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Original Research Article

Revitalization of thiazolidinedione the optimum agents to be combined with SGLT 2 inhibitors to optimize glycemic control and reduce cardiovascular mortality: randomized control trial

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ABSTRACT

Background: Type 2 diabetes mellitus (T2DM) significantly increases morbidity and mortality from cardiovascular disease. The present study was conducted to know the effect of thiazolidinedione and SGLT2 inhibitor on glycemic control, blood pressure and lipid profile and effect on cardiovascular mortality in T2DM.
Methods: A total 80 patients of aged ≥40 years with T2DM were included and divided into 4 groups based on ongoing treatment i.e., (lifestyle modification + Tab metformin 500mg BD) + 1) Tab metformin 500mg; 2) Tab dapagliflozin 10mg OD; 3) Tab pioglitazone 15mg OD; 4) Tab pioglitazone 15mg OD + Tab Dapagliflozin 10mg OD.
Results: The change in FBS, PLBS and HbA1C from pre-intervention to post-intervention was highest in the patients with DAPA + pioglitazone group followed by patients with pioglitazone group then the patients with DAPA group and lowest in patients with metformin group. There was a statistically significant difference between them, ($p<0.001$). The weight reduction was highest in the patients with DAPA 10mg group followed by patients with metformin group, ($p<0.001$). The change in SBP, DBP and change in lipid profile (triglyceride and cholesterol, LDL and HDL) from pre-intervention to post-intervention was highest in the patients with DAPA+ pioglitazone group. This change was statistically significant ($p<0.001$).
Conclusions: The combination of pioglitazone and dapagliflozin not only helped in glycemic control but also had reduction in blood pressures, improvement in the lipid profile and caused slight weight reduction. There were no major adverse drug reactions, and no MACE was observed during the study. Hence this combination of pioglitazone and dapagliflozin may reduce the cardiovascular mortality (which needs longer duration study).

Keywords: Cardiovascular disease**,** Dapagliflozin, Mortality, Pioglitazone, Thiazolidinedione, Type 2 diabetes mellitus

INTRODUCTION

The occurrence of both type 1 and type 2 DM is increasing throughout the world. Yet, due to raised obesity incidence and physical inactivity, which is a result of countries becoming more industrialized, the type 2 DM prevalence has been rising more rapidly. These high prevalence trends of DM are mostly seen in Asian countries with India being one among them.[1,2]

In principle, the treatment of DM aims on the prevention of organ damage caused by high blood glucose levels or AGEs. Beside recommendations in physical activity and dietary patterns, multiple drugs with different

pharmacological mechanisms have been developed and are currently in clinical use.[3] The drug classes are composed of the biguanide metformin, sulfonylureas, glinides, thiazolidinediones, alpha-glucosidase inhibitors, insulin, GLP-1 receptor agonists, DPP4 inhibitors, and SGLT2 inhibitors. The latter three drug classes have been developed in the late 2000s and considered as modern antidiabetic concepts.[4]

Based on multiple epidemiological studies, compared to the non- diabetics of same sex and age, risk of developing cardiovascular disease is doubled in diabetics. The mortality due to cardiovascular diseases in type 2 DM also increased.[5] Although hyperglycemia is the principal factor responsible for the development of microvascular complications, and lowering the plasma glucose concentration reduces or prevents the development of such complications, this has little effect on decreasing macrovascular complications.[4] It is critical, therefore, to develop therapeutic strategies to reduce macrovascular risk in order to decrease mortality in patients with T2DM. In this context, the present study was conducted to know the effect of thiazolidinedione and SGLT2 inhibitor in glycemic control, blood pressure and lipid profile to reduce cardiovascular mortality in type 2 DM.

METHODS

After obtaining Institutional Ethical Committee approval and written informed consent from all the patients, this hospital based randomized control trial was conducted in the Tertiary care hospital, Government Medical College, Nagpur in central India during the period from November 2020 to October 2022.

