EMPAGLIFLOZIN (SGLT2 INHIBITOR) IN TYPE 2 DIABETES MELLITUS

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ABSTRACT

BACKGROUND

To study the analysis of metabolic parameters in patients with type 2 diabetes mellitus on empagliflozin, which is a SGLT2 inhibitor.

MATERIALS AND METHODS

This study was a prospective study of 120 patients with uncontrolled type 2 diabetes mellitus who were admitted as outpatients in JLNMCH Hospital, Bhagalpur. This study was conducted from February 2017 to April 2017. Informed consent was taken from each patient who participated in the study and the study protocol was approved by the institutions ethics and review board.
Inclusion Criteria- Patients with type 2 diabetes mellitus and HbA1c >8% meeting any one of the criteria- Patients who were on dual therapy (metformin + sulfonylurea/DPP4 inhibitor); patients who were on triple therapy (metformin + sulfonylurea + DPP4 inhibitor); patients who were on insulin and triple oral therapy (metformin + sulfonylurea + DPP4 inhibitor).
Exclusion Criteria- Patients who had history of genital mycotic infections, recurrent urinary tract infections, pyelonephritis, acute illness, type 1 diabetes, pregnant or lactating women, those patients who were with an eGFR below 45.

RESULTS

The mean age, duration of diabetes, weight and HbA1c in the study population was 54.36 ± 0.88 years, 14.2 ± 3.6 years, 76.25 ± 2.11 kgs and 9.66 ± 0.22%, respectively. The changes in weight and HbA1c were statistically significant across all groups. In 5% of the patients, genital pruritus was reported. Mycotic genital infection was seen in none of the patients on examination. All the four groups chose to discontinue the use of empagliflozin as a result of pruritus at follow up. The baseline daily insulin dose was 42 ± 25 units, and at 4 months, it was reduced to 34 ± 20 units. At follow up, the reduction in insulin level was 19.1% when compared to baseline.

CONCLUSION

This study showed that there was an improvement in glycaemic control and body weight with minimal side effects when SGLT2 inhibitor was added at any stage of disease with any of the pre-existing therapeutic agents for patients who had uncontrolled T2DM.

KEYWORDS

Empagliflozin, Diabetes Mellitus, Sulfonylurea.

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BACKGROUND

Type 2 diabetes is a disease that results in the levels of sugar in the blood being too high. This can cause damage to the eyes, nerves, kidneys and other tissues and can greatly increase the chances of heart attacks and strokes, especially when combined with high blood pressure and high blood cholesterol levels.[1] Type 2 diabetes mellitus is a chronic metabolic disorder, the prevalence of which has been increasing steadily in all parts of the world. Type 2 diabetes mellitus consists of an array of dysfunctions characterised by hyperglycaemia and resulting from the combination of resistance to insulin action, inadequate insulin secretion and excessive or inappropriate glucagon secretion. Symptoms of type 2 diabetes include- polyuria, polydipsia, polyphagia, weight loss, blurred vision, paraesthesia of the lower extremities and yeast infections.[2] Type 2 diabetes can cause serious long-term health problems such as diabetic retinopathy and kidney failure and patients with type 2 diabetes are up to five times more likely to have cardiovascular diseases such as strokes or ischaemia.[3] Type 2 diabetes is due primarily to lifestyle factors and genetics. A number of lifestyle factors are known to be important to the development of type 2 diabetes such as physical inactivity,sedentary lifestyle, cigarette smoking and generous consumption of alcohol. Obesity has been found to contribute to approximately 55% of cases of type 2 diabetes. There is a strong inheritable genetic connection having relatives with type 2 diabetes increases the risks

