To compare the efficacy and safety of combination therapy Metformin +Sulfonylureas and Metformin +DPP-4 in 24 weeks. Patients who were consecutive to the outpatient clinic or hospitalized and met the eligibility criteria were screened. Eligible and willing participants were randomized to Met+SU versus Met+DPP-4 1: 1. The randomization was performed by the computer-generated sequence based on sealed opaque envelopes. The practice of allocation concealment was upheld in the study. The sample size of 148 patients was calculated as per WHO sample size calculator taking CI 95% and margin of error 5%. The research was done with informed consent of institutional ethical review board, vide letter No. 132654.

Inclusion criteria

1. Adults aged 30–75 years.
2. Diagnosed Type 2 Diabetes Mellitus patients
3. On metformin monotherapy (≥1500 mg/day or maximally tolerated dose) for ≥3 months with inadequate glycemic control: HbA1c 7.5%–10.5%.
4. BMI 18.5–40 kg/m².
5. Capable and willing to give written informed consent and make follow-up visits.

Exclusion criteria

1. Type 1 diabetics or non-insulin-dependent diabetes (e.g. pancreatogenic).
2. Previous treatment with sulfonylurea or DPP-4 inhibitor in the past 3 months.
3. eGFR <45 mL/min/1.73 m 2 (or local prescribing recommendation on a particular agent).
4. Hepatic impairment of great significance (ALT/AST >3× upper limit normal).
5. Recent history of serious hypoglycemia within the past 6 months or not aware of hypoglycemia.
6. Women who have not reached childbearing age or those who are pregnant or breastfeeding.
7. Active malignancy, acute infection, recent cardiovascular (MI/stroke within 3 months) event.

8. Simultaneous administration of drugs that interact with glucose (i.e. systemic steroids, antipsychotics) unless dose stable and acceptable to investigator.
9. A state that is likely to disrupt protocol adherence or follow-up (e.g. a severe psychiatric illness).

All participants were to continue metformin at pre-study dose (or optimized to ≥1500 mg/day as tolerated).

Met+SU group: A sulfonylurea—either gliclazide MR 30–120 mg once daily or glimepiride 1–4 mg once daily— was added and titrated every 2–4 weeks to achieve glycemic targets while minimizing hypoglycemia.

Met+DPP-4 group: A DPP-4 inhibitor—sitagliptin 100 mg once daily (or equivalent dose of linagliptin/saxagliptin) was added.

Dose changes were based on a pre-specified algorithm: uptitrate at visits in case of fasting glucose exceeded the target and in the absence of hypoglycemic events; down-titrate or keep medication in case of reported hypoglycemia (<70 mg/dL) or other adverse event. The outcomes were measured.

Primary outcome: Mean change in HbA1c baseline- 24 weeks.

Secondary outcomes:

- 12 and 24-week change in fasting plasma glucose (FPG).
- Percentage patients who attain HbA1c of less than 7.0 at 24 weeks.
- Change in body weight and BMI.
- Confirmed cases of hypoglycemia (blood glucose less than 70 mg/dL) and severe hypoglycemia (needs help).
- Negative events, discontinuations of treatment, and lipid profile alterations.
- Patient-reported treatment satisfaction (express validated questionnaire).

Screening/Baseline (Week 0): Medical history, physical examination, vitals, weight/BMI, baseline HbA1c, FPG, renal and liver function analysis, lipids, ECG, in case of necessity; consent and randomization.

The visits: Week 4, Week 12, Week 24 (study termination). During each visit: intermediate history, adherence to medication, adverse experience, hypoglycemia journal review, vital signs, weight. Labs (HbA1c Week 12 and 24; FPG Week 12 and 24; renal/liver function Week 12 and 24). Further visits or telephone contacts were permissible.

Symptomatic readings were provided with glucometers and patients were taught to document the readings; confirmatory lab glucose will apply to events.

Analysis of data was done on the intention-to-treat basis. Continuous variables (mean ± SD or median (IQR)) were given, and categorical variables (counts and percentages). ANCOVA was used to compare primary outcome (change in HbA1c) with baseline HbA1c. Paired t-tests or Wilcoxon signed-rank tests were used when the changes were within-groups. The result of the chi-square or Fisher exact test involved categorical outcomes (proportion who achieved HbA1c less than 7 mmHg). Incidence rate ratios were used to compare the level of hypoglycemia. A significance of two-tailed p-value below 0.05 was taken to be significant. The statistical analysis was done on SPSS v26.