A total 80 patients of aged ≥40 years with T2DM with 7.0 % <HbA1c <10.0 % despite diet and exercise therapy and on Tab Metformin 500mg BD for at least 3 months prior to randomization were included in the study. Patients with type 1 diabetes mellitus, with history of severe ketosis, diabetic coma, or precoma attack ≤6 months prior to informed consent, severe infection or trauma at trial screening, patients in perioperative period around trial screening, severe renal dysfunction (eGFR<45 ml/min/1.73 m^2) or patients receiving dialysis, patients with history of coronary artery disease, coronary vascularization, open-heart surgery, stroke, or transient ischemic attack ≤3 months prior to eligibility, CHF (NYHA functional classification III and IV), history of administration of SGLT2 inhibitor 1 month prior to study initiation, pregnant or suspected pregnancy in females, lactating female and malignancy were excluded from the study.

The participants were divided into 4 groups based on ongoing treatment i.e., (lifestyle modification + Tab metformin 500mg BD). Group 1 was Tab metformin 500mg , Group 2 was Tab dapagliflozin 10mg OD, Group 3 was Tab pioglitazone 15mg OD, and Group 4 was Tab pioglitazone 15mg OD+ Tab dapagliflozin 10 mg OD. The investigations were repeated after 3 months and were noted.

Statistical analysis

The data were analyzed with SPSS V.24 software. The continuous variables were presented with mean and standard deviation. The categorical variables were presented with frequency and percentage. One way ANOVA was used for the comparisons. The p value ≤0.05 was considered as statistically significant.

RESULTS

A total of 80 patients aged ≥40 years with T2DM were enrolled in the study. The maximum patients were from the age group of 50-60 years (50%), followed by >60 years (40%) with male predominance (60%) as shown in Table 1.

Table 1: Demographics profile of patients.

Demographics		No. of patients	Percentage
Age groups (years)	<50	8	10.0
	50-60	40	50.0
	>60	32	40.0
Sex	Male	48	60.0
	Female	32	40.0

Table 2: Change in glucose level from pre-intervention to post-intervention.

Parameters		Pre-intervention	Post-intervention	P value
FBS	Tab Dapa (10) + Pioglitazone (15)	285.3±42.2	103.1±43.5	<0.001*
	Tab Pioglitazone (15)	281.6±35.0	132.4±48.0	<0.001*
	Tab Dapa (10)	282.4±41.8	133.7±37.6	<0.001*
	Tab Metformin (500)	280.2±59.2	135.1±57.1	<0.001*
PLBS	Tab Dapa (10) + Pioglitazone (15)	355.4±51.7	158.9±69.5	<0.001*
	Tab Pioglitazone (15)	355.2±27.7	180.9±51.8	<0.001*
	Tab Dapa (10)	354.1±53.8	182.7±53.3	<0.001*
	Tab Metformin (500)	352.7±73.0	185.3±54.1	<0.001*

The change in FBS and PLBS from pre-intervention to post-intervention was highest in the patients with DAPA+ pioglitazone group followed by patients with pioglitazone group then the patients with DAPA group and lowest in patients with metformin group. There was a statistically significant difference between them, (Table 2).

The change in HbA1C from pre-intervention to post-intervention highest in the patients with DAPA+ pioglitazone group followed by patients with pioglitazone group then the patients with DAPA group and lowest in patients with metformin group as depicted in Figure 1. There was a statistically significant difference between them, (p<0.001).

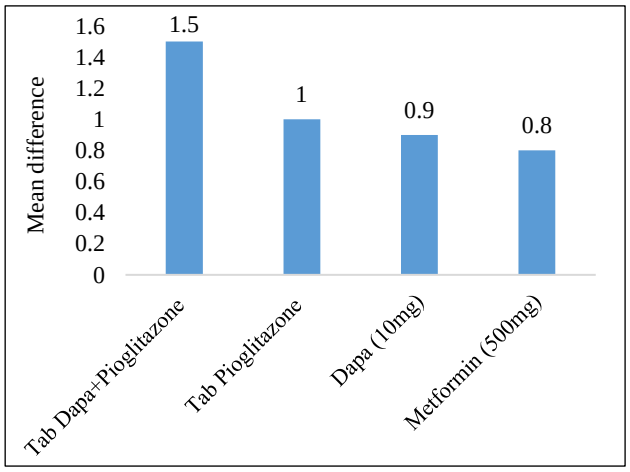

Figure 1: Change in HbA1C from pre-intervention to post-intervention.