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substantially.[4] Recently, genes discovered to be significantly associated with developing type 2 diabetes include- TCF7L2, PPARG, FTO, CDKAL1, KCNJ11, NOTCH2, WFS1, IGF2BP2, SLC30A8, JAZF1 and HHEX KCNJ11. However, individually these account for only a small proportion of cases. It is estimated that more than 1 in 16 people in the UK has diabetes (diagnosed or undiagnosed). There are almost 3.5 million people diagnosed with diabetes in the UK with 90% of these having type 2 diabetes.[5] In addition, it is estimated that there are around 5,49,000 people in the UK who have diabetes, but have not been diagnosed. Research suggests that people from South Asian and Black communities are two to four times more likely to develop type 2 diabetes than those from White ethnic groups. Diabetes care is estimated to account for up to 10% of NHS expenditure. Empagliflozin is a drug currently used to treat type 2 diabetes. It is given as a tablet that is taken once daily.[6] In a large study of patients, empagliflozin reduced the risk of getting high blood pressure, heart attacks and strokes in people with type 2 diabetes. Empagliflozin will offer type 2 diabetes patients who are at risk of developing heart disease and strokes, an additional treatment option, which can be used with other diabetes drugs.[7] Empagliflozin is a reversible, highly potent and selective competitive inhibitor of sodium-glucose co-transporter 2 (SGLT2). Empagliflozin does not inhibit other glucose transporters important for glucose transport into peripheral tissues and is 5,000 times more selective for SGLT2 compared to SGLT1. SGLT2 is highly expressed in the kidney, whereas expression in other tissues is absent or very low. It is responsible for the reabsorption of glucose from the glomerular filtrate back into the circulation. Empagliflozin improves glycaemic control in patients with type 2 diabetes by reducing renal glucose reabsorption. Empagliflozin is administered orally as either a 10 mg or 25 mg single tablet taken once daily. It is expected that this treatment will continue indefinitely as part of long-term diabetic glucose and complication management.[3] Empagliflozin is currently licensed in the EU for the treatment of adults with type 2 diabetes mellitus to improve glycaemic control as a monotherapy and as an add-on combination therapy with other glucose-lowering medicinal products. Common adverse events include hypoglycaemia (when used with sulphonylurea or insulin), genital infections, urinary tract infections, pruritus and increased urination.

MATERIALS AND METHODS

This study was a prospective study of 120 patients with uncontrolled with type 2 diabetes mellitus who were admitted as an outpatient in JLNMCH Hospital, Bhagalpur. This study was conducted from February 2017 to April 2017. Informed consent was taken from each patient who participated in the study and the study protocol was approved by the institutions ethics and review board.

Inclusion Criteria

Patients with type 2 diabetes mellitus and HbA1c >8% meeting any one of the criteria- Patients who were on dual therapy (metformin + sulfonylurea/DPP4 inhibitor); patients who were on triple therapy (metformin + sulfonylurea + DPP4 inhibitor); patients who were on insulin and triple oral therapy (metformin + sulfonylurea + DPP4 inhibitor).

Exclusion Criteria

Patients who had history of genital mycotic infections, recurrent urinary tract infections, pyelonephritis, acute illness, type 1 diabetes, pregnant or lactating women, those patients who were with an eGFR below 45. Screening and evaluation of all patients were done for complications of diabetes as per standard of care. Following investigations were done- Fasting Plasma Glucose (FPG), Postprandial Plasma Glucose (PPG), haemoglobin A1c, lipid profile, renal function tests and urine analysis. The patients were categorised into 4 groups of 30 each as follows- Group I- Metformin + sulfonylurea + empagliflozin (SGLT2i); Group II- Metformin + DPP4 inhibitor + empagliflozin (SGLT2i); Group III- Metformin + sulfonylurea + DPP4 inhibitor + empagliflozin (SGLT2i); Group IV- Insulin + metformin + sulfonylurea + DPP4 inhibitor + empagliflozin (SGLT2i). Glimepiride (4 mg/day) and gliclazide (120 mg/day) were given as sulfonylureas; sitagliptin 100 mg/day, saxagliptin 5 mg/day, vildagliptin 100 mg/day, linagliptin 5 mg/day and teneligliptin 20 mg/day were given as DPP4 inhibitors. Metformin 2 g/day was given. The importance of Self-Monitoring Blood Glucose (SMBG) were given to patients who were on insulin and dosage adjustments were made twice a week. The duration of follow up was 4 months.