RESULTS

One hundred and forty-eight patients with Type II Diabetes Mellitus were enrolled and assigned to two groups power equal, one (Group A) with Metformin + Sulfonylurea and another one (Group B) with Metformin + DPP-4 inhibitor. Among them, 138 of the patients (93.2% out of all) participated in 24 weeks of study, 6 dropped out of Group A and 4 dropped out of Group B because of follow-up loss or other adverse events.

The average age of the participants was 54.8 -9.7 years and 58 of them were male. The baseline demographic and clinical features were similar in the two groups, and there were no statistically significant differences in the age, gender distribution, BMI, months of diabetes duration, HbA1c, fasting plasma glucose (FPG), and lipid profile ($p > 0.05$).

Variable	Group 1 (Met + SU)	Group 2 (Met + DPP4)
Age Y	55.2 ± 10.1	54.5 ± 9.3
Gender M/F	43/31	43/31
BMI	27.9 ± 3.8	28.2 ± 3.6
Disease duration	6.7 ± 3.1	6.5 ± 3.0
Fasting glucose mg/dl	172.6 ± 25.4	170.2 ± 27.1
Total cholesterol mg/dl	196.4 ± 34.2	192.8 ± 32.5
LDL-C mg/dl	122.3 ± 28.4	120.7 ± 27.5
Baseline HBA1C	8.6 ± 0.7	8.5 ± 0.8
HDL-C	43.7 ± 6.2	44.3 ± 6.0
Triglycerides mg/dl	154.8 ± 46.9	150.6 ± 48.3

Table 1: demographic data of both groups

Both groups showed a large decrease in HbA1c and FPG at the 12 weeks relative to control ($p < 0.001$ within-group comparisons). At 24 weeks, Met + SU group and Met + DPP-4 group had mean HbA1c reduction of -1.46 +0.52 and -1.31 +0.49 respectively. The groups showed no statistically significant difference even though both therapies had clinically significant changes in reduction ($p = 0.07$).

Nevertheless, the HbA1c of less than 7.0% at 24 weeks was slightly higher in the Met+SU (59.4% vs. Met+DPP-4 54.3%), although this trend was not considered significant ($p = 0.49$).

Parameter	Group 1 (Met + SU)	Group 2 (Met + DPP4)
HBA1C		
Baseline	8.6 ± 0.7	8.5 ± 0.8
Week 12	7.5 ± 0.6	7.6 ± 0.5
Week 24	7.1 ± 0.5	7.2 ± 0.4
HBA1C (baseline – Week 24)	−1.46 ± 0.52	−1.31 ± 0.49
Fasting plasma glucose		
Baseline	172.6 ± 25.4	170.2 ± 27.1
24 weeks	131.4 ± 18.2	136.8 ± 19.6
HBA1C <7 in patients	59.4%	54.3%

Table 2: glycemic outcomes 12 and 24 weeks

Body weight changes differed significantly between groups. The Met+SU group showed a **mean weight gain of +1.2 ± 1.6 kg**, whereas the Met+DPP-4 group showed a **modest reduction of −0.4 ± 1.3 kg** ($p < 0.001$).

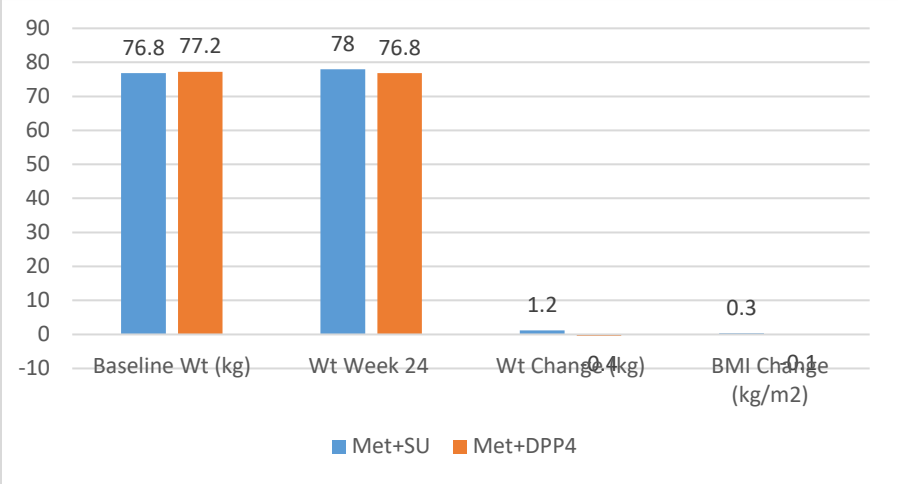


Chart 3: Change in body Weight and BMI

Hypoglycemia of mild to moderate intensity was more prevalent in Met+SU (17.5) than in Met+DPP-4 (4.1, p = 0.01). There were no serious cases of hypoglycemic episodes that led to hospitalization.