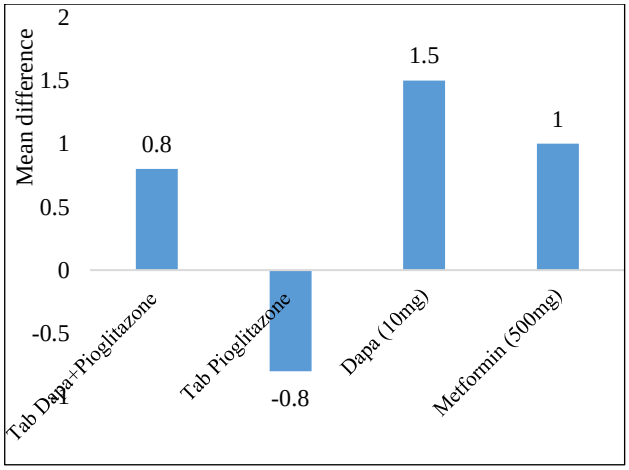

Figure 2: Weight reduction from pre-intervention to post-intervention.

The weight reduction was highest in the patients with DAPA 10mg group followed by patients with metformin group then the patients with DAPA+ pioglitazone group and the patients in the pioglitazone group experienced weight gain, (Figure 2). There was a statistically significant difference between them (p<0.001) except for the patients with Pioglitazone (p=0.496).

The change in SBP and DBP from pre-intervention to post-intervention was highest in the patients with DAPA+ pioglitazone group. There was a statistically significant difference between them except for the patients with metformin and pioglitazone groups as shown in Table 3.

Table 3: Change in blood pressure from pre-intervention to post-intervention.

Parameters		Pre-intervention	Post-intervention	P value
SBP	Tab Dapa (10) + Pioglitazone (15)	145.20±9.60	135.20±10.10	<0.001*
	Tab Pioglitazone (15)	149.10±4.20	144.10±4.70	0.508
	Tab Dapa (10)	131.50±13.20	124.50±13.70	<0.001*
	Tab Metformin (500)	141.70±16.00	135.70±16.50	0.338
DBP	Tab Dapa (10) + Pioglitazone (15)	94.70±0.70	87.70±1.20	<0.001*
	Tab Pioglitazone (15)	81.30±0.10	78.30±0.60	0.622
	Tab Dapa (10)	88.80±0.50	84.80±1.00	<0.001*
	Tab Metformin (500)	85.90±1.00	82.90±1.50	0.118

Table 4: Change in lipid profile from pre-intervention to post-intervention.

Parameters		Pre-intervention	Post-intervention	P value
TG	Tab Dapa + Pioglitazone	171.8±17.2	141.3±10.9	<0.001*
	Tab Pioglitazone (15)	170.1±16.8	149.4±11.3	<0.001*
	Tab Dapa (10)	164.6±13.4	149.5±11.7	<0.001*
	Tab Metformin (500)	167.5±15.3	153.2±12.5	0.479
Cholesterol	Tab Dapa + Pioglitazone	164.3±21.8	153.9±18.9	<0.001*
	Tab Pioglitazone (15)	159.1±20.1	152.3±18.6	<0.001*
	Tab Dapa (10)	162.4±20.9	157.1±17.5	<0.001*
	Tab Metformin (500)	158.7±19.7	155.6±17.3	0.229
LDL	Tab Dapa + Pioglitazone	82.5±19.1	74.2±15.4	<0.001*
	Tab Pioglitazone (15)	80.7±19.4	78.3±14.8	0.297

Continued.