RESULTS

The mean age, duration of diabetes, weight and HbA1c in the study population was 54.36 ± 0.88 years, 14.2 ± 3.6 years, 76.25 ± 2.11 kgs and 9.66 ± 0.22%, respectively.

Group	Baseline Weight (Kgs)	Weight at 4 Months (Kgs)	P Value
G-1	82.08 ± 25.87	77.65 ± 12.09	<0.05
G-2	73.28 ± 9.11	70.23 ± 3.25	<0.05
G-3	75.34 ± 12	73.28 ± 8.25	<0.05
G-4	75.89 ± 44	74.53 ± 1	<0.05

Table 1. Shows Changes in Weight

Group	Baseline HbA1c	HbA1c at 4 Months	P Value
G-1	9.69 ± 1.22	8.88 ± 1.09	<0.05
G-2	8.11 ± 0.87	7.33 ± 0.85	<0.05
G-3	9.81 ± 1.2	8.45 ± 0.5	<0.05
G-4	10.22 ± 1.47	8.54 ± 1.01	<0.05

Table 2. Shows Changes in HbA1c

The changes in weight and HbA1c were statistically significant across all groups. In 5% of the patients, genital pruritus was reported. Mycotic genital infection was seen in none of the patients on examination. All the four groups chose to discontinue the use of empagliflozin as a result of pruritus at follow up. Side effects like urinary tract infections, polyuria, thirst, giddiness, postural hypotension, dehydration, hypovolaemia, haemoconcentration, euglycaemic ketoacidosis, worsening of eGFR, electrolyte imbalance, increase in LDL were not observed. In group

which took insulin, i.e. group IV, hypoglycaemia was reported. None of the patients had severe hypoglycaemia or loss of consciousness requiring hospitalisation or intravenous dextrose administration, however, the number of episodes of hypoglycaemia were not documented. The patients had reduced their insulin dose based on SMBG. The baseline daily insulin dose was 42 ± 25 units and at 4 months it was reduced to 34 ± 20 units. At follow up, the reduction in insulin level was 19.1% when compared to baseline.