Transient gastrointestinal symptoms (primarily nausea and diarrhea) were other adverse incidences that occurred in 9.4% patients in the Met+DPP-4 group and 12.2% in the Met+SU group (p = 0.54). There was no pancreatitis or hepatic dysfunction.

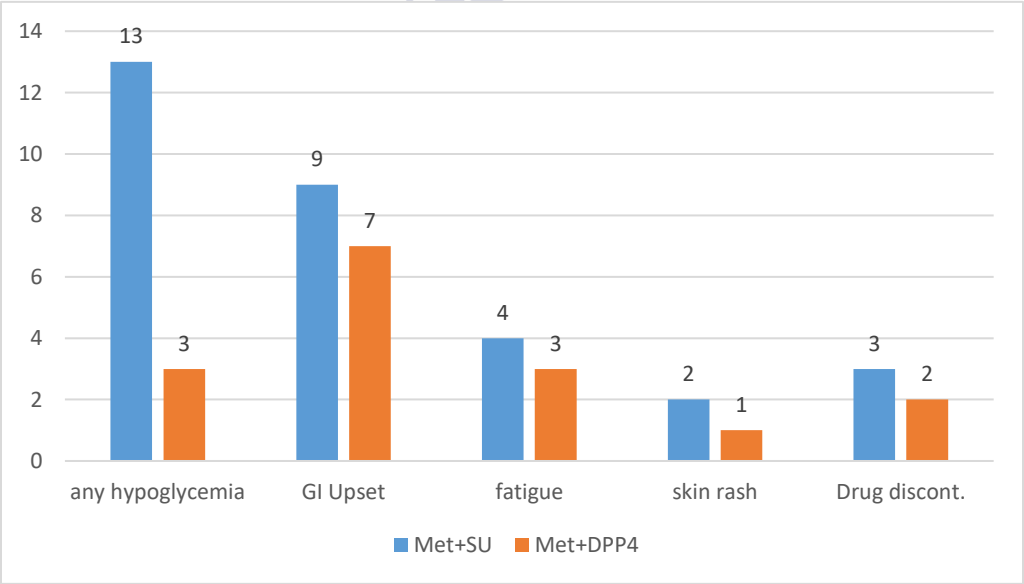


Chart 4: Adverse effects in both groups

Both groups exhibited modest improvements in lipid parameters, with non-significant differences between groups. Total cholesterol, LDL-C, and triglycerides decreased slightly, while HDL-C increased modestly in both arms, suggesting a neutral-to-favorable metabolic impact.

Lipid parameters	Met+SU	Met+DPP4
Total Cholesterol	−6.4 ± 12.8	−8.1 ± 13.1

LDL-C	−5.2 ± 10.4	−6.6 ± 11.3
HDL-C	+1.5 ± 3.8	+1.8 ± 3.5
Triglycerides	−8.9 ± 24.3	−10.6 ± 22.9

Table 5: Lipid parameters in both groups at 24 weeks

Summary of Key Findings

Both combination therapies demonstrated a significant reduction in glycemic control (reduction of HbA1C above 1.3) after 24 weeks.

- Met +SU had slightly higher reduction in HbA1c, but not statistically significant than Met + DPP-4.
- Met+DPP-4 was superior to weight neutral and with a much lower probability of hypoglycemia.
- The change in lipids was similar in both groups.
- Neither of the two regimens showed any significant adverse safety signals.

Discussion:

This paper compared the performance of two common combination regimens in Type II Diabetes Mellitus (T2DM): Metformin plus Sulfonylurea (Met+SU) and Metformin plus Dipeptidyl Peptidase-4 inhibitor (Met+DPP-4) based on their efficacy, safety, and metabolic outcomes. The two combinations of treatments showed a high level of reduction in HbA1c and fasting plasma glucose after 24 weeks and hence proved effective in glycemic control of patients who were insufficiently controlled using metformin monotherapy. Nevertheless, the decrease in HbA1c was slightly higher in the Met+SU, but not significantly different between the two regimens. Notably, Met+DPP-4 was better tolerated, with less hypoglycemia and weight neutrality compared to that of Metformin, which implies that it is a more acceptable choice to use as a long-term management of diabetes regimen.[4]

