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ORIGINAL ARTICLE

Role of Metformin Monotherapy Vs Metformin Plus Dapagliflozin in New Onset T2DM Among 40 Plus Obese Women in Glycaemic Control

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Abstract

Objective: A Randomized, open-label comparative clinical study was conducted to evaluate the comparative efficacy and safety of Metformin 500mg twice daily versus Metformin 500mg twice daily Plus Dapagliflozin (10mg) once daily in achieving glycemic control among new onset T2DM in forty plus obese women.**Method:** A total of 100 subjects were enrolled in the study and after inclusion exclusion criteria 60 subjects were randomized into two groups. Group A received Metformin 500mg twice daily and Group B received Metformin twice daily and Dapagliflozin 10 mg once daily. FBS and PPBS were done at Day 0, 4th week,8th week, 12th week, HbA1c was done on 0 days and 12 weeks. **Results:** Metformin plus Dapagliflozin) was found to be significantly superior at the 4th-week p value < 0.001 and remained comparable at the 8th and 12th weeks to Metformin alone on FBS and PPBS. The percentage reduction was clinically significant (>10%) reduction for the Metformin plus Dapagliflozin group when compared to the Metformin group (4.46%).**Conclusion:** Dapagliflozin in combination with Metformin had superior efficacy to Metformin alone in achieving tight glycemic control.

Keywords: Metformin plus Dapagliflozin, SGLT2 inhibitors, Post menopausal, Obese, women.

Introduction

T2DM is a major public health problem that has affected more than 400 million people in the world so far, manifesting as chronic microvascular, macrovascular, and neuropathic life-threatening complications. Patients with T2DM often have comorbid conditions that lead to increased morbidity and mortality and make the treatment more difficult Common comorbidities in patients with T2DM include obesity, hypertension, and dyslipidemia.[1,2] Patients with T2DM are mostly characterized by being obese or having a higher body fat percentage, distributed mainly in the abdominal region. Global rise in obesity, sedentary lifestyle, high caloric intake, and an aging population have increased the incidence and prevalence of T2DM.[3] Dapagliflozin in combination with metformin and metformin alone proposes various glycaemic

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advantages as well as advantages on various metabolic, cardiovascular, and weight both in western populations and Indian cohorts amongst T2DM.[4-9]

Metformin is the first-line pharmacotherapy recommended for glycaemic control in patients with T2DM and has proven efficacy in achieving a clinically relevant reduction in glycated hemoglobin (HbA1c) levels. However, most patients eventually require treatment with 2 or more antidiabetic agents to maintain adequate control of blood glucose levels.[10] Treatment of T2DM often begins with lifestyle management and metformin. [11] Dapagliflozin a new class of oral sodium-glucose cotransporter 2 (SGLT-2) inhibitor has demonstrated a reduction in Glycated Haemoglobin (HbA1c) and body weight in patients with T2DM when used as a monotherapy as well as in combination with other glucose-lowering agents.[12]

Further obesity and diabetes incidence increase during the transition of menopause and take a huge toll after menopause. This completes the outcome of diseases in many ways; thus, it was felt important to evaluate a new group of antidiabetic drug (SGLT-2) inhibitors as an adjuvant to Metformin in this special population.

Hence, the current study was done to evaluate the comparative efficacy and safety of Metformin (500 mg) twice daily versus Metformin (500 mg) twice daily & dapagliflozin (10 mg) once daily in achieving glycaemic control among new-onset T_2DM in forty-plus obese women

Material and Methods

The present prospective, randomized, open-label, intention-to-treat comparative study was conducted in the Department of Pharmacology Government Medical College, Jammu in collaboration with the Department of Endocrinology S.S.H Jammu for 6 months. The study was initiated after necessary approval from the Institutional Ethics Committee, Government Medical College, Jammu. Vide NO: IEC/GMC/2021/641/A. dated: 25. 10. 2021. A written, informed consent was obtained from all the patients fulfilling inclusion and exclusion criteria after explaining the nature and purpose of the study. The study participants included recent onset T_2DM in plus forty obese women attending Endocrinology OPD. All basic principles of bioethics as recorded were followed. A total of 100 patients were screened but after applying the inclusion and exclusion criteria, a total of 60 patients with new onset T2DM from the endocrinology OPD of a tertiary care teaching hospital were included in the study. ***Group A*** *was allocated Metformin 500mg daily plus a Tablet of dapagliflozin 10mg once daily*
Group B *were allocated to Metformin 500mg twice daily*
Inclusion Criteria: Age 40 to 65 years, Premenopausal , Postmenopausal, Perimenopausal Recent onset T2DMWith Controlled Co Morbid Conditions, Overweight/obesity as defined by WHO Criteria.[13]
Exclusion Criteria: Complicated T_2DM,Uncontrolled T_2DM, Uncontrolled Co Morbid Conditions, Already on some oral hypoglycemic agents,Old T_2DM,Breastfeeding,Pregnancy,Unwilling to participate,H/O Allergy or intolerance with any of the drug,H/O urinary tract infection or pelvic inflammatory diseases, H/O Diabetic kidney diseases/chronic kidney disease, Heart failure, Normal Baseline GFR/Renal Function Test.