DISCUSSION

Many studies from literature were reported for SGLT2 inhibitors in type 2 diabetes mellitus. Bhavana Sosale et al[8] have conducted a study to analyse the metabolic parameters in patients with T2DM on SGLT2i in real world clinical practice. The number of patients with Type 2 Diabetes Mellitus (T2DM) is increasing. Most patients with T2DM are uncontrolled and failed to achieve their target HbA1c. In recent years, newer agents such as SGLT2 inhibitors (SGLT2i) have been approved for clinical use. Though data from clinical trials and subset analysis of Indian patients in global studies are promising, real world evidence from standard clinical practice in India is lacking. This was a prospective, longitudinal study of 100 patients with uncontrolled T2DM attending the outpatient of a specialised diabetes hospital. Their metabolic parameters were evaluated at baseline and after 3 months of follow up. They were categorised based on their baseline antidiabetic medications into four groups (25 in each). The groups were as follows- metformin plus sulfonylurea, metformin plus DPP4 inhibitor, triple drug regimen with metformin plus DPP4 inhibitor plus sulfonylurea, and patients on insulin and on triple drug therapy with metformin plus sulfonylurea plus DPP4 inhibitor. Patients in each group were initiated with a SGLT2i. Descriptive statistical analysis was carried out using Microsoft Excel. T-test was used to calculate the p value at 5% level of significance. The mean age of the subjects in the study population was 53.20 ± 12.1 years and the duration of diabetes was 13.1 ± 7.26 years. The mean HbA1c reduction and weight reduction observed was 1.02 ± 0.24% and 2.64 ± 1.27 kg, respectively. Genital pruritus was reported in 4% of the patients. There was a 16.6% reduction in the daily insulin requirement at follow up when compared to baseline. No other side effects were observed. The reductions in HbA1c and weight were statistically significant ($p<0.05$) across all groups. The mean age of the subjects in the study population was 53.20 ± 12.1 years and the duration of diabetes was 13.1 ± 7.26 years. The mean HbA1c reduction and weight reduction observed was 1.02 ± 0.24% and 2.64 ± 1.27 kg, respectively. Genital pruritus was reported in 4% of the patients. There was a 16.6% reduction in the daily insulin requirement at follow up when compared to baseline. No other side effects were observed. The reductions in HbA1c and weight were statistically significant ($p<0.05$) across all groups. Mandal K et al[9] conducted a study in which most of current guidelines for management of diabetes mellitus are recommending comprehensive strategy inclusive of adequate control of blood pressure and weight apart from hyperglycaemia. Several innovative antidiabetic molecules have been launched in recent years. Out of these agents, injectable incretin-based therapy like GLP1 receptor agonist has shown great promise, but high cost and injectable route of administration have prevented their wide acceptance. In the last 4 years, sodium-glucose co-transporter inhibitor, which works in kidney to induce excess glucose elimination through urine has been launched globally. This oral antidiabetic agent works comprehensively and more intensively than existing dipeptylpeptidase 4 inhibitors (DPP4i). Apart from its' excellent glycaemic benefit with negligible risk of hypoglycaemia and extra-glycaemic benefits like weight loss and blood pressure control, compatibility with almost all existing antidiabetic agents, possible positive impact on cardiovascular and renal outcomes and rapid reversal of glucotoxicity in type 2 diabetes mellitus patient whose renal function is intact, make them irresistible options for management of type 2 diabetes mellitus. However, despite huge advantages, injudicious use of agents, this class throws up unique challenges like genitourinary infections, euglycaemic ketoacidosis, electrolyte imbalance, etc. This review tries to give a comprehensive and balanced view of this class of drug. Hans-Ulrich Haring et al[10] conducted a study to investigate the efficacy and tolerability of empagliflozin as an add-on to metformin therapy in patients with type 2 diabetes. Patients with HbA1c levels of ‡7% to £ 10% (‡53 to £86 mmol/mol) while receiving metformin (‡1,500 mg/day) were randomised and treated with once daily treatment with empagliflozin 10 mg (n=217), empagliflozin 25 mg (n=213) or placebo (n=207) for 24 weeks. The primary endpoint was the change in HbA1c level from baseline at week 24. Key secondary endpoints were changes from baseline in weight and Mean Daily Glucose (MDG) at week 24. At week 24, adjusted mean (SE) changes from baseline in HbA1c were 20.13% (0.05)% (21.4 (0.5) mmol/mol) with placebo, 20.70% (0.05)% (27.7 (0.5) mmol/mol) with empagliflozin 10 mg and 20.77% (0.05)% (28.4 (0.5) mmol/mol) with empagliflozin 25 mg (both P <0.001). Empagliflozin significantly reduced MDG level and systolic and diastolic Blood Pressure (BP) versus placebo. Adjusted mean (SE) changes from baseline in weight were 20.45 kg (0.17 kg) with placebo, 22.08 kg (0.17 kg) with empagliflozin 10 mg and 22.46 kg (0.17 kg) with empagliflozin 25 mg (both P <0.001). Adverse Events (AEs) were similar across groups (placebo 58.7%; empagliflozin 49.5-57.1%). Confirmed hypoglycaemic AEs were reported in 0.5%, 1.8% and 1.4% of patients receiving placebo, empagliflozin 10 mg and empagliflozin 25 mg, respectively. Events consistent with urinary tract infections were reported in 4.9%, 5.1% and 5.6% of patients and events consistent with genital infections were reported in 0%, 3.7% and 4.7% of patients, respectively. Empagliflozin 10 and 25 mg for 24 weeks as add-on to metformin therapy significantly improved glycaemic control, weight and BP and were well-tolerated.

CONCLUSION

This study showed that there was an improvement in glycaemic control and body weight with minimal side effects when SGLT2 inhibitor was added at any stage of disease with any of the pre-existing therapeutic agents for patients who had uncontrolled T2DM.

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