Parameters		Pre-intervention	Post-intervention	P value
	Tab Dapa (10)	78.3±18.7	75.2±15.1	<0.001*
	Tab Metformin (500)	79.9±18.3	77.4±16.7	0.438
HDL	Tab Dapa + Pioglitazone	38.7±9.2	34.5±8.1	<0.001*
	Tab Pioglitazone (15)	34.5±9.4	33.2±7.9	<0.001*
	Tab Dapa (10)	35.3±8.6	35.2±7.4	0.623
	Tab Metformin (500)	35.9±8.5	34.9±7.8	0.513

The change in lipid profile (triglyceride and cholesterol, LDL and HDL) from pre-intervention to post-intervention was highest in the patients with DAPA+ pioglitazone group. This change was statistically significant (p<0.001), (Table 4). During the study period, we didn't come across any major adverse cardiovascular events (MACE).

DISCUSSION

As there are many oral hypoglycemic agents available and the recent guidelines promote the use of combination drugs, there should be appropriate selection of drugs, the drugs should have synergistic actions and should have additional benefits too. In the present study, rationale behind choosing the combination of pioglitazone and dapagliflozin was that; pioglitazone being a potent insulin sensitizer had some major side effects like fluid retention and weight gain, however dapagliflozin has diuretic action and is known to cause weight reduction, thus neutralizing the effect of pioglitazone. Most of our patients were from the age group of 50 to 60 years (50%) followed by >60 years (40%) with male predominance (60%), this is comparable with the study conducted by Langenfeld et al and Viollet et al.[6,7]

The change in FBS and PLBS from pre-intervention to post-intervention was highest in the patients with DAPA+ pioglitazone group followed by patients with pioglitazone group then the patients with DAPA group and lowest in patients with metformin group. There was a statistically significant difference between them, (P<0.001). However, the change in HbA1C from pre-intervention to post-intervention was highest in the patients with DAPA+ pioglitazone followed by patients in pioglitazone group then the patients in DAPA 10mg group and lowest in patients in metformin group. There was a statistically significant difference between them. These findings are correlated with the previous studies.[8,9]

The combination of drugs in addition to control of the glycemic parameters also caused reduction of the blood pressures and improved the lipid profile super added benefit being weight reduction. The change in SBP and DBP from pre-intervention to post-intervention was highest in the patients with DAPA+ pioglitazone group. There was a statistically significant difference between them except for the patients with metformin and pioglitazone groups.

The change in triglyceride and total cholesterol from pre-intervention to post-intervention was highest in the patients with DAPA+ pioglitazone group followed by patients with pioglitazone group then the patients with DAPA 10mg and lowest in patients with metformin. There was a statistically significant difference between them except for the patients with metformin. Whereas the change in LDL from pre-intervention to post-intervention was highest in the DAPA+ pioglitazone group followed by patients in DAPA 10mg group then the patients in metformin group and lowest in the pioglitazone group. There was a statistically significant difference between them except for the patients in pioglitazone and metformin groups. The change in HDL from pre-intervention to post-intervention was highest in the DAPA+ pioglitazone group followed by patients in pioglitazone group then the patients in metformin group and lowest in patients in DAPA 10mg group. There was a statistically significant difference between them except for the patients in DAPA and in metformin groups. Thus, the change in lipid profile of patients from pre-intervention to post-intervention was highest in the patients with DAPA+ pioglitazone group. These findings are correlated with the study conducted by Hayashi et al and Comaschi et al.[10,11] During the study, there were no ADRs also we didn't come across any MACE. These findings suggest that the combination therapy of dapagliflozin with pioglitazone is more effective than the single therapy.

This study has several limitations. Study was open label (non-blinded) hence chances of selection/ performance/ detection bias even if minimal can't be ruled out. Neither MACE nor ADR were observed during study. This may be due to shorter duration study of three months and small sample size. Hence blinded study with larger sample size for sufficiently longer duration is suggested to note the occurrence of MACE and ADR.

CONCLUSION

The present study found that the combination of pioglitazone and dapagliflozin not only helped in glycemic control but also had reduction in blood pressures, improvement in the lipid profile and caused slight weight reduction. There were no major adverse drug reactions, and no MACE were observed during the study. Hence this combination of pioglitazone and dapagliflozin may reduce the cardiovascular mortality,

but this assumption needs to be substantiated by longer duration of study with sufficiently larger sample size to note the objective reduction in cardiovascular mortality.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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