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Original Research Article

Assess the Efficacy of Increasing the Metformin Dosage Instead of Adding Empagliflozin to Uncontrolled Type 2 Diabetes Patients

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Conflict of interest: Nil

Objective: This prospective observational study's main aim was to determine whether increasing the dose of metformin rather than adding empagliflozin to individuals with type 2 diabetes who were uncontrolled on it was more beneficial.

Method: This was a prospective observational study carried out in Prasad Institute of Medical Science (PIMS) & Hospital, Lucknow that included 100 patients who met the inclusion and exclusion requirements. Upon inclusion, patients were split into two groups, one of which received 1000 mg of metformin OD along with 10 mg of empagliflozin OD (N = 50), and the other of which had metformin up-titrated to the maximum tolerated dose of 1000 mg (N = 50).

Results: In the Empa + Met group, there was a considerable weight loss of up to 2 kg over a period of 23 weeks. Despite effective anti-hypertensive therapy in both groups, a statistically significant drop in SBP and DBP (10.1±3.4 mmHg and 7.1±2.1, respectively) was seen in the Empa+Met group, which was not seen in the Met group. Despite the group receiving the recommended amount of lipid-lowering treatment, there was a further statistically significant decrease in total cholesterol, triglycerides, and LDL cholesterol.

Conclusion: Instead of increasing the dose of metformin, patients who were initially uncontrolled with metformin monotherapy should be added to empagliflozin 10 mg. If metformin is used with empagliflozin as a second-line treatment, the pleiotropic benefits are improved.

Keywords: Uncontrolled Type 2 Diabetes, Empagliflozin and Metformin.

Introduction

The health and economics of the country are being increasingly burdened by the epidemic of diabetes [1]. Prior attempts to control the disease's consequences and its progression through aggressive care were hampered by a number of issues, including metabolic side effects, lethal complications, and occasionally elevated overall mortality [2–5].

One of the primary causes of mortality and morbidity worldwide is diabetes, along with its complications. A strict management strategy is necessary because the disease and its consequences are spreading rapidly [6]. The risk of cardiovascular (CV) events can rise by 18% with every 1% increase in the glycated hemoglobin (HbA1c) level [Figure 1]. Also, it has been highlighted that the risk of death might increase by 12–14%, and the risk of retinopathy or renal failure can increase by 37%, indicating a clear need to control blood sugar [6,7].

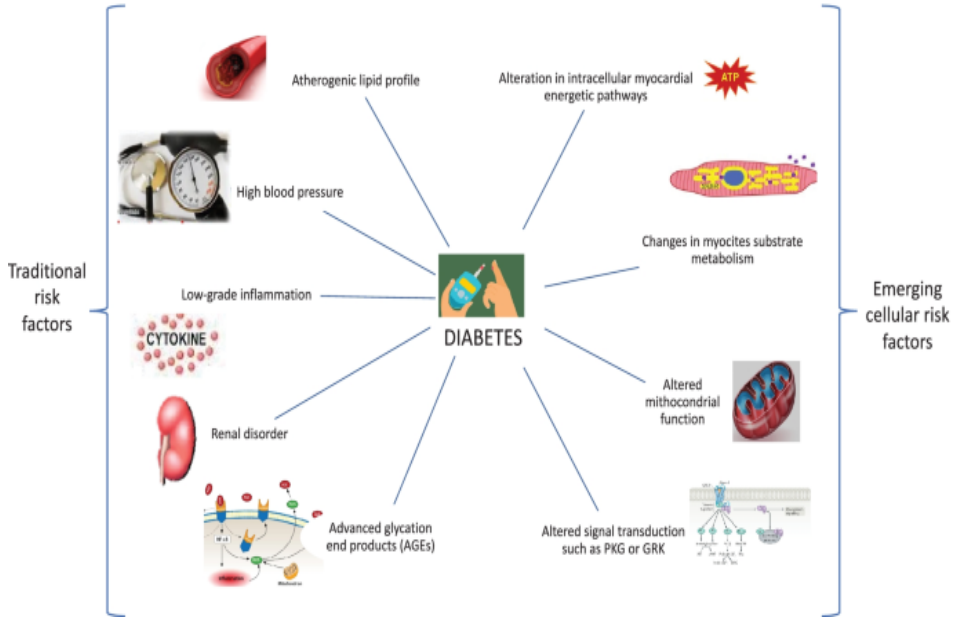

Figure 1: An increase in hemoglobin (HbA1c) levels results in an increase in the risk of cardiovascular (CV) events.

Controlling blood sugar has always required a fine balance. The patient must be educated sufficiently to develop or change decision-making methods, volitional control, and common sense to prevent hypo- and hyperglycemia in addition to maintaining a euglycemic condition. The majority of individuals with type 2 diabetes are currently advised to use the biguanide medication metformin as their first line of treatment [8–10].