The results correspond to the already known use of metformin as the basis of pharmacologic treatment of T2DM because of its insulin-sensitizing effect, low expense, as well as cardiovascular protective effect (UKPDS, 1998). Monotherapy would not be adequate as the disease develops and b-cells become ineffective and so a second agent is required to achieve glycemic targets. Add-on therapy needs to be selected optimally based on its efficacy, safety, effects on weight, likelihood of hypoglycemia, and patient preference.[5]

The mean decrease in HbA1c of both regimens in the current study was more than 1.3, which is congruous to the previous randomized controlled trials assessing combination therapies. Other studies like Holman et al. (2008) and Klaman et al. (2014) found a range of HbA1c decreases of 1.0-1.5 percent with the add-on therapy of sulfonylureas, similar to our results. Equally, Gallwitz (2019) and Charbonnel et al. (2006) showed that the combination of DPP-4 inhibitors and metformin results in a reduction in HbA1c of about 0.7% to 1.2 and that both combinations provide significant glycemic improvements.[6,7]

Even though Met+SU group showed a comparatively higher mean change in HbA1c (−1.46% vs. -1.31%), the difference was not significant (p = 0.07). This move towards increased glucose-lowering by sulfonylureas could be explained by the fact that they directly stimulate insulin secretagogue activity on pancreatic 2 cells to generate a powerful, fast-acting glucose-lowering effect. DPP-4 inhibitors, in their turn, hasten through the stimulation of endogenous incretin hormones (GLP-1 and GIP) and result in the secretion of insulin under the influence of glucose and the suppression of glucagon (Nauck, 2016). The benefit of the sulfonylureas on glycemic incretin should, however, be gauged against the elevated risk of hypoglycemia and potential weight gain both of which were established in this study.[8]

Met+SU induced hypoglycemia in 17.5 and Met+DPP-4 in 4.1, which is in compliance with the past reports (DeFronzo et al., 2012; Gallwitz, 2019). There are no serious cases of hypoglycemia, which is indicative of attentive

titration and patient education. However, mild hypoglycemia is also associated with an adverse effect on quality of life and adherence and can discourage the intensification of treatment. The mechanism of DPP-4 inhibitors which is glucose-dependent explains why they have a significantly lower risk of hypoglycemia; a significant clinical benefit, particularly in older or comorbid patients.[9,10]

The two regimens can also be differentiated in terms of body weight. Met + SU group gained weight (+1.2 kg), and the patients on Met + DPP-4 lost weight (0.4 kg on average) ($p < 0.001$). The neutral or small loss with DPP-4 inhibitors has been described in many studies.[11]

The findings of the present study can be utilized as living evidence of the similar efficacy of two frequently prescribed combination treatments of Type II Diabetes Mellitus (T2DM): Metformin plus Sulfonylureas (Met+SU) and Metformin plus Dipeptidyl Peptidase-4 inhibitors (Met+DPP-4). Although the two regimens achieved dramatic glycemic results, the noted disparity in the safety and tolerability issues holds key implications to customized management of diabetes.

Pharmacologically, sulfonylureas stimulate insulin secretion by closing ATP-dependent potassium channels in pancreatic 0 cells, which are independent of the level of glucose (Inzucchi et al., 2015). This process has powerful glycosylation-reducing impacts but is associated with an intrinsic threat of glycemic downturn and inexorable 8 - cell weariness. Conversely, DPP-4 inhibitors stimulate the physiological incretin effect by inhibiting the degradation of GLP-1 and GIP and stimulate insulin secretion and reduce glucagon glucose-dependently (Nauck & Meier, 2021). The quantity of glucose dependency explains the considerably reduced risk of hypoglycemia that we have found and observed previously in large-scale trials, such as SAVOR-TIMI 53 and TECOS.[12,13]

The gain in weight of the sulfonylureas in this study (+1.2 kg) has got clinically significant implications. Major causes of insulin resistance and cardiovascular risks are obesity, and thus, weight-neutral or weight-reducing treatments are superior. The neutral impact of DPP-4 inhibitors on body weight, which is consistent with Gallwitz (2019) and Nauck (2016) and additional evidence of their metabolic benefit. The difference in weight might be insignificant, but even the minor ones can enhance insulin sensitivity and cardiometabolic outcomes.[14]

Another important factor is the long-term sustainability of the glycemic control. The UKPDS showed that sulfonylureas are effective in the first instance of glucose level control, but their effectiveness reduces with time since the b-cell functioning decreases with time (UKPDS, 1998). Conversely, incretin-based interventions such as DPP-4 inhibitors could save and maintain b-cell mass and functionality through elimination of glucotoxicity and oxidative stress (Ahren, 2018). The evidence in the VERIFY trial (Matthews et al., 2019) indicated that there was a significant delay in the disease progression and target level of HbA1c could be maintained significantly longer in the early combination therapy with metformin and vildagliptin compared to stepwise intensification. This would imply that starting combination therapy at a younger age, especially with DPP-4 inhibitors, could bring about better long-term results as well as slow down the progression of b-cell weakening.[15,16]