Parameters

Primary endpoint: To compare the overall efficacy of Dapagliflozin plus metformin over metformin alone.

Fasting blood sugar (FBS) levels were recorded at the first visit of the patient to OPD i.e., Day 0, then after 4 weeks, 8 weeks, and 12 weeks respectively. The normal values of fasting blood sugar were as per the American Diabetes Association (2021).[14]

Normal – less than 100mg/dl; Prediabetes- 100mg/dl to 125mg/dl Diabetes- 126mg/dl or higher.

The target value of fasting blood sugar < 126 mg/dl was considered significant for the said study.

Post-prandial blood sugar level (PPBS) which was taken on Day 0, 4 weeks, 8 weeks, and 12 weeks. Post-prandial blood sugar is the blood glucose level that was recorded after 90 minutes of meals. American Diabetes Association (2021).[14]

The normal values considered were 140 to 199 mg/dl. The target value of less than 200 mg/dl was considered as significant.

Hb_{A1c} levels were studied on Day 0 and the 12th week as per the American Diabetes Association (2021).[14]

Normal < 5.7%; Pre-diabetes 5.7% to 6.4%; Diabetes 6.5% or higher

The target value of < 6.5% was considered significant for this study.

Patients with baseline FBS in the range of (180-200mg/dl) were recruited in both groups and Glycosylated hemoglobin at the baseline was between 8-9% as per the ADA guidelines.More than 10% reduction in HbA1c level was considered clinically significant.

Patients in both groups were observed for the occurrence of any adverse drug reactions during the study

Table 1. Comparative Effect of Metformin Plus Dapagliflozin (M+D) Vs Metformin (M) Alone on FBS in New Onset T2DM Among Plus Forty Obese Women

Variable	FBS MEAN ± SD (- Difference in mg/dl)		t value	p value
	Metformin Plus Dapagliflozin (n=30)	Metformin (n=30)		
Baseline	203.63 ± 35.38	198.23 ± 35.32	-0.59	0.98 ^{NS}
4TH Week	154.0 ± 11.23*** (-49.6)	152 ± 22.16*** (-46.13)	-0.42	0.00 †††
8TH Week	139.63 ± 9.44*** (-64.0)	137.17± 14.72*** (-61.06)	-0.77	0.68 ^{NS}
12TH week	132.07 ± 7.12*** (-71.56)	126.43 ±11.18*** (-71.80)	-2.32	0.15 ^{NS}

Paired 't' test in comparison to respective baselines *p<0.05; **p<0.01; ***p<001; non-Significant (NS). Comparison between the groups at the baseline with unpaired student 't' test, significant= † p<0.05, †† p<0.01, ††† p <0.001. Non-significant (NS) (-X) = Reduction from baseline value in mg/d

Table 2. Comparative Effect of Metformin Plus Dapagliflozin (M+D) Vs Metformin (M) Alone on PPBS.

TIME	PPBS MEAN ± SD (- Mean Difference in mg/dl)		P value	t value
	Metformin Plus Dapagliflozin (n=30)	Metformin (n=30)		
0 DAY	238.33 ± 50.08	232.70 ± 50.19	-0.43	0.94 ^{NS}
4TH WEEK	191.40 ± 12.50*** - (46.93)	194.17 ± 26.37*** -(38.53)	0.51	0.009 †
8TH WEEK	182.0 ± 18.14*** - (56.33)	180.93 ±18.14 *** - (51.76)	-0.28	0.07 ^{NS}
$_{12}$TH WEEK	177.00 ± 9.86*** -(61.33)	174.33 ± 10.30*** - (58.36)	-1.02	0.98 ^{NS}

*Paired 't' test in comparison to respective baselines *p<0.05; **p<0.01; ***p<001; non-Significant (NS).*

Comparison between the groups at the baseline with unpaired student 't' test, significant= † p<0.05,

†† p<0.01, ††† p <0.001. Non-significant (NS) (-X) = Reduction from baseline value in mg/dl.

period and were documented in PvPI form version 1.4 and causality assessment was done as per WHO causality assessment scale.

Results

Effect On Fasting Blood Glucose Levels: Both the groups caused a statistically and clinically significant reduction in FBG levels with a p-value (<0.001) commencing from the 4th week to the 12th week of therapy, with maximum reduction at the 12th week, from their respective baseline. However, while comparing both groups (Metformin plus Dapagliflozin) was found to be significantly superior at the 4th week p value < 0.001 and remained comparable at the 8th and 12th week.

Effect on Post Prandial Blood Glucose Levels: Both the groups caused a statistically and clinically significant reduction in PPBG levels with a p-value of <0.001 commencing from the 4th week to the 12th week of therapy, with maximum reduction at the 12th week, from their respective baseline. However, while comparing both the groups Metformin plus Dapagliflozin was found to be significantly superior in the 4th week p <0.05 and remained comparable in the 8th and 12th week of therapy.