Less risk of hypoglycemia, a small decrease in weight, and minimal cost are some of its benefits. By blocking the SGLT2 transporter on the proximal convoluted tubule of the nephron, sodium glucose cotransporter 2 (SGLT2) inhibitors lower hyperglycemia [11–14]. By way of glycosuria, this causes a sizable amount of the filtered glucose to be lost. Duel inhibitors, which also inhibit SGLT1, the enzyme responsible for absorbing glucose, have recently been discovered [15].

This prospective observational study's primary objective was to determine the effectiveness of empagliflozin addition rather than metformin dose titration in individuals with type 2 diabetes who remained uncontrolled despite taking the medication.

Method:

Study design: This study was conducted prospectively at Prasad Institute of Medical Science (PIMS) & Hospital, Lucknow.

Methodology: Patients with type 2 diabetes who were under the age of 17, had an HbA1c of at least 8%, were taking 1000 mg of metformin alone, and were prepared to give informed consent met the primary inclusion criteria. Individuals with confirmed micro and macrovascular difficulties, women who were pregnant or nursing, and people with liver function issues were all excluded from the study. Upon inclusion, patients were split into two groups, one of which received 1000 mg of metformin OD along with 10 mg of empagliflozin OD (N = 50), and the other of which had metformin up-titrated to the maximum tolerated dose of 1000 mg (N = 50). A pre-designed proforma was used to collect demographic information such as age, gender, duration of diabetes, weight, BMI, and other prescription facts. A clinic manual BP measurement device was used to monitor blood pressure at the beginning of the study and at each subsequent

checkup. At baseline and throughout each follow-up, serological tests such as FBS, PPBS, HbA1c, lipid profile, blood urea, and serum creatinine were assessed.

Sample Size: 100 patients met the inclusion and exclusion criteria, making them eligible.

Exclusion Criteria: 110 patients were initially found, however, 10 were later removed from the study because 7 were not found during follow-up and 3 had inconsistent follow-up checkups

Statistical Analysis: Microsoft Excel sheets were utilized to collect the data, which were then analyzed with the aid of SPSS 22.0. In a descriptive bivariate analysis, significance was set at $P<0.04$ for the chi-squared distribution.

Ethical Consideration: This prospective study was approved by the ethical committee of Prasad Institute of Medical Science (PIMS) & Hospital, Lucknow.

Results:

Table 1 contained demographic information. It was found that both groups' demographic characteristics were quite comparable. A sizable portion of the patients in both groups shared co-morbid conditions like hypertension and dyslipidemia. Most patients in both groups were taking lipid-lowering and antihypertensive medications.

Table 1: Demographic characteristics of the participants in both group

Criteria	Met Gr.	Empa+ Met Gr.	P-Value
Gender (M/F)	23/37	22/38	0.944
Age (years)	53.1±6.8	52.7±7.1	0.670
BMI	30.6±5.1	30.4±5.2	0.741
Duration of Diabetes	2.2±0.7	2.0±1.2	0.036
SBP (mg/dl)	127.1±13.6	127.3±14.7	0.582
DBP (mg/dl)	78.4±8.0	79.2±9.3	0.490
Weight (kg)	83.1±19.0	82.7±19.7	0.384
Hypertension medication in patients (%)	61%	68%	0.853
Lipid-lowering drugs in patients (%)	82.1%	84.3%	0.984

In the Empa + Met group, there was a considerable weight loss of up to 2 kg over a period of 23 weeks. Despite effective anti-hypertensive therapy in both groups, a statistically significant drop in SBP and DBP (10.1±3.4 mmHg and 7.1±2.5, respectively) was seen in the Empa+Met group, which was not seen in the Met group.

Compared to the metformin group, the empa + met group has shown a greater influence on lipid profiles. Despite the group receiving the recommended amount of lipid-lowering treatment, there was a further statistically significant decrease in total cholesterol, triglycerides, and LDL cholesterol.

The details of the reduction in HbA1c (Figure 2), FBG, and PPG (Figure 3) are shown below.