The cardiovascular outcomes also determine the overall benefit of antidiabetic therapy very critically. Although it was claimed that sulfonylureas are linked to a potential cardiovascular risk because they are nonselective KATP channel inhibitors of the pancreas and the heart, more recent studies have indicated that this approach has neutral or slightly negative effects according to the agent. On the other hand, DPP-4 inhibitors have been firmly demonstrated to be cardio vascularly safe in several randomized clinical trials including CAROLINA, SAVOR-TIMI 53, and TECOS. These results reinforce the argument according to which DPP-4 inhibitors are safer, better tolerated, and especially in individuals with an established cardiovascular disease or a combination of risk factors.[17]

In spite of these benefits, price and availability have been the major drawbacks to the usage of

DPP-4 inhibitors, in particular in third world nations. Sulfonylureas are affordable and available over the counter and remain a primary option in the treatment of diabetes in low- and middle-income countries (Khunti et al., 2022). Thus, decision-making in treatment should be personalized, and clinical effectiveness, safety, cost-effectiveness, and compliance of the patient should be considered. Sulfonylureas are also a reasonable and useful choice in one of the environments where the newer agents are prohibited due to cost considerations, although patients should be closely educated on the issues of hypoglycemia awareness and dietary compliance.[18]

The application of this study in real life is high. It is a mirror of the usual clinical practice within a tertiary care hospital with the resource-limited environment, and the findings are very applicable in the same healthcare systems. The two regimens demonstrated significant glycemic control in 6 months, which is consistent with existing international guidance that recommends early combination therapy to patients who do not attain glycemic targets using metformin monotherapy (ADA, 2023; Davies et al., 2022). DPP-4 inhibitors have a better tolerability profile and could facilitate patient satisfaction and treatment adherence-factors that long-term glycemic stability needs but are not always considered in clinical trials.[19]

However, the findings should be supported with further studies using bigger cohorts and longer follow-up periods to determine the results in terms of b-cell maintenance, cardiovascular events, and long-term cost-effectiveness. Moreover, the comparative studies that would be measuring more recent classes of drugs including the GLP-1 receptor agonists and the SGLT2 inhibitors would yield a more all-inclusive understanding of the best second-line treatment in various patient groups.[20]

To sum up, the current paper supports the idea that the Metformin + Sulfonylurea and Metformin + DPP-4 inhibitor medications are effective in enhancing glycemic regulation in Type II Diabetes Mellitus. Nevertheless, DPP-4 inhibitor combination has significant benefits in safety, weight neutrality and prevention of hypoglycemia. DPP-4 inhibitors can be the option of choice in patients with the risk of cardiovascular or those that value the safety of treatment and metabolic balance. In the meantime, sulfonylureas still have therapeutic potential where cost and access are considered the primary factors. Finally, the patient-focused model incorporating effectiveness, safety, and socioeconomic background is the foundation of the best disease management.

Limitation of study:

The research had a limitation of the open-label nature of the study, which can bring bias of performance and reporting. The 24 weeks follow-up time may be inadequate to measure long-term efficacy and safety, especially long-term glycemic control. The single-center study makes the study less generalizable, and the sample size, which is sufficient, might fail to identify smaller intergroup differences. Also, the use of patient self-reporting hypoglycemia may result in underreporting.

Conclusion:

This study illustrates that combination therapies, Metformin and Sulfonylurea or Metformin and DPP-4 are effective in producing meaningful glycemic in Type II Diabetes Mellitus patients after 24 weeks. Despite the fact that the reduction in HbA1c was a little higher with the Met+SU regimen, the difference between the groups was not significant, which implies the similar effectiveness of the two. Nevertheless, the results of safety and tolerability showed a definite advantage towards the Met+DPP-4 combination that was accompanied by weight loss, significantly reduced cases of hypoglycemic events, and a comparable level of other undesirable occurrences. Both regimens exhibited an unbeneficial-beneficial effect on lipid profiles. On the whole, even though Met+SU is an affordable and effective glycemic control tool, Met +DPP-4 has a safer profile and better weight and hypoglycemia results that make it a more preferable treatment option in most patients. These results endorse personalized selection of

treatment, according to clinical priorities, the risk of hypoglycemia and patient-specific features.

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