Effect on Glycosylated Haemoglobin Levels (HbA1c):

HbA1c was reduced significantly in both groups in the 12th week (p<0.001) from their respective baseline. while inter-group comparisons failed to demonstrate any statistical difference. The percentage reduction was clinically significant (>10%) reduction for the Metformin plus Dapagliflozin group when compared to the Metformin group (4.46%).

Safety

While comparing the safety profile of the two groups largely at 12 weeks both the groups appeared to be safe as no moderate or serious/ severe drug reaction was reported in any of the groups. All the adverse events were milder in both groups and didn't warrant any cessation of the treatment or modification of the ongoing drug therapy. No patient in any of the Groups experienced a hypoglycemic episode, thereby suggesting that the addition of Dapagliflozin to Metformin doesn't change the profile

Table 3. Comparative Effect of Metformin Plus Dapagliflozin (M+D) Vs Metformin (M) Alone on Mean HbA1c in New Onset T2DM Among Forty Plus Obese Women.

TIME	HbA1C MEAN ± SD (- Difference in %)		p VALUE	t VALUE
	Metformin Plus Dapagliflozin (n=30)	Metformin (n=30)		
0 DAY	9.14 ± 1.29	8.40 ± 1.06	0.26 ^{NS}	-2.40
12TH WEEK	8.01 ± 1.06*** - (1.13)	8.01±1.26*** - (0.39)	0.20 ^{NS}	-1.10

*Paired 't' test in comparison to respective baselines *p<0.05; **p<0.01; ***p<001; non-Significant (NS).*

Comparison between the groups at the baseline with unpaired student 't' test, significant= † p<0.05,

†† p<0.01, ††† p <0.001. Non-significant (NS) (-X) = Reduction from baseline value in %

of Metformin for Hypoglycemia. In the metformin group nausea and loss of appetite were reported by 6.6% of the study population, whereas in another group, UTI and Vaginitis were reported in 9.9% of the study population.

Discussion

Our results are consistent with Zhang *et al* [15] who analyzed combination therapy of SGLT2- inhibitors along with metformin and proposed SGLT-2 inhibitors – Metformin combination significantly lowered FBG after 24th weeks, 1 year, and 2 years. However, the current study was only 12 weeks. Both the groups caused a statistically and clinically significant reduction in FBG levels with a p-value of <0.001 commencing from the 4th week to the 12th week of the therapy, with maximum reduction at the 12th week from their respective baseline.

Kuecker *et al* [16] conducted a randomized trial on Dapagliflozin and Metformin alone and combined in overweight women also suggested a significant decrease in FBG levels with p=0.02 at 24 weeks of therapy which was by our study except for the duration of the study.

Similarly, a study conducted by Henry *et al* [17] compared Dapagliflozin alone and in combination with metformin and placebo in adults with T2DM, and suggested a clinically and statistically significant decrease in Postprandial blood glucose levels (-49.5mg/dl) and (48.9mg/dl) respectively. Similar, results were depicted by the current study where the Dapagliflozin and Metformin group showed a clinically and statistically significant decrease in Postprandial blood glucose to levels of (-61.3mg/dl) more than the Metformin alone group (-58.36mg/dl) suggesting combination therapy of Dapagliflozin plus Metformin superior to monotherapy.

A randomized double-blind placebo-controlled trial was conducted by Bailey *et al* [18] in which dapagliflozin as an added therapy to Metformin in T2DM patients inadequately controlled with metformin in a dosage of 2.5mg, 5mg, and 10mg was compared with placebo. In the 24th week of the study dapagliflozin plus metformin group significantly decreased HbA1c levels to the tone of (-0.82%). The results were in comparison to our study where the Dapagliflozin Plus Metformin combination brought a statistically and clinically significant decrease in HbA1c levels (-1.13%). In a study conducted by Sethi B *et al* [19] where Dapagliflozin when added to Metformin showed significant improvement in Glycemic parameters like our study.

A randomized placebo control study by Rosenstock *et al* [20] suggested a similar safety profile as reported in the current study. They reported like our study, minimal incidence of UTI or vaginitis in comparison to non SGLT2 inhibitors. It's worth mentioning these events were more common in women and were usually mild which responded to routine management mainly the local hygiene and local care. Rarely a few patients required oral antifungal treatment, unlike our study. Further, such infections usually appeared after the 24th week of therapy in their study, and our study being 12 weeks failed to document much of such cases. The above observation is relevant in the elderly age group, particularly in women either in transition to menopause or who have attained menopause as they can have inherent potential to acquire more urinary tract infections. However, they behave similarly to the young population. Various studies reported adverse drug reactions like Nausea, metallic taste, hypoglycemia, back pain, urinary tract infections vaginitis, which were not very severe, and both drugs were tolerated very well in our study.

Conclusion

Dapagliflozin in combination with Metformin had superior efficacy to Metformin alone in achieving tight glycemic control. Both the groups proved to have comparable safety and tolerability with regard to all the studied parameters in forty-plus obese women with T_2DM.

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