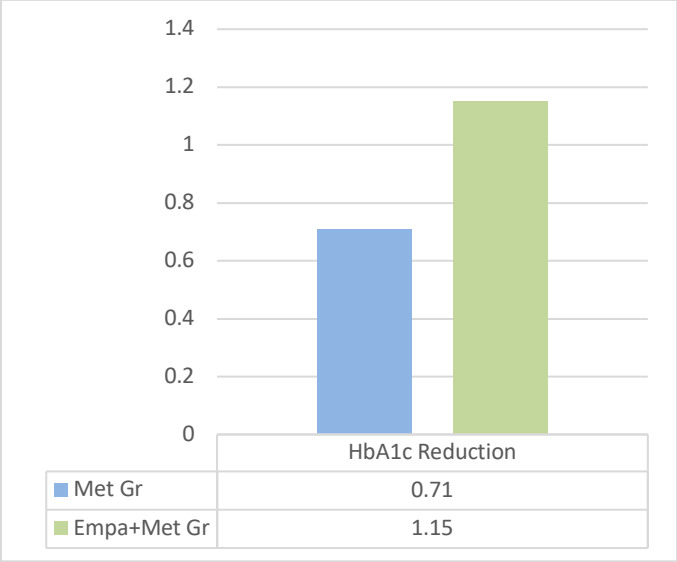

Figure 2: HbA1c Reduction in Two Groups Over 23 Weeks

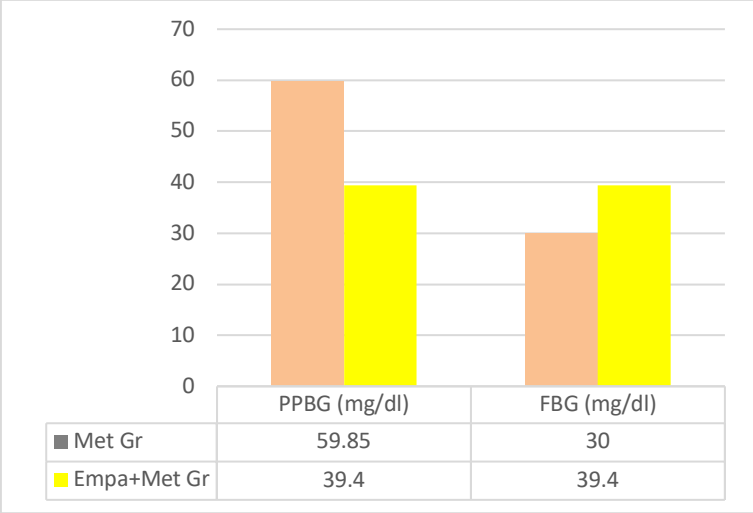

Figure 3: After 23 weeks, both groups' FBG and PPBG levels decreased.

Discussion:

Metformin has a long history of use in the management of type 2 diabetes. Its broad range of effects and strong safety profile have made it the most often used oral anti-diabetic medication. Promising findings have been reported in recent literature and current investigations of its effects on a number of diabetes risk variables and consequences (including lipid profile, body weight, cardiovascular risk, antiaging, and antineoplastic). It is important to not undervalue this drug's ability to control diabetes in the future [16,17].

Inhibitors of sodium glues transporter 2 (SGLT2) work by lowering blood glucose by glycosuria and decreasing renal glucose reabsorption. Two post-marketing CV outcome trials with the SGLT2 inhibitors empagliflozin and canagliflozin, titled the EMPAREG OUTCOME and CANVAS programmes, respectively, demonstrated significant reductions in the 3 point MACE with these drugs [18–20].

The EMPAREG OUTCOME was used to measure the impact of empagliflozin.

Study that randomly assigned 7,200 T2DM patients with CV disease to receive either a

placebo or an empagliflozin dose of 10 mg to 25 mg per day. Patients were then monitored for 3.1 years. More than 75% of patients in the EMPAREG OUTCOME trial received medication for their CV risk, which included More than 95% of people who used a statin also got antihypertensive therapy, and over 90% took anticoagulant/antiplatelet medications [20]. Empagliflozin appeared to considerably lower hospitalization for heart failure even though it had no effect on the occurrence of nonfatal MI or stroke [21]. Within the first six months following randomization, there was a considerable difference in the rates of MACE, death, and heart failure hospitalization between the empagliflozin and placebo groups. [22]

The most important clinical question that the present study has addressed is whether to add a second therapy or increase the dose of monotherapy. In this trial, it became obvious that adding empagliflozin to metformin monotherapy provided patients with superior pleiotropic effects, such as a reduction in weight, BMI, blood pressure, and lipid profile, in addition to helping them achieve better glycemic control than high-dose titration. A statistically significant drop in SBP and DBP was shown in the Empa+Met group (10.1±3.4 mmHg and 7.1±2.5, respectively) but not in the Met group, despite both groups receiving sufficient antihypertensive treatment. Despite the group receiving the recommended amount of lipid-lowering treatment, there was a further statistically significant decrease in total cholesterol, triglycerides, and LDL cholesterol.

Conclusion

Instead of increasing the dose of metformin, patients who were initially uncontrolled with metformin monotherapy should be added to empagliflozin 10 mg. If metformin is used with empagliflozin as a second-line treatment, the pleotropic benefits are improved. Beyond its glucose-lowering effectiveness, the use of SGLT2i is a unique method of glycemic control that also has other proven cardio-metabolic and renal benefits